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# Dendritic Excitability and Synaptic Plasticity

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**Sjöström PJ, Rancz EA, Roth A, Häusser M.** Dendritic Excitability and Synaptic Plasticity. *Physiol Rev* 88: 769–840, 2008; doi:10.1152/physrev.00016.2007.—Most synaptic inputs are made onto the dendritic tree. Recent work has shown that dendrites play an active role in transforming synaptic input into neuronal output and in defining the relationships between active synapses. In this review, we discuss how these dendritic properties influence the rules governing the induction of synaptic plasticity. We argue that the location of synapses in the dendritic tree, and the type of dendritic excitability associated with each synapse, play decisive roles in determining the plastic properties of that synapse. Furthermore, since the electrical properties of the dendritic tree are not static, but can be altered by neuromodulators and by synaptic activity itself, we discuss how learning rules may be dynamically shaped by tuning dendritic function. We conclude by describing how this reciprocal relationship between plasticity of dendritic excitability and synaptic plasticity has changed our view of information processing and memory storage in neuronal networks.

## I. INTRODUCTION

One of the most striking features of neurons is their extensive dendritic arbor. The shape of these dendritic

trees is highly specific and is in fact often used to define neuronal types. More importantly, the vast majority of synaptic inputs impinge on the dendrites rather than the soma or the axon. Therefore, dendrites probably serve an

important role in the integration of information delivered by the synapses. Synapses themselves are plastic, with the plasticity being governed by the temporal patterns of pre- and postsynaptic activity, a process that is widely held to underlie learning and memory. On the other hand, postsynaptic activity is in turn determined by the properties of the dendritic arbor itself, implying that the dendrites must in part determine the rules that govern synaptic plasticity. It follows that the type of dendritic excitability associated with a synapse should help to regulate the plastic properties of that synapse. Similarly, since the dendrite transforms the electrical and chemical signals it conveys, the location of a synapse in the dendritic tree will indirectly influence its plasticity rules. In this review, we discuss how dendritic properties control synaptic plasticity rules.

In recent years, it has been discovered that not only synapses are plastic, but also the dendritic tree itself. Although dendritic morphologies are typically relatively static on the time scales discussed here, their electrical properties can change in an activity-dependent manner with a time course of milliseconds up to hours and perhaps even days, which means there exist dendritic as well as synaptic learning rules. In addition, neuromodulators hold additional sway over dendritic excitability. We discuss in this review how synaptic learning rules may be dynamically shaped by the continuously ongoing tuning of dendritic function.

Finally, we show that the activity-dependent regulation of dendritic excitability means synaptic plasticity must indirectly control dendritic computations, just like dendritic integration controls synaptic plasticity. We are thus faced with an intricate set of interdependencies: synapses transmit information via dendrites to the soma to trigger output via axonal action potentials, while dendrites help determine synaptic plasticity, and synaptic activity in turn regulates dendritic excitability. We therefore argue that there must exist an activity-dependent reciprocal loop between synaptic plasticity and dendritic excitability.

We begin this review by revisiting the basic properties of synaptic plasticity, from classical synaptic potentiation to homeostatic synaptic scaling, in a historical context that begins with Donald Hebb's visionary postulate.

## A. Hebbian Plasticity

It is widely believed that learning and memory (2, 73, 371, 455, 479, 488, 489, 713, 737), as well as the development of neural circuitry (139, 151, 209, 295, 358, 379, 874), depend critically on long-term changes in the strength of synaptic connections. This view is often attributed to the Canadian neuropsychologist Donald Olding Hebb and to

his 1949 book *The Organization of Behavior* (290). However, Hebb was not the first to suggest that synaptic plasticity, or something like it, might underlie learning and memory. For example, both the neuroanatomist Santiago Ramón y Cajal (619) and the psychologist William James (333) came to similar conclusions (for a more detailed historical review, see Ref. 352). Regardless, the Hebbian postulate for cellular learning has remained the most widely quoted, undoubtedly because it constitutes a prediction that is experimentally testable, but perhaps also because of its simple and appealing phrasing (290): "When an axon of cell A is near enough to excite B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."

The Hebbian postulate is schematically summarized in Figure 1A. To reiterate, Hebb proposed that if the presynaptic cell A is repeatedly taking part in activating the postsynaptic cell B, along with a set of other presynaptic neurons, then the strength of the synaptic connection between A and B should be increased. Hebb argued that a memory trace of the event that triggered the synchronous firing of cells A and B could be stored in this way.

Several important aspects of the Hebbian postulate are worth noting. First of all, a temporal and causal order is implied: cell A evokes the firing of cell B, so the presynaptic cell A is active before the postsynaptic cell B (see sect. 1H). Second, cell A needs to act in cooperation with other presynaptic cells to induce synaptic strengthening (see sect. 1, B and L). Third, the weakening of the connection is never mentioned, nor implied (see sect. 1C). Fourth, strengthening is synapse-specific, which means that only active inputs are affected by this learning rule (97) (see sect. 1B). Fifth, Hebbian plasticity is in and of itself unstable: correlated firing leads to synaptic strengthening, which in turn generates more correlated firing (see sect. 1D). Finally, the Hebbian postulate treats all synapses as if they are equal and disregards any impact that the dendritic location of a synapse may have on the induction of synaptic plasticity, as Hebb explicitly treats both dendritic and somatic synapses as somatic (290). In fact, Hebb suggests in a later book that "dendrites have the function of receiving excitation from other cells" and that "this is the primitive arrangement, and that direct excitation of the cell-body is an evolutionary development which permits more efficient conduction" (289). To summarize this view, dendrites serve to connect neurons and conduct information from synapses to the soma, but they serve little or no specific role in triggering synaptic plasticity. The lumping of dendritic and somatic synapses in the Hebbian postulate is clearly an oversimplification, given that most neuronal types have a remarkable and cell type-specific dendritic arbor onto which the majority of

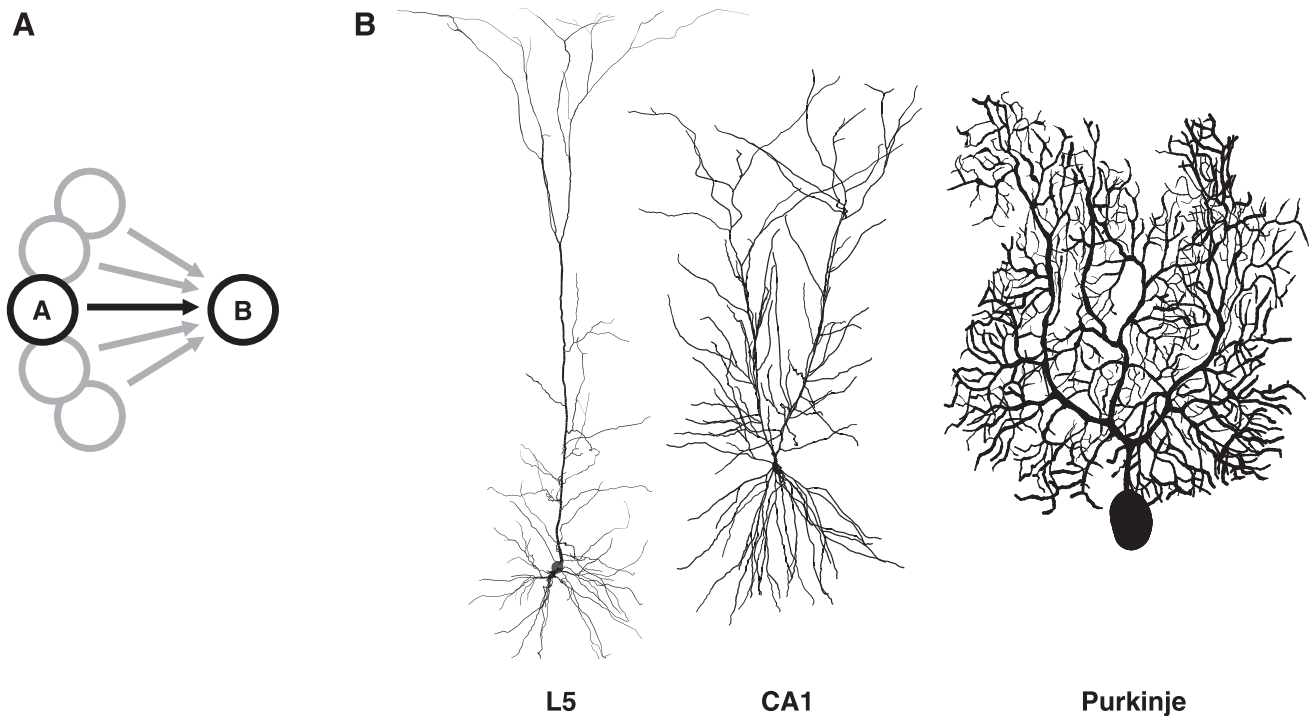


FIG. 1. The Hebbian postulate is based on an oversimplified view of neuronal morphology. *A*: schematic illustration of the Hebbian postulate. Briefly, if the presynaptic neuron A repeatedly and persistently takes part, along with a set of other presynaptic cells, in evoking the firing of the postsynaptic neuron B, then the connective strength between A and B should be increased. Hebb argued that this would be a way of storing a memory trace of the event that triggered the correlated firing of cells A and B (290). Note that the induction of synaptic plasticity according to the Hebbian postulate does in no way require dendrites, although dendrites could in principle be involved in the expression of plasticity by providing new connections through growth (also see Ref. 289). *B*: three sample neurons (the neocortical L5 pyramidal cell, the hippocampal CA1 pyramidal neuron, and the cerebellar Purkinje cell) that all have prominent dendritic trees. The vast majority of excitatory synaptic inputs are made onto the dendrites (86), which means that the induction of synaptic plasticity must depend on dendritic properties.

synaptic connections are made. This perhaps deliberate oversight is especially striking given that cell type-specific dendritic morphologies were known in the 19th century, decades before Hebb wrote his celebrated book (290). It is tempting to guess that the neglect of dendrites in the Hebbian postulate was due to their complexity, which must have seemed overwhelming at the time.

In the past few decades, however, many neuroscientists have come to appreciate the importance of the vast dendritic arborizations with which most neurons are endowed (445). One reason for these developments is the emergence of novel techniques such as dendritic patch-clamp recordings (162, 746, 748), multicompartmental computer modeling (298), and advanced imaging techniques (178), which have made the study of the dendritic arbor and its involvement in cellular learning rules considerably more tractable. We argue that some of the aspects, implied as well as explicit, of the Hebbian postulate are much better understood once dendrites and their biophysical properties are taken into account. In addition to claiming that dendrites affect synaptic plasticity, we shall also make the case that dendritic excitability can be regulated by the same activity patterns that evoke synaptic plasticity. In other words, there are complex interac-

tions between activity patterns, synaptic plasticity, and dendritic excitability.

## B. Long-Term Potentiation

Hebb argued that the learning rule he proposed would be sufficient to store memories, but little experimental evidence in support of such a mechanism existed at the time. The first electrophysiological data lending credence to the Hebbian postulate came some 20 years after its publication (74, 75, 444). In particular, Bliss and Lømo (74) demonstrated that excitatory postsynaptic potentials (EPSPs) evoked by electrical stimulation in the dentate gyrus of the rabbit hippocampus increased in amplitude after repeated high-frequency stimulation, a phenomenon they termed long-term potentiation (LTP). This high-frequency activity presumably led to correlated activity in connected cells, so the ensuing synaptic strengthening is consistent with the Hebbian postulate. The superficial similarity of LTP and the Hebbian postulate, and the fact that LTP was discovered in the hippocampus, a region known to be crucial for long-term memory formation, spawned thousands of further studies

on similar phenomena in the hippocampus as well as other brain regions (479). In particular, LTP of hippocampal Schaeffer collateral-CA1 synapses has been the most extensively studied and has become the dominant mammalian model for synaptic plasticity (73, 430, 479). In spite of this, the involvement of LTP in learning and memory remains to be conclusively demonstrated (49, 431, 490, 737). In particular, there remains some controversy regarding whether or not synaptic plasticity alone is both necessary and sufficient to fully account for memory storage in the brain (499). There is, however, relatively strong evidence in favor of the view that LTP underlies learning and memory in some mammalian brain regions, in particular the amygdala (488, 489, 640). In the giant marine snail *Aplysia*, the evidence for a critical role of synaptic plasticity in the gill withdrawal reflex is overwhelming (351). Nevertheless, some have argued that many LTP paradigms have little or possibly even nothing to do with learning and memory, but perhaps underlie a form of attention (337, 651, 705) or represent a form of neuropathology (507). In our opinion, the evidence favoring a critical role for LTP in learning and memory in mammals is continuously growing, even in complex brain regions such as the hippocampus (538, 828) and neocortex (632, 633), and that it is only a matter of time before this role is conclusively proven. This does not mean that there do not exist alternative mechanisms for memory storage, such as changes in intrinsic excitability (see sect. 1E; 371, 877) and structural plasticity (130, 167, 199, 312, 347, 378, 407, 480, 610, 777, 866). This review, however, will largely leave such structural plasticity aside, even though there probably exists a direct link between structural plasticity and LTP (587), and focus on plasticity of existing synapses and of intrinsic excitability.

Since most studies of synaptic plasticity over the years have been carried out at the hippocampal Schaeffer collateral-CA1 synapse (73, 97, 479), the properties of this form of LTP can be regarded as “classical” or “canonical.” Thus hippocampal LTP may serve as a useful framework or a yardstick to which one can compare plasticity at other types of synapse, because there exist numerous kinds of synaptic plasticity (191, 477). For example, although neocortical LTP typically shares several characteristics with hippocampal LTP (372, 374, 717), there are many forms of plasticity that, from the point of view of classical CA1 LTP or the Hebbian postulate, possess “odd” properties. For example, correlated firing may produce weakening of some synapse types (194) while anti-correlated activity may produce strengthening of other kinds of synapses (399). However, let us first examine the canonical form of LTP, which classically exhibits the following key features.

To a first approximation, LTP, like the Hebbian postulate, is input specific, which means that only stimulated

synapses are potentiated (73, 97, 479; although see Refs. 200, 277, 304, 680).

Typically, LTP depends on *N*-methyl-D-aspartate (NMDA) receptor-mediated  $\text{Ca}^{2+}$  influx (see sect. 1K) (430, 453, 468, 478, 550, 673, 867; although see Refs. 343, 556).

LTP is frequency-dependent (374, 717), a property that probably is connected to the need for NMDA receptor-mediated  $\text{Ca}^{2+}$  influx (see sect. 1, *G* and *J*).

In hippocampal CA1 LTP, in parallel with potentiation of synaptic responses, there is a reduced threshold for postsynaptic spiking. This concept is termed EPSP-spike potentiation (73, 76, 877) and will be revisited in section 1D2.

In many classical studies, LTP exhibits cooperativity and associativity (51, 171, 372, 417, 471, 509, 872) (see sect. 1L). These two closely related and somewhat poorly defined concepts are believed to enable behavioral associative learning (627).

The requirements for LTP induction mean LTP is inherently unstable (see sect. 1D). Correlated activity leads to synaptic strengthening so that the presynaptic cell drives the postsynaptic cell more reliably. This, in turn, results in more correlated activity and synaptic strengthening. This means stabilizing mechanisms are required, which include synaptic scaling (788, 790, 791) and metaplasticity (55, 70).

Finally, LTP is by definition long-lasting, and this durability of LTP is typically thought to be essential for its proper functioning as an information storage mechanism (although see Ref. 11). While there is some debate regarding the longevity of LTP (4, 880), it is typically understood that the duration is at least an hour and up to days, weeks, and even months (8, 730). LTP also exhibits at least two phases, denoted early and late LTP (4, 73, 351, 628). The early phase of LTP lasts only 1–3 h and does not require protein synthesis, whereas the late phase lasts for at least a day and requires both translation and transcription (351, 628).

It is worth emphasizing that several of the above key features of classical LTP are consistent with and even implied by the Hebbian postulate (290). In this review, we focus on mechanisms underlying the early phase of synaptic plasticity processes such as LTP and long-term depression (LTD) (see sect. 1C). In addition, we focus mainly on the induction of synaptic plasticity. We thus leave the expression mechanisms largely aside, unless they have a clear dendritic component (e.g., as in sect. 11, *D* and *F*). To limit the scope, we also largely leave aside the invertebrate literature on learning and memory, whether or not mechanisms involve dendrites (for invertebrate cellular learning mechanisms, we refer the reader to Refs. 29, 104, 111, 351, 805, 849).

### C. Long-Term Depression

Hebb never suggested the existence of the inverse of his postulate (290), i.e., the weakening of a synapse. However, the inverse of LTP, or LTD, is necessary to optimize information storage in a neural network (476, 688, 840). Around the same time that LTP was discovered and characterized, Gunther Stent (732) suggested an addition to the Hebbian postulate to account for the classical monocular deprivation experiments in kittens by Hubel and Wiesel (316, 832). Stent postulated the following: "When the presynaptic axon of cell A repeatedly and persistently fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is decreased."

Because the depressing synapse is not active during LTD induction in Stent's formulation, this synaptic weakening is termed heterosynaptic LTD (344, 425, 476). The synaptic strengthening that Hebb posited (290), on the other hand, was homosynaptic, since active but not inactive synapses are affected. Electrophysiological evidence for heterosynaptic LTD was found in the hippocampus a few years after the publication of Stent's conjecture (732): attempting to induce LTP by high-frequency stimulation of one pathway produced LTD of other, inactive pathways (6, 417, 454; although see Ref. 9). Heterosynaptic LTD does not always involve LTP expression of the pathway stimulated at high frequency; high-frequency stimulation without LTP expression may be sufficient in some preparations (6), although this result could be an artifact due to failure of LTP expression (6, 425).

More recently, homosynaptic LTD (344) was discovered in hippocampus (87, 190, 540) and cortex (374). Here, prolonged low-frequency stimulation (LFS; typically 900 pulses at 1–4 Hz) resulted in LTD. In other words, homosynaptic and heterosynaptic LTD are both the functional inverse of the Hebbian postulate, but in different manners.

### D. The Plasticity Versus Stability Conundrum

In the intact brain, the dendritic tree of a typical neuron receives tens of thousands of inputs exhibiting different strengths and activity patterns (86). However, as we discussed earlier, Hebbian plasticity (see sect. 1A) and LTP (see sect. 1B) are intrinsically unstable, simply because Hebbian plasticity is a positive feedback mechanism; the more potentiation that is evoked, the more correlated activity is produced, which in turn results in more potentiation. In addition, developmental synaptogenesis results in a massive increase in the number of inputs that a neuron receives, yet this does not result in the saturation of neuronal firing rates (163, 181, 786, 791).

Stability-promoting mechanisms are therefore required to keep activity levels within useful bounds so that neurons are neither saturated nor quiescent (181, 791). Such stabilizing mechanisms can be based on negative feedback. Too much activity brings about downregulation of the synaptic gain, whereas too little activity results in increased gain. As Hebbian and homeostatic plasticity have opposite sign, it has been assumed that homeostatic synaptic plasticity has to act on a time course that is considerably slower than that of Hebbian learning to avoid erasure of stored information (163, 181, 791). However, recent studies suggest a slow time course may not be necessary but that apparently homeostatic mechanisms are sometimes rapidly induced (222, 631, 750, 798, 799). In addition, stability-promoting mechanisms need not be due to homeostatic control of specific currents, since they can result from dynamic regulatory mechanisms (497, 797), nor need they even be activity-dependent (459, 460), as discussed below.

Multiple stability-promoting mechanisms have been proposed (163, 487, 523, 788, 790, 791). First, individual synaptic strengths could be scaled up or down globally, to counteract decreased or increased levels in synaptic drive. Evidence for such synaptic scaling in the mammalian central nervous system was first discovered by Turrigiano et al. (789) in neocortical cell cultures, and Desai et al. (182) subsequently verified their *in vivo* existence (also see Refs. 247, 248). Synaptic homeostasis has also been discovered in the retinotectal system of *Xenopus laevis* tadpoles (609) and at the neuromuscular junction of *Drosophila melanogaster* embryo (164, 738), although this latter case obviously does not involve dendrites. In synaptic homeostasis, excitatory inputs are typically downregulated by extended high-activity periods, whereas upregulation is brought about by episodes of low activity, and this holds true for  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (789) as well as NMDA receptors (823). As one might expect, inhibitory synapses exhibit the opposite activity dependence (367, 652, 653, 759), although inhibitory synaptic scaling may depend in complex ways on interneuron subclass (463). In synaptic scaling, either the presynaptic release machinery can be regulated (43, 100, 585) or the postsynaptic sensitivity to neurotransmitter can be altered (247, 367, 566, 572, 789, 823, 830). Whether primarily the pre- or the postsynaptic side is homeostatically regulated may depend on developmental stage (830, 831). In some cases, both the pre- and the postsynaptic sides are modified simultaneously (542, 772, 773, 831). Whether the change is pre- or postsynaptic has important implications for signal processing in neuronal circuits. Presynaptic regulation will not only alter the gain but also the short-term depression (STD) of the synapse (497, 715, 716), which produces a dynamic form of gain control (3). This dynamic form of gain control may make the postsynaptic cell more sensi-

tive to the temporal coherence of its inputs, rather than to their absolute firing rates (783). Presynaptic regulation in homeostatic synaptic scaling may therefore do more than just maintain stability.

Second, the intrinsic excitability of a neuron can be controlled to compensate for changes in synaptic drive (163, 487, 523, 788, 790, 791). Indeed, this type of neuronal homeostasis has been discovered in neocortex (183, 184), cerebellum (93), hippocampus (207, 546, 798, 799), *Xenopus* tadpole optic tectum (16, 18, 609), *Drosophila* motor neurons (45, 46), and crustacean stomatogastric neurons (258, 459, 460, 787). It should be noted that some cases of negative feedback appear not to be homeostatic, such as in the case of brain stem medial vestibular nucleus (285, 548, 549), where downregulation of intrinsic firing leads to an overshooting compensatory upregulation of intrinsic excitability. Surprisingly, and seemingly paradoxically, some forms of homeostatic regulation of intrinsic excitability are actually independent of activity (459, 460). Homeostasis of intrinsic excitability raises the intriguing possibility that individual sections of the dendritic tree might be separately regulated (see sect. II, *D* and *E*).

Third, alterations in the relative contributions of excitation and inhibition may also help stabilize neural networks. Concerted opposing forms of synaptic scaling of excitatory and inhibitory synapses obviously have an overall greater regulatory impact on stability (354, 367, 435, 652, 653, 759). As different types of inhibitory input may selectively target different dendritic compartments (496, 608, 708, 811), it is possible that subregions of the dendritic tree are selectively balanced in such a manner (249).

Additional potentially stability-promoting mechanisms may include those based on STD (749), enhanced STD upon LTP induction (99, 218, 497), enhanced inhibition upon LTP of excitation (134, 398, 590), reduced inhibition upon LTD of excitation (529), and neuronal gain control by background synaptic activity (120, 213, 214, 706). Simultaneous LTP of inhibition and excitation may also help maintain temporal fidelity during information transfer (398; compare Ref. 529).

Finally, metaplasticity has been proposed as a means to maintain stability. In general, metaplasticity refers to the activity-dependent regulation of plasticity rules themselves, or the “plasticity of plasticity” (5). Although alternative metaplasticity rules have been proposed (37), the most well known is without a doubt the BCM rule, named after its authors Bienenstock, Cooper, and Munro (70). In this paradigm, low-frequency correlated activity results in LTD, whereas correlated activity above a threshold frequency evokes LTP. Importantly, this plasticity modification threshold is itself modifiable and increases or decreases with high or low activity levels, respectively (55). Electrophysiological evidence in support of the BCM learning rule has been found, e.g., in the visual cortex

(376, 595, 596, 665) and hippocampus (10, 126, 567). The BCM model was originally created to account for the development of orientation tuning and ocular dominance in cat visual cortex (316, 832), which both require competition among synapses and an overall normalization of synaptic strength (70). This normalizing feature of the BCM rule means that it also has a form of global homeostasis built in (181, 791). There may also be a direct link between metaplasticity and homeostatic plasticity, since NMDA receptor currents scale in response to long-term changes in activity (823), which presumably alters the sensitivity of synapses to LTP and LTD induction (also see Ref. 772). Similarly, LTP induction results not only in AMPA receptor insertion (452, 482) but also in a concomitant but slower delivery of NMDA receptors to activated synapses (822; also see Ref. 452), which again is likely to subsequently influence their plasticity. It is worth noting, however, that the BCM rule, just like the Hebbian postulate (see sect. 1A), completely disregards the existence of the extensive dendritic arbor with which the vast majority of neurons are endowed with (Fig. 1) (249).

Several studies have found that the percentage amount of LTP produced at individual unitary synapses is negatively correlated with the initial synapse strength (69, 172, 421, 535, 717, 878; also see Ref. 272). This means that strong, perhaps already potentiated, synapses are less likely to undergo LTP due to correlated firing. That such a constraint on synapse strength in and of itself promotes stability has been demonstrated in a theoretical study by van Rossum et al. (797; for a review, see Ref. 362). What is the reason for this negative correlation between LTP and initial synaptic weight (69, 421, 535, 717, 878)? To our knowledge, no study has directly addressed this question so far, but it is tempting to speculate that some form of metaplasticity is the key to the answer; synapses that have undergone many rounds of LTP may be less susceptible to further potentiation. Alternatively, perhaps there is simply a soft upper limit to synapse strength. After all, synapses cannot grow indefinitely large, so there must exist some volume constraints (801).

The negative correlation between LTP and initial unitary synapse strength (69, 421, 535, 717, 878), however, implies synapse-specific regulation of the modification threshold. The BCM rule, on the other hand, assumes that the modification threshold is set globally, based on the overall postsynaptic activity. Similarly, synaptic scaling is typically assumed to act globally (although see Refs. 435, 614, 615, 649, 650), as local synaptic scaling might erase information stored through synapse-specific Hebbian-type learning rules (791). It remains an intriguing possibility, however, that metaplasticity or synaptic scaling, or both, can act locally, perhaps by normalizing synapse strength in parts of the dendritic tree. In fact, some have argued for the need of homeostatic rules to balance out synaptic weights in the dendritic tree (249). In fact, one

study suggests the existence of local metaplasticity in hippocampal CA1 neurons (126), although this form of metaplasticity is not normalizing. A recent study even proposes a form of structural homeostasis of the dendritic morphology (660). The importance of dendrite morphology will be further discussed in section *III B 3*, while dendritic normalization of synaptic weights and local homeostatic rules will be discussed in more detail in sections *IV* and *III F*.

Why are there so many stability-promoting mechanisms? Perhaps it is because biological systems tend to function imperfectly; redundant mechanisms may take over when others fail. Similarly, regulation of intrinsic excitability need not be exact, as several distinct regions of the entire possible parameter space may result in the same or similar outcome, such as demonstrated for the homeostasis of firing patterns in the crustacean stomatogastric ganglion (612). Different mechanisms may be more or less suited to promote stability under different circumstances or in different initial regions of the parameter space. In particular, it is conceivable that different stability-promoting mechanisms act at the spike initiation zone (138, 365, 386, 584) compared with mechanisms acting in distal dendritic compartments that may have less of a direct impact on spike output (406, 836, 837). Finally, it should be noted that, with respect to the possible redundancy of stability-promoting mechanisms, only a few of these have been verified by *in vivo* studies (e.g., Refs. 182, 463). Future *in vivo* experiments might therefore demonstrate that some are artifacts of the *in vitro* experimental paradigm and not physiologically relevant.

Above, we have discussed how stability in neuronal circuits is essential for proper brain functioning and how homeostasis of activity can be achieved. However, it should be noted that many brain regions are not actually entirely stable and can over a period of days be gradually driven to the point of epilepsy via repeated electrical stimulation (246), a concept termed “kindling” (106, 410, 507). Interestingly, kindling shares several properties with LTP (cf. sect. *I, B, J, and K*), such as similar induction requirements, NMDA receptor dependence, a need for postsynaptic  $\text{Ca}^{2+}$  elevation, and an involvement of synaptic growth (106, 410, 507). Furthermore, kindling is promoted by prior LTP induction (754) and can be reversed by LTD-like paradigms (825), suggesting a close link between synaptic plasticity and some forms of epilepsy. In this view, neuronal circuits are normally stable, but only when within certain activity bounds; excessive activity may push neuronal networks into epileptic states, by pathological recruitment of positive-feedback plasticity mechanisms that normally subserves learning and memory (507). Interestingly, recent reports indicate that there is also a link between certain forms of epilepsy and increased excitability of dendrites (66, 695, 851, 856), a topic that will be revisited in section *II A*.

### E. Learning and Memory Through Changes in Intrinsic Excitability

Although it is widely believed that memory is due to changes in synaptic strength, this does not mean that the synapse is the only place where storage of information may occur (cf. sect. *I B*). Some have proposed that changing in the excitability of parts of or the entirety of a neuron is an alternative mode of storing a memory (371, 877). Although storage capacity due to changes in intrinsic excitability must be considerably smaller than that for synaptic plasticity, this does not mean that the involvement of intrinsic excitability in learning and memory is necessarily negligible (877). In fact, changes in intrinsic excitability may serve specific functional purposes. For example, the induction of local dendritic hyperexcitability may prime a subset of neighboring synapses so that they more readily undergo LTP (340), which may serve a generalizing purpose in subsequent learning (877). Although largely left aside in this review, it should be noted that there is a formidable literature on the cellular mechanisms underlying learning and memory in invertebrates (29, 104, 111, 351, 805, 849); these learning mechanisms include alterations of intrinsic excitability (104, 111, 351).

As discussed in the previous section, activity-dependent changes in intrinsic excitability may help maintain stability in several neuronal circuits (16, 85, 93, 181, 183, 184, 207, 258, 485, 546, 787, 798, 799). In the case of stability promotion, the nature of the regulation is such that increased activity results in downregulation of excitability, and vice versa; this constitutes a negative-feedback loop that perhaps typically acts on a slow time scale (487), although there are several examples of fast-acting presumably homeostatic mechanisms (222, 750, 798, 799). Regardless, storage of information necessitates positive feedback (see sect. *IA*) that is typically relatively rapid. This combination of positive feedback and speed inevitably leads to instability (181, 791) (also see sect. *I, A, B, and D*). Indeed, positive-feedback loops in the activity-dependent regulation of intrinsic excitability have been found in neural systems as diverse as cerebellum (17, 35), neocortex (156, 727), entorhinal cortex (195), hippocampal CA1 region (854), and in hippocampal cell culture (234, 419). It should be noted that what appears to be a positive-feedback loop when regarded at the level of the synaptic inputs of a single neuron may actually result in negative feedback on the circuit level (e.g., compare Ref. 736), so, in principle, some of these mechanisms could in fact be homeostatic.

In all of the above-mentioned examples, the regulation of intrinsic excitability is global and affects the neuron in its entirety. It becomes even more interesting, of course, once the excitability of individual dendritic compartments can be specifically regulated to store information or to affect dendritic computations. Indeed, evidence



for such mechanisms has recently been discovered in hippocampal CA1 neurons (228, 813). Regulation of dendritic excitability will be further discussed in sections II and III.

## F. Transient Suppression of Neurotransmission: DSI and DSE

Depolarization-induced suppression of inhibition (DSI) was first discovered by Llano and Marty more than 15 years ago in cerebellar Purkinje cells (437). This form of plasticity is classically evoked by strong postsynaptic depolarization for a second or so, and the resulting suppression of inhibitory neurotransmission lasts ~20–40 s. Similar forms of DSI have also been described in the hippocampus (603, 843) and neocortex (779, 780). Depolarization-induced suppression of excitation (DSE) was discovered relatively more recently in the cerebellum (393) as well as in neocortex (221). Although typically labeled as a form of short-term plasticity (128), DSI and DSE have intermediate time course compared with those of LTP (73, 455, 488, 489) and of classical STD (883).

The mechanistic underpinnings of DSI and of DSE are relatively well known at this point. It was appreciated early on that postsynaptic  $\text{Ca}^{2+}$  elevation (437) as well as presynaptic G protein (602) and retrograde signaling (21) are necessary for triggering DSI. Initially, it was believed that this retrograde signal was postsynaptically released glutamate (245), but later studies strongly implicated retrograde endocannabinoid signaling in both DSE (392) and DSI (187, 393, 571, 843, 862; although see Refs. 152, 192). In fact, there is also strong evidence supporting the need for cannabinoid signaling in several forms of long-term plasticity in hippocampus, neocortex, cerebellum, nucleus accumbens, and striatum (128, 191, 241, 391, 634, 658, 711, 712, 716), suggesting that endocannabinoids play a general and widespread role in synaptic plasticity, in particular as a retrograde signal. In DSI and DSE, the endocannabinoid is released postsynaptically and acts on presynaptically located endocannabinoid CB1 receptors that briefly reduce neurotransmitter release by acting on specific presynaptic  $\text{Ca}^{2+}$  (96, 841) or  $\text{K}^+$  channels (188).

Although the need for postsynaptic  $\text{Ca}^{2+}$  elevation in both DSI and DSE (92, 392, 843) is consistent with the finding that  $\text{Ca}^{2+}$  can trigger cannabinoid production (186), subsequent studies have implicated both metabotropic glutamate receptors (mGluR; 95, 461, 462, 658) and NMDA receptors in triggering endocannabinoid production (56). Apparently, multiple pathways for endocannabinoid production and for the triggering of DSI and DSE may coexist in the same neuronal type (462, 658). The mechanism of induction is very important for our understanding of the spatial confinement of DSI and DSE. For example, induction of DSE by cerebellar parallel fiber

(PF) bursts appears to be somewhat synapse-specific due to the local activation of mGluR (95). Coincident activation of PFs and climbing fibers (CFs), on the other hand, provides an associative form of DSE (91) (compare sect. I.L). Furthermore, the spatial pattern of PF activation critically determines cannabinoid signaling, as activation of synapses that are spatially dispersed in the dendritic tree does not appear to provide sufficient glutamate spillover to stimulate metabotropic glutamate receptor (484). Finally, dendritic  $\text{Ca}^{2+}$  spikes in Purkinje cells underlie a local dendritic coincidence detection mechanism that briefly modulates synaptic weight through DSE (620). The regulation of synaptic plasticity through dendritic excitability will be revisited in section III.

The precise roles of DSI and DSE in brain functioning are hard to pin down (128, 225, 394, 842). It has been demonstrated that DSI promotes the induction of LTP (113), perhaps because induction of DSI briefly increases postsynaptic excitability. However, abolishing endocannabinoid signaling in fact promotes epilepsy (498, 533), strongly suggesting that the endocannabinoid signaling system actually serves to protect neurons and circuits from excessive excitation. In agreement, marijuana, which activates the endocannabinoid CB1 receptor, has been known for hundreds of years to possess anticonvulsant properties (20, 601). In addition, it has been demonstrated that the endocannabinoid system is critically involved in the maintenance of oscillatory states that are important for hippocampus-dependent memory (268, 635). That such oscillations and thereby spike timing are impaired by blocking CB1 receptor signaling (635) is perhaps consistent with the finding that CB1 receptor-expressing hippocampal interneurons are specifically activated at different times compared with other interneurons (244). The available evidence thus favors a regulatory role of endocannabinoids in maintaining levels of excitation within reasonable bounds, as well as a role in hippocampal spike timing, oscillations, and memory formation (for detailed reviews, see Refs. 601 and 128). How exactly this is done remains unknown. However, given that CB1 receptor-positive inhibitory interneurons in neocortex (80), in some amygdala nuclei (356), and in hippocampus (13, 357) specifically target and inhibit the perisomatic region, it is tempting to speculate that differential somatic-dendritic inhibitory control plays an important role in maintaining firing patterns, oscillations, and spike timing. In fact, there is direct evidence for specific downregulation of the synaptic gain of perisomatic inhibition by postsynaptic spiking activity in neocortex (778). This type of dynamic balancing of somato-dendritic excitation and inhibition has important implications for the spatial-temporal structure of neuronal activity (244), a topic that will be revisited in section II. Many reviews have been written on DSI, DSE, endocannabinoid signaling, and its role in plas-

ticity; we refer the reader to these for additional information (128, 225, 241, 394, 601, 842).

### G. Does Frequency or Timing Govern Long-Term Synaptic Plasticity?

A critical factor in classical Hebbian plasticity is the frequency at which the inputs are recruited (see sect. 1B). High-frequency stimulation (“tetanization”) leads to LTP, whereas low frequencies yield LTD (713). This frequency dependence appears to be a widespread feature of long-term plasticity (231, 374, 717), although there are as always exceptions to the rule. In striatum, high-frequency stimulation in the presence of a physiological  $Mg^{2+}$  concentration results in LTD *in vitro* (119). It is widely believed that the frequency dependence of LTP and LTD is at least in part due to the degree and time course of postsynaptic NMDA receptor-mediated  $Ca^{2+}$  influx (see sect. 1K). Brief high-frequency stimulation results in strong postsynaptic depolarization and NMDA receptor activation, whereas sustained low-frequency stimulation evokes less NMDA receptor-dependent  $Ca^{2+}$  influx (430, 713).

Apart from the theta-burst protocol of inducing LTP (340, 569, 578, 589), few *in vitro* synaptic plasticity experimental paradigms are based on realistic firing patterns (although see Refs. 101, 118, 231, 626). Importantly, one study directly demonstrates that whereas prolonged stimulation at low frequency and with regularly spaced times intervals robustly evokes neocortical LTD (372–376) (cf. sect. 1C), more realistic and relatively irregular low-frequency firing patterns actually fail to evoke any plasticity (593). Conversely, some have argued that many LTP paradigms are simply pathological, because they involve activity patterns that are completely outside the physiological range of firing frequencies, which renders them not only synapse strengthening but also epilepsy inducing (507). These two points stress the importance of examining the impact of physiologically relevant *in vivo* firing patterns in *in vitro* synaptic plasticity experiments.

Many have emphasized the role of high-frequency bursts in information transfer and in plasticity (102, 380, 434, 598). Rate-dependent induction of cortical plasticity has also served as a starting point for very influential models of learning and development (70, 314, 426–429, 804). For example, Bienenstock, Cooper, and Munro (discussed in sect. 1D) developed a rate-based model of plasticity that could account for the development of orientation tuning and ocular dominance in cat visual cortex (70). Indeed, thalamic relay neurons are known to convey information to the neocortex using both bursts and individual spikes (625), and several studies have found *in vivo* burst firing in visual cortex during presentation of natural visual scenes, especially in developing animals (129, 220, 826).

However, very low firing rates are also often observed during natural *in vivo* conditions (118, 166, 185, 409, 491, 817). In addition, even pairs of action potentials (APs) in individual motor cortical pyramidal neurons can control motor patterns (89), suggesting that high-frequency bursts of many spikes are not necessary to convey physiologically relevant cortical information. In agreement with the view that single spikes convey important information in neocortical circuits, repeated single spike pairings delivered at very low frequencies are also quite efficient at eliciting LTP and LTD under many circumstances, a concept that will be discussed in the next section. It is quite conceivable that such a trickle of spike pairings is of prime importance for memory formation in many neocortical regions (412). Nevertheless, the relative importance of spike timing and burst firing in eliciting synaptic plasticity, in carrying information, in forming memories, and in refining cortical maps has been hotly debated over the years (692–694, 721). Although it would seem likely that the answer depends on which precise brain region is discussed, it remains largely unknown at this point.

### H. STDP: The Role of Timing in Long-Term Synaptic Plasticity

Inherent to the Hebbian postulate is causality and a need for temporal order, because, by definition, synaptic strengthening occurs when cell A is helping cause activity in cell B (see sect. 1A and Fig. 1A), but this also means cell A is firing before cell B. In studies prior to 1990, the timing requirements of long-term plasticity were often not studied or deemphasized. There were some exceptional and very important pioneering studies showing that afferent activation had to be coincident within a hundred milliseconds for LTP to occur (264, 265, 359, 418). Some even found that asynchronous activation of afferent fibers with certain timings led to LTD (418). These results were typically interpreted within the framework of heterosynaptic LTD. Heterosynaptic LTD is defined as depending on high-frequency stimulation and LTP of another pathway, but need not depend on spiking of the postsynaptic neuron (425) (cf. sect. 1C).

Recent results have elaborated on this timing dependence of long-term plasticity by showing that long-term plasticity depends critically on the millisecond timing of pre- and postsynaptic spikes. Typically, if the presynaptic cell fires an AP a few milliseconds before the postsynaptic cell, LTP is produced, whereas the opposite temporal order results in LTD (Fig. 2), a notion termed spike timing-dependent plasticity (STDP) (2). Although STDP was perhaps not predicted in the same explicit manner that Hebb postulated LTP (290) (sect. 1B) or that Stent postulated LTD (732) (sect. 1C), the discovery of such tempo-

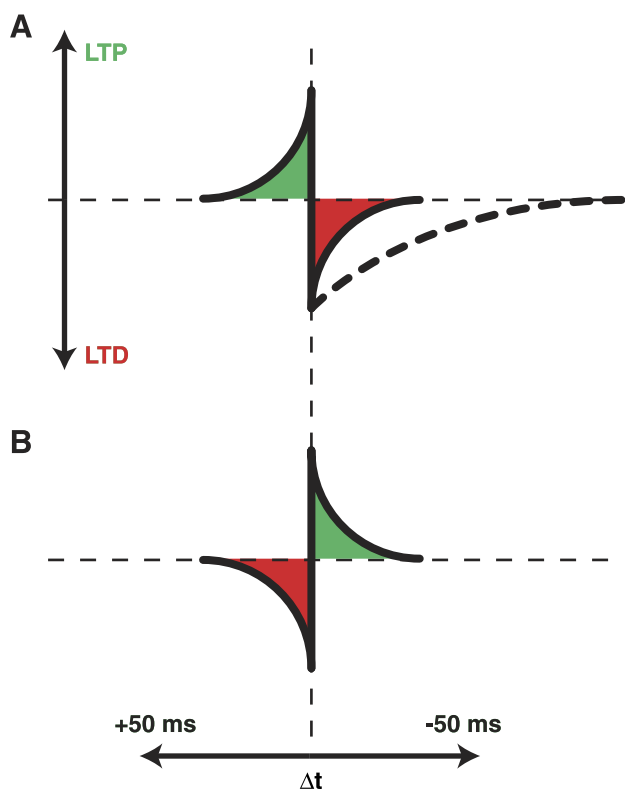


FIG. 2. Multiple forms of STDP exist. *A*: for the canonical form of spike timing-dependent plasticity (STDP) (494), pre-before-post pairings within a narrow timing window result in long-term potentiation (LTP), whereas the opposite temporal order evokes long-term depression (LTD) (2). The dashed line illustrates the fact that the size of the LTD timing window varies with brain region (2) and activity patterns (170, 714, 716). *B*: in some systems (60, 269), the temporal requirements are the exact opposite compared with the canonical type of STDP that is illustrated in *A* (494).

rally asymmetric learning rules was anticipated on theoretical grounds (1, 79, 242, 622, 753). Briefly, the temporal asymmetry found in STDP is useful for learning temporal delays (242) and sequences (1, 79).

STDP has been found in several neocortical layers, such as layer 4 (194), layer 2/3 (L2/3; 61, 208, 229, 230, 553), and layer 5 (L5; 149, 494, 717), as well as in a number of brain regions, including the hippocampus (69, 173), striatum (219), cochlear nucleus (792, 793), entorhinal cortex (881), prefrontal cortex (149), visual cortex (229, 230, 717), sensory cortex (208, 553), and the amygdala (319). Interestingly, STDP appears to exist, albeit in different forms (see below), in species as diverse as the rat (516), the *Xenopus laevis* tadpole (875), the locust *Schistocerca americana* (115), the zebra finch (81), the mormyrid electric fish (59, 60), cat (224, 232, 864), and probably also humans (232, 846, 847, 858, 859). This preservation of STDP over millions of years of evolution suggests that the specific asymmetry of this learning rule is critical for proper nervous system functioning.

If we for a moment disregard the fact that Hebb did not propose synaptic weakening (sect. 1C), then at least the temporal window for synaptic strengthening in STDP is consistent with the Hebbian postulate: LTP is produced when the presynaptic cell helps produce the postsynaptic spike (Fig. 2). Indeed, STDP exhibits several of the hallmark features of LTP (see sect. 1B), such as NMDA receptor dependence (69, 208, 494), cooperativity (717), frequency dependence (231, 717), and intrinsic instability at high frequencies (231, 717, 782). It is worth noting that, as opposed to the heterosynaptic LTD discussed earlier (418), spike timing-dependent LTD does not depend on LTP of a parallel pathway, but does require postsynaptic spiking (although see Refs. 256, 433, 712, 714). Heterosynaptic LTD and spike timing-dependent LTD are strictly speaking different concepts, although their respective mechanisms may of course overlap.

To intuitively understand the functional importance of STDP, it is useful to think of the predictive power of the presynaptic spike; if it precedes and predicts the postsynaptic spike, the synaptic connection is rewarded through strengthening, whereas a “postdiction” results in the punishment of the synapse by its weakening. In other words, a synapse with STDP is not only a coincidence detector but also an extractor of temporal order and of causal connections. Furthermore, STDP may provide important functional features such as synaptic competition (724), predictive coding (622), and the functional development of neural circuits (723). Despite the instability inherent to Hebbian plasticity (791), STDP may actually impart onto synapses a degree of stability (2, 360, 537, 689, 723, 724, 797) (cf. sect. 1D), although this may require that firing rates remain below a critical frequency (231, 717, 782). In addition, stability requires that spike pairings summate roughly linearly and that the temporal window for LTD is larger than that for LTP (724, 797).

Interestingly, the rules of timing-dependent synaptic plasticity vary widely with brain region, cell, and synapse type (2), and many of these differences may ultimately be linked to dendrites, their mechanisms, and their biophysics (230, 256, 413, 664, 666, 712). For example, the width of the LTD timing window is nearly as narrow as the window for LTP in some brain regions (69, 558, 875) but much longer in others (208, 717) (Fig. 2A). There also exist STDP rules that are “inverted” (Fig. 2B): the timing requirements in the cerebellar-like electrosensory lobe of the mormyrid electric fish (59, 60, 269, 666) and at inhibitory connections onto neocortical L2/3 pyramidal neurons (307) are exactly the opposite to the typical STDP described above (Fig. 2A). Perhaps it makes sense from a functional point of view that these inhibitory connections employ a learning rule with opposite temporal requirements compared with excitatory connections. Indeed, a theoretical study of the electrosensory lobe of the weakly electric fish showed that this inverse STDP rule allowed

the storage of negative images of sensory inputs in the Purkinje-like cells (636, 637). On the other hand, similar reversed STDP timing requirements were recently reported at corticostriatal synapses (219), indicating that such noncanonical timing requirements do not necessarily go hand-in-hand with inhibitory neurons. In fact, spiny stellate L4 neurons of rat somatosensory cortex exhibit yet another set of timing-dependent synaptic plasticity rules (194). Within a narrow timing window and over a wide range of frequencies, these neurons produce LTD regardless of the temporal order of presynaptic and postsynaptic firing.

Why do the rules of STDP vary with brain region and neuronal type (2)? It is well established by now that long-term plasticity is involved in the refinement of neural circuits during development (139, 358, 874). This means that the development of neural circuitry depends jointly on the synaptic plasticity rules of the involved neurons and their history of activity. The functionality of a mature circuit thus depends on the plasticity rules that were active during its development. One has to conclude that the fact that STDP varies dramatically from one neuronal type to another is hardly coincidental, but a reflection of the specific functionality of these same neuronal types in the mature brain circuitry. As STDP by definition depends on postsynaptic spiking (although see Refs. 433, 714) and thereby also on AP backpropagation, the different manners by which STDP is controlled by the computations and biophysics of dendrites will be discussed throughout this review, but in particular in section III.

The rules that govern STDP are also quite malleable, even for a given synapse type. For example, STDP depends on frequency (713) in a manner similar to classical LTP/LTD (sect. I G), with depression dominating at low frequencies (208, 231, 717, 792) while potentiation is favored at high frequencies (101, 231, 494, 717). In fact, high-frequency bursting appears pivotal for plasticity at some synapse types under some circumstances (380, 598). The frequency dependence of STDP means that the relative timing of pre- and postsynaptic spikes does not alone determine plasticity (433). In particular, timing-dependent LTP at neocortical L5 synapses requires a threshold postsynaptic depolarization, which can be provided either by high-frequency temporal summation or by low-frequency spatial summation (717). In fact, during postsynaptic hyperpolarization, high-frequency pre- and postsynaptic spike pairings are not sufficient for LTP (712, 717), even though superficially such a firing pattern appears to satisfy the Hebbian postulate (sect. I A), the need for high frequency in classical LTP (sect. I G), as well as the timing requirements of typical STDP (Fig. 2A). Based on this and other observations, Lisman and Spruston (433) questioned the validity and biological relevance of the STDP paradigm. As we shall see in section III B, such gating of

STDP by membrane potential is at least in part due to a specifically dendritic mechanism.

STDP also depends on the details of spike patterns: on a short time scale, LTP-promoting spike pairings override those that favor LTD (101, 494, 717). Moreover, the timing window for LTD dynamically widens with increased postsynaptic activity (170, 714, 716) (Fig. 2A), and it appears that the first spike pairing in spike triplets and quadruplets may cancel out subsequent ones (229, 231), although such spike triplet supralinearities also vary with synapse type (101, 806). Regardless, such cancellation rules may help explain the presence of timing requirements even for high-frequency spike trains found in some systems (81; although see Ref. 231). STDP is also dramatically altered by neuromodulators, acting at, e.g.,  $\beta$ -adrenergic (690; also see Refs. 422, 423) and nicotinic receptors (149). The rules for STDP are thus complicated, variable, and dynamically changing. In addition, the amount of long-term plasticity due to an arbitrary firing pattern is not likely to be predicted quantitatively simply by summing linearly pre-before-post and post-before-pre pairings (229, 231, 717). In fact, it appears that some of these nonlinearities are due to specifically dendritic properties (230, 350, 413, 712). Some of these nonlinearities will be discussed further in section III, B, C, and E.

However, plasticity rules are clearly not exclusively determined by dendrites but also by mechanisms residing in the synapse itself. For example, excitatory inputs of different origin that converge onto neighboring dendritic locations of lateral amygdala projection neurons have different forms of plasticity. Inputs from the thalamus readily undergo typical STDP, whereas cortical afferent synapses do not (315, 319, 321). This difference appears to be largely due to morphological and functional differences of the cortical and thalamic afferent spines (319; although for a different view, see Ref. 704). Interestingly, the corresponding example of differential plasticity at divergent synapses also exists. Connections originating from the same somatosensory cortical L2/3 pyramidal neuronal type have distinct plasticity rules and mechanisms depending on the interneuronal type they target (451; for another example, see Refs. 792, 793). Here, connections onto low-threshold spiking interneurons exhibit NMDA receptor-dependent plasticity and the typically asymmetric STDP, whereas those impinging on fast-spiking interneurons undergo mGluR-dependent LTD with symmetric timing requirements (451).

Finally, it is worth noting that many studies of STDP have been performed *in vitro*, using slices or cultured cells from very young animals. Extrapolating the exact rules that govern STDP from these limited preparations to the *in vivo* situation may thus not always be justified. This caveat obviously holds true for any form of *in vitro* plasticity paradigm, not just for STDP, but also for the classical rate-dependent forms of LTP and LTD (sect. I, B and

C), homeostatic plasticity (sect. 1D), plasticity of intrinsic excitability (sect. 1E), as well as for DSI and DSE (sect. 1F). In the case of STDP, phenomena consistent with an *in vivo* role for STDP have been repeatedly discovered, for example, in rat (24, 118, 330, 516, 678), cat (224, 232, 864), *Xenopus* tadpoles (201, 539, 803, 875, 876), as well as in humans (232, 846, 847, 858, 859). In particular, although the formation of cortical maps during development can be explained by correlation-based learning rules (e.g., Refs. 70, 426, 524, 804), Young et al. (864) recently demonstrated that some aspects of cortical map reorganization after retinal injury can only be explained by STDP but not by a correlation-based learning rule. The results of Young et al. (864) thus go a step further and suggest necessity for, and not just consistency with, STDP *in vivo* (see Refs. 24, 118; also see above and sect. 11B). To conclude, these studies thus strongly argue that temporally asymmetric cellular learning rules such as STDP are active *in vivo* and that they are also oftentimes necessary to explain *in vivo* plasticity phenomena (cf. Refs. 158, 159, 412).

### I. The Spine as a Coincidence Detector in Synaptic Plasticity

Hebbian synaptic modification requires that coincident pre- and postsynaptic activity is somehow detected (290). It is widely accepted that the NMDA receptor can act as such a coincidence detector. At resting hyperpolar-

ized membrane potentials, NMDA receptors open only modestly, even in the presence of glutamate (505, 563). In the presence of sufficiently strong depolarization, however,  $Mg^{2+}$  are expelled from the channel pore, which unblocks the receptor channel and allows for  $Ca^{2+}$  influx (38, 457) (Fig. 3). Postsynaptically located NMDA receptors can thus detect the coincidence of glutamate release due to presynaptic activity and depolarization due to postsynaptic spiking (Fig. 3B). The result is a supralinear rise in postsynaptic  $Ca^{2+}$  concentration compared with either pre- or postsynaptic activity alone. Evidence for this by now canonical view on the NMDA receptor-based spine coincidence detector has been obtained in hippocampus (78, 867, 870) as well as neocortex (384, 673; see Fig. 4). The supralinear  $Ca^{2+}$  signal is read out by downstream molecular machinery (sect. 1J), eventually resulting in the expression of LTP (for a review, see Refs. 455, 477, 479, 713).

In this view, the coincidence detector relevant for synaptic plasticity resides in the synaptic spine (Fig. 4A) (78, 349, 384, 673, 867). This does not exclude the coexistence of presynaptic coincidence detection mechanisms (61, 147, 191, 711, 714, 716), nor does it mean that postsynaptic coincidence detection requires the existence of spines (869, 871) (cf. sect. 11A). Regardless, it is important to note that this view on the spine coincidence detector presupposes that the backpropagating action potential (bAP) reliably makes it to the synapse (Fig. 3). If a syn-

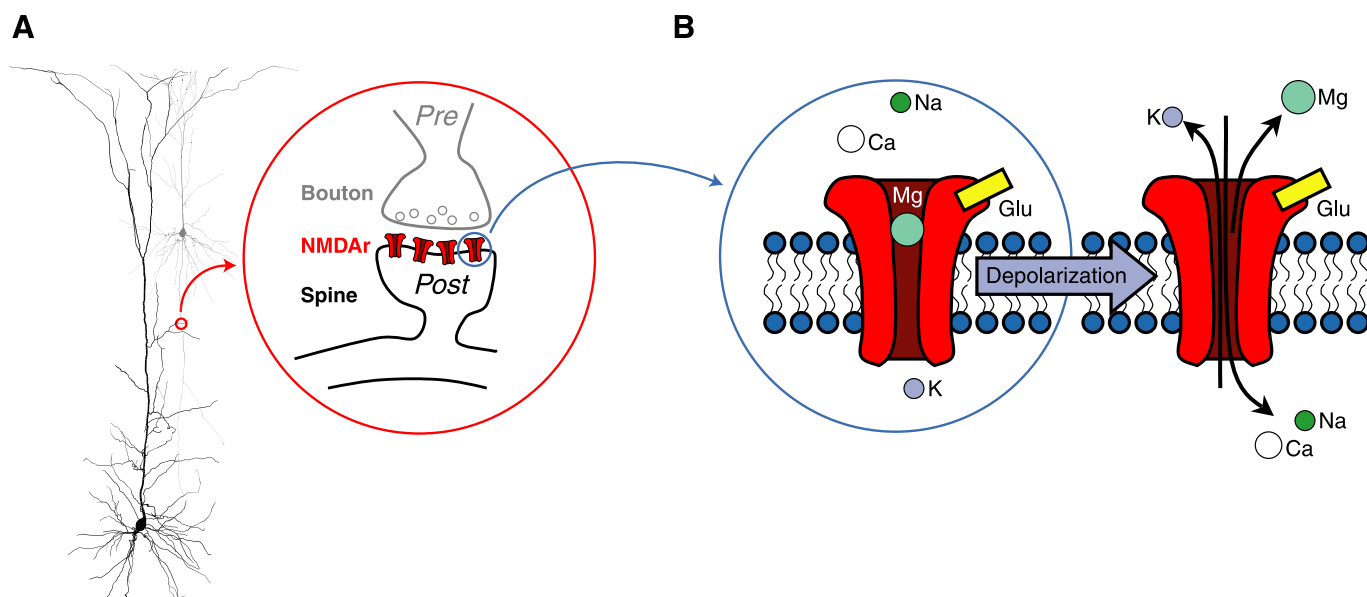


FIG. 3. The canonical spine coincidence detector is based on the NMDA receptor. *A*: in this illustration of a connected pair of neocortical neurons (L2/3 gray, L5 black), the synapse (red circle) is relatively far from the soma, which means that the somatically initiated action potential (AP) will be attenuated considerably before it reaches the NMDA receptors residing in the spine. *B*: a backpropagating action potential (bAP) of insufficient amplitude cannot expel the  $Mg^{2+}$  from the pore of a glutamate-bound NMDA receptor (left). With adequate degree of depolarization, however, the NMDA receptor will be unblocked (right), resulting in ion flux and dramatically increased spine levels of  $Ca^{2+}$ . The reliability of AP backpropagation thus has a critical impact on the induction of synaptic plasticity.

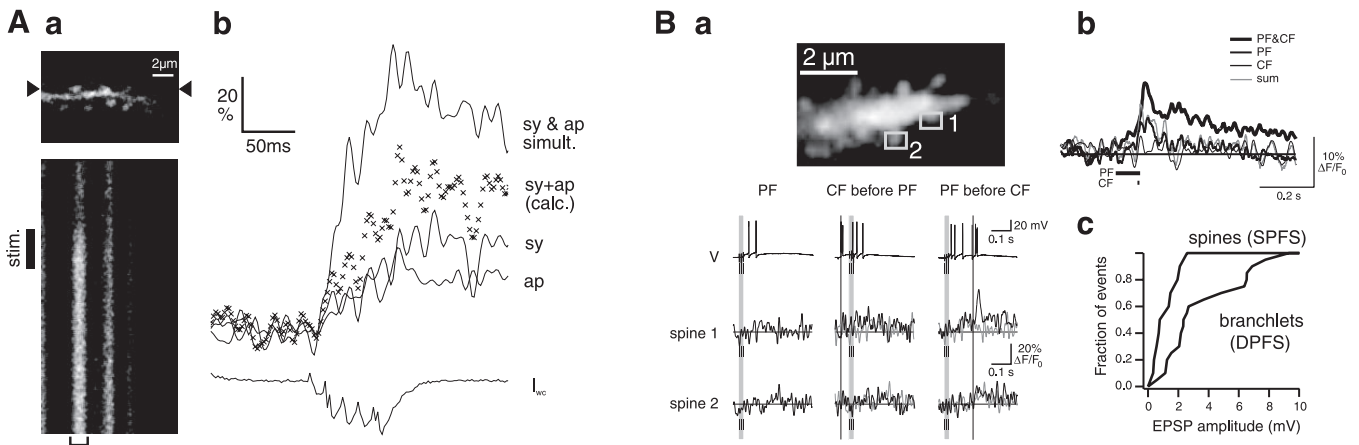


FIG. 4. In multiple brain regions, a spine coincidence detector triggers long-term synaptic plasticity. *A*: in the spines of hippocampal CA1 neurons (*a*), pairing of extracellular stimulation and somatic APs results in supralinear spine Ca<sup>2+</sup> responses (*b*) (867). This form of coincidence detection depends on NMDA receptors. Similar NMDA receptor-dependent supralinearities in spines have been described in neocortical L5 (384, 673) and L2/3 (553) pyramidal cells as well as in L4 spiny stellate cells (552). [From Yuste and Denk (867), with permission from Macmillan Publishers Ltd, copyright 1995.] *B*: in Purkinje cell parallel fiber spines (*a*), coincident activation of VDCCs and mGluRs can under certain circumstances evoke supralinear Ca<sup>2+</sup> responses (*b*) due to synergistic Ca<sup>2+</sup> release from internal stores (808), thus illustrating the fact that not all spine coincidence detectors rely on the NMDA receptor. These spine supralinearities were only restricted to spines during sparse PF stimulation (*c*, “SPFS”), whereas entire dendritic branchlets were engaged by dense PF stimulation (*c*, “DPFS”). [From Wang et al. (808), with permission from Macmillan Publishers Ltd, copyright 2000.]

apse is far enough from the soma, then a somatically initiated AP may fail to reach it and may not provide sufficient depolarization to unblock the spine NMDA receptors (256, 413, 712). In section III, we revisit this point and discuss, e.g., conditions under which bAPs impact synaptic plasticity, as well as conditions under which somatic APs are of little relevance, but local dendritic spikes matter.

One aspect of NMDA receptor activation in STDP that is a bit puzzling is the fact that NMDA receptors have high affinity for glutamate (EC<sub>50</sub> of ~20 μM) (588). It appears, therefore, that NMDA receptors should remain glutamate-bound for several hundred milliseconds (471), which appears inconsistent with the brief ~20-ms-long temporal window for timing-dependent LTP (Fig. 2). Kampa et al. (349), however, found that Mg<sup>2+</sup> actually reduces the NMDA receptor affinity for glutamate dynamically, with decreased glutamate affinity later after glutamate application. This means that a depolarization immediately after glutamate release onto NMDA receptors opens the channel more efficiently than a depolarization later in time (349). Although this facet of NMDA receptor kinetics may help explain the narrow window for timing-dependent LTP, the temporal NMDA receptor activation curve still does not seem brief enough (349; also see Ref. 553). It is therefore quite conceivable that additional dendritic mechanisms, such as AP amplification (747) and inactivation of I<sub>A</sub> (303, 520), play an important role in sharpening the STDP window for potentiation. Mechanisms relevant to this point will also be revisited later in the review (sect. III, *B* and *D*).

Spine coincidence detectors need not rely on NMDA receptors, however (Fig. 4*B*). Mature Purkinje cells, for example, do not have any NMDA receptors (97, 438, 592, 644; although see Ref. 600), yet cerebellar PF LTD depends on the coincident activation of PFs and the CF (326). How do the PF synapses on Purkinje cells detect this coincident activation of PFs and the CF? It is well established that induction of cerebellar PF LTD depends on large dendritic Ca<sup>2+</sup> signals and on Ca<sup>2+</sup> release from intracellular stores (654). In addition, it is known that the PFs trigger mGluR-dependent inositol 1,4,5-trisphosphate (IP<sub>3</sub>) production, which in turn results in Ca<sup>2+</sup> release from IP<sub>3</sub>-sensitive internal stores (216, 765), while CF activation results in Ca<sup>2+</sup> influx through voltage-dependent calcium channels (VDCCs) (530). Since simultaneous elevations of Ca<sup>2+</sup> and IP<sub>3</sub> synergistically activates IP<sub>3</sub> receptor-mediated Ca<sup>2+</sup> release from internal stores (68, 217, 323, 769), IP<sub>3</sub>-sensitive internal stores are ideally suited as coincidence detectors in cerebellar PF LTD. Indeed, Wang et al. (808) demonstrated that, when PF were weakly activated in a physiological manner, spine Ca<sup>2+</sup> signals summated supralinearly when stimulation of PFs and the CF were appropriately timed (Fig. 4*B*). In addition, spine Ca<sup>2+</sup> signals matched closely the outcome of plasticity so that Ca<sup>2+</sup> response supralinearity went hand in hand with PF LTD (cf. Ref. 769). Stronger PF stimulation, however, resulted in large VDCC-mediated Ca<sup>2+</sup> influx in entire dendritic branchlets, thus obviating the need for Ca<sup>2+</sup> release from internal stores (808; also see Ref. 276). Nevertheless, even though the spine coincidence detector of Wang et al. (808) does not depend on

NMDA receptors, the need for depolarization of the spine in coincidence detection remains.

The results of Wang et al. (808) nicely illustrate the existence of multiple pathways to induce the same form of plasticity (713), although it is of course not evident that all pathways found *in vitro* are biologically relevant. The existence of a spine coincidence detector does not suggest that it is the only trigger of plasticity (276), nor does it suggest that other coincidence detectors are not simultaneously required, such as dendritic (sect. III B), presynaptic (61, 147, 191, 716), or downstream coincidence detectors (278, 279, 711).

### J. Postsynaptic Calcium Dynamics and the Sign of Synaptic Plasticity

An important feature of both LTP and LTD induction is that they both depend on elevations in intracellular  $\text{Ca}^{2+}$  concentration, although in different ways. Brief and strong postsynaptic  $\text{Ca}^{2+}$  elevations signal LTP, while smaller, more prolonged  $\text{Ca}^{2+}$  transients induce LTD. Several lines of evidence support this view. First, adding  $\text{Ca}^{2+}$  chelators at sufficiently high concentration to the intracellular milieu of the cell blocks both LTP (131, 270, 453, 478) and LTD (131, 194, 540). Second, photolytic  $\text{Ca}^{2+}$  uncaging (550, 769, 857) and  $\text{Ca}^{2+}$  influx produced by glutamate iontophoresis (148) produce either LTP or LTD depending on the level and time course of the evoked intracellular  $\text{Ca}^{2+}$  transient. Third, electrophysiological protocols that reliably produce LTP also evoke high levels of  $\text{Ca}^{2+}$  (131, 270, 384, 468, 673, 867), whereas LTD induction is associated with low  $\text{Ca}^{2+}$  elevations (131, 270, 384).

The current consensus view, that strong postsynaptic  $\text{Ca}^{2+}$  elevations result in potentiation, whereas small  $\text{Ca}^{2+}$  transients result in depression (430), is to a first approximation consistent with measurements obtained both for classical frequency-dependent LTP/LTD induction protocols and for STDP. Coincidence of EPSPs and APs results in high  $\text{Ca}^{2+}$  influx (384, 468, 673, 867) and LTP (468, 494), just as high-frequency stimulation results in strong  $\text{Ca}^{2+}$  elevation and LTP (131, 270). Although the mechanism behind this consensus view remains unclear, perhaps the properties of calmodulin (177) may help explain how the same messenger,  $\text{Ca}^{2+}$ , can trigger both up- and downregulation of synaptic strength (see sect. II C2). The possible role of spines and dendrites in compartmentalization of  $\text{Ca}^{2+}$ , voltage, as well as other signals will be revisited in section III A, where we shall also find that this consensus view on the role of  $\text{Ca}^{2+}$  transients in determining the sign of plasticity is probably an oversimplification; spatial aspects also matters considerably.

### K. The NMDA Receptor and Other Sources of Calcium

Above, we touched on the NMDA receptor dependence of synaptic plasticity. That NMDA-receptor-mediated  $\text{Ca}^{2+}$  influx is necessary for induction of long-term plasticity does not mean that NMDA receptors are the only source of  $\text{Ca}^{2+}$ . LTD by LFS stimulation (135, 136, 814, 850) as well as timing-dependent LTD (69) have been shown to depend on  $\text{Ca}^{2+}$  influx through VDCCs. Similarly, LTP by either classical tetanization (256, 262, 324) or an STDP-style protocol (468) rely at least in part on VDCC-mediated  $\text{Ca}^{2+}$  influx.

As discussed in sect. I above,  $\text{Ca}^{2+}$  release from internal stores has a well-established role in cerebellar LTD (641, 654). Here,  $\text{Ca}^{2+}$  responses to trains of PF stimulation are mediated by an early influx through VDCCs, and by a later mGluR-dependent  $\text{Ca}^{2+}$  release from  $\text{IP}_3$ -sensitive stores (216, 765). CF stimulation at the end of trains of such PF stimulation produces supralinear spine  $\text{Ca}^{2+}$  responses that depend on mGluRs and internal  $\text{Ca}^{2+}$  stores (808). Strong spine  $\text{Ca}^{2+}$  signals lead to LTD induction (809). Importantly,  $\text{Ca}^{2+}$  responses are only dependent on  $\text{Ca}^{2+}$  release from internal stores with weak, sparse PF stimulation, which is probably the physiologically relevant case; with stronger, denser stimulation, VDCCs produced  $\text{Ca}^{2+}$  signals in whole branchlets, obviating the need for calcium release from internal stores (808) (also see sects. I and III A3).

A role for  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release (CICR) from internal stores in hippocampal long-term plasticity remains controversial (641, 654, 757). Internal stores in spines of CA1 pyramidal neurons are devoid of  $\text{IP}_3$  receptors, but instead contain ryanodine receptors (RyR). Dendritic shafts, on the other hand, contain both receptor types (641, 654). The function of CICR in long-term plasticity is therefore likely to be different in CA1 pyramidal neurons and cerebellar Purkinje cells, and the exact role of the CA1 pyramidal spine RyR remains unclear. Whereas some have found CICR from CA1 pyramidal internal stores due to NMDA receptor-mediated  $\text{Ca}^{2+}$  influx (197), others have not (390, 471). Perhaps these differences boil down to the infamous variability of the slice preparation. Nishiyama et al. (558) found that CICR from hippocampal CA1 internal stores are involved in long-term plasticity. Here, spine RyRs appear to be critically involved in homosynaptic LTP, whereas  $\text{IP}_3$  receptors seem to control heterosynaptic LTD (cf. sect. III A3). Raymond and Redman (623), on the other hand, found that internal stores are necessary for LTP of intermediate duration, but not for short- or long-lasting LTP. Consequently, perhaps the controversy can be partially explained by the differential involvement of internal stores in LTP of different durations.

## L. Cooperativity and Associativity

The Hebbian postulate states that the presynaptic cell takes part in firing the postsynaptic cell (Fig. 1A), which implies that the presynaptic neuron cooperates with other inputs to evoke postsynaptic spiking and synaptic strengthening. McNaughton et al. (509) found the first experimental evidence for such a phenomenon in LTP. They demonstrated that high-frequency stimulation of a weak pathway produced LTP only if in synchrony with a stronger pathway, a notion they termed cooperativity (509). Cooperativity has been hypothesized to underlie associative learning (627), since an ineffective stimulus can become suprathreshold for plasticity if paired repeatedly with a strong suprathreshold stimulus, and in the end even drive a neuron in the absence of the strong stimulus. In a very simplified view, the weak pathway would correspond to the conditioned stimulus and the strong pathway to the unconditioned stimulus in classical Pavlovian conditioning (627), although most would agree that this is much too simplistic a model of associative learning.

In addition to being cooperative (509), LTP is classically also associative. In the LTP literature, researchers often try to make a distinction between the associativity and the cooperativity of LTP (for a detailed background, see Ref. 344), a distinction that may appear subtle. Associativity is typically taken to denote the need for simultaneous activation of a strong and a weak pathway using two extracellular electrodes to evoke LTP of both pathways; without this temporal contiguity, the strong but not the weak pathway potentiates. Cooperativity, however, signifies the need for a sufficient number of afferent fibers to be recruited by one extracellular electrode to reach the threshold for LTP (51, 171, 372, 417, 471, 872). Given that for a weak pathway the threshold for LTP can be reached either by increased stimulation via the same extracellular electrode, or by activating a strong pathway via another electrode, it may seem pedantic to try to distinguish cooperativity from associativity. However, as we shall in section III, B and D, the fact that two distinct pathways are required for associativity adds a spatial aspect; these two pathways need not impinge at the same location of the dendritic arbor (256, 712).

Although the subtle distinction between the associativity and the cooperativity of LTP can be justified for the above reasons, these two terms are not used consistently in the literature. To begin with, McNaughton et al. (509) used the term cooperativity to denote both concepts in their original report. In addition, some reports simply use the concept of associativity to denote synaptic plasticity paradigms that depend on the repeated pairing of pre- and postsynaptic activity (e.g., Refs. 170, 562, 690, 726). When postsynaptic APs are evoked by current injection (170, 562, 690, 726), this definition of associativity is overly restrictive as it makes STDP associative by default. It

does, for example, not leave room for subtleties such as the need for cooperation among inputs that exists even for STDP (712, 717; see below and sect. III B), a form of cooperativity that might underlie associative learning, clearly a nonsensical notion if STDP were considered associative by definition. In addition, such a definition of associativity would also make cooperative forms of synaptic plasticity that do not require somatic spiking nonassociative (256) (see sect. III D), again a nonsensical notion.

Because of the confusion and because of the lack of consistent use in the field, we avoid employing the term associativity in this review, except to denote associative behavioral learning (627). As outlined above, the concept of associativity in LTP is nevertheless very important for historical reasons. In the end, both the cooperativity and the associativity of LTP probably refer to the same underlying plasticity phenomena. We use in this review the notion of cooperativity as a blanket term to cover any LTP phenomenon with cooperative characteristics (712, 713, 717).

What is the mechanism that underlies cooperativity? Some have hypothesized (73, 143, 471, 833) that cooperativity is needed because weak inputs do not depolarize NMDA receptors sufficiently (sect. I K and Fig. 3) so that the  $\text{Ca}^{2+}$  threshold for LTP is not reached (sect. I J). This hypothesis predicts that NMDA receptor-independent forms of LTP may not necessarily exhibit cooperativity. One example of NMDA receptor-independent LTP exists at mossy fiber inputs onto hippocampal CA3 neurons (343, 556). Indeed, mossy fiber LTP does not appear to exhibit cooperativity (872; although see Ref. 676), lending some support to this view. However, hippocampal CA1 LTP does not only depend on NMDA receptor activation, but also on  $\text{Ca}^{2+}$  influx through VDCCs (256, 262, 324, 468). In fact, it has been demonstrated that NMDA receptor-dependent and -independent forms of hippocampal LTP can be dissociated (256, 262, 468), indicating that cooperativity cannot be due to NMDA receptors only.

In a different view on cooperativity, some have argued that the need for postsynaptic somatic spiking provides a mechanistic explanation, as synaptic activation that is suprathreshold for somatic APs would ensure that NMDA receptors are unblocked, but subthreshold synaptic inputs would not (171). In support of this view, blocking backpropagation of somatic APs in hippocampal CA1 neurons using the selective  $\text{Na}^+$  channel antagonist TTX abolishes LTP (468). However, it has also been demonstrated that postsynaptic APs per se are not required for hippocampal LTP (264, 265, 359, 509). It may be that any form of depolarization is sufficient for LTP. In fact, LTP of weak synaptic inputs by pairing with strong continuous postsynaptic depolarization to  $\sim 0$  mV does not exhibit cooperativity (Sjöström and Nelson, unpublished data) (481, 483). With this unbiological plasticity paradigm, the



voltage-clamp amplifier provides the necessary depolarization even in the absence of postsynaptic spiking and thus overrides the physiological mechanism of cooperativity.

In section III, we will take a “dendritic view” on cooperativity. As will be discussed in section III D, Golding et al. (256) discovered a mechanism for the cooperativity of hippocampal LTP that depends on local dendritic spikes. Recently, we revealed a different dendritic cooperativity mechanism that explains the threshold for potentiation that exists in neocortical L5 STDP (717). Our mechanism (712), which is due to the need for dendritic depolarization to boost bAPs that otherwise fail as they invade the dendritic tree, will be discussed in section III B. To conclude, cooperativity may be due to diverse mechanisms that depend on brain region, neuronal type, and synapse location in the dendritic tree. Regardless of whether cooperativity relies on bAPs, local dendritic spikes or otherwise, the need for postsynaptic depolarization remains a common thread in most studies (cf. 471).

## II. REGULATION OF ELECTRICAL PROPERTIES OF DENDRITES

Most of the synaptic input to a neuron arrives on its dendrites. Here, inputs may passively and rather linearly evoke voltage deflections. Alternatively, nonlinear responses may ensue as voltage-dependent active mechanisms are recruited by the synaptic activation. Thus both the passive and active electrical properties of the dendrites critically determine the effect of any given input on the spike output, since they both impact the local integration as well as the forward propagation of synaptically evoked responses. Passive and active properties also play a key role in influencing synaptic plasticity, as they define the electrical and chemical signals experienced by each synapse, and also determine the interplay between synapses. Finally, because both the passive and active properties of the dendritic tree can be modulated, dendritic electrical properties offer a rich palette of mechanisms for regulating plasticity. In this section, we review some key aspects of dendritic excitability related to the induction and maintenance of synaptic modification.

### A. The Input-Output Relationship of Single Neurons and Neuronal Computation

Dendritic excitability plays a crucial role in determining both the processing and storage capacities of single neurons. Both the time course and spatial spread of synaptic input is determined by the passive cable properties of the dendrite (331) (sect. II B3) together with the distribution (sect. II B4) and functional state (sect. II, C1 and C2) of voltage-gated channels. Regenerative activity in the

dendrites, such as backpropagation of APs (sect. II B1) or local dendritic spikes (sect. II B2), is regulated by dendritic excitability. In some cases, the intrinsic excitability of dendrites may be more important in determining output spike patterns than the synaptic input (291).

Several diseases affecting the central nervous system stem from pathological disturbances of ion channel function (for review, see Ref. 395). Although many of these ion channels are also expressed in dendrites, only a few studies have addressed the involvement of dendritic excitability in neuronal diseases (851). The functional downregulation of A-type  $K^+$  channels in hippocampal CA1 neuron dendrites in the pilocarpine epilepsy model (66) and the increase in dendritic excitability of entorhinal cortex neurons in the latent period leading to epilepsy (695) are key examples illustrating the importance of disease-associated modifications of dendritic excitability. A recent study also implicates T-type  $Ca^{2+}$  channels of CA1 neuron apical dendrites in pilocarpine-induced chronic epilepsy, during which this channel type contributes to abnormal burst firing (856).

Both the passive and active properties of neurons can vary widely, giving rise to a plethora of different possible input-output (I/O) functions. One way of characterizing the I/O function of a neuron is to record the frequency of somatic APs (the output) in response to injected current (or conductance) input. The result is called a frequency-current ( $f/I$ ) curve. Typical  $f/I$  curves obtained with current injection in the form of square pulses, steps, or ramps show a threshold below which no APs are generated, and a linear or sublinear increase in AP frequency above that threshold. The exact shape of the  $f/I$  curve, e.g., whether it is continuous (type I) or discontinuous (type II) at threshold, depends on the intrinsic properties of a given cell type (144, 770). The interactions between different intrinsic mechanisms shaping the  $f/I$  curve can be complex. For example, intrinsic currents providing slow negative feedback can both linearize an originally highly nonlinear  $f/I$  curve (202) and transform an originally linear  $f/I$  curve into a nonlinear, logarithmic one (198). The  $f/I$  curve can also be modulated by background synaptic activity. Changes in the statistics of noisy synaptic inputs and changes in the ratio of excitation to inhibition can change the slope of the  $f/I$  curve and thus the gain of the neuron (120, 528, 611). Using two-photon calcium imaging of bulk-labeled tissue, Kerr et al. (363) recently measured the I/O functions of single neurons in the functioning cortical network in vivo, with input statistics generated by ongoing activity in the network itself, and found a threshold-linear relationship similar to those obtained using current injection and widely used in current neural network models. Measuring and understanding the I/O functions of neurons in the presence of network activity in awake animals will be an important goal for future experimental and theoretical studies.

The I/O functions have boundaries, such as the limits of AP initiation and propagation (138, 364, 534, 613), and are influenced by the morphology of the cell and the dendritic distribution and functional state of voltage- and  $\text{Ca}^{2+}$ -dependent conductances in several ways. First, the dendrites constitute a large passive load that raises AP threshold and effectively shifts the  $f/I$  curve to the right, as larger input currents are required to generate a given output frequency (58). Second, dendritic inputs can be boosted by voltage-dependent  $\text{Na}^+$  and  $\text{Ca}^{2+}$  channels leading to increased somatic firing frequency (33, 580, 581), and the gain of the I/O function for somatic inputs can be altered by input to the dendrites that activates dendritic voltage-gated  $\text{Ca}^{2+}$  channels (402). Third, while these mechanisms rely on dendritically initiated spikes or amplification of synaptic inputs, voltage- and state-dependent modulation of active backpropagation of the AP to the dendrites can also change the gain of the neuron via changes in the depolarizing afterpotential generated by each AP at the soma (512). Finally, in addition to changing the mean firing rate, regenerative electrical activity in dendrites can modify the temporal structure of firing patterns of cortical pyramidal neurons in vitro (405) and in vivo (155, 404, 756). These changes of the shape of the  $f/I$  curve, as well as the switch in the output firing pattern of pyramidal neurons in response to appropriately timed proximal and distal synaptic input (405), can be viewed as computations performed by the neuron. In fact, shifts of the  $f/I$  curve can be interpreted as additions or subtractions, changes of its slope constitute multiplications or divisions, and changes in the firing pattern in response to coincident distal and proximal inputs can be viewed as a logical AND operational (296). Taking this view to the level of single dendritic branches, Bartlett Mel (514) proposed a two-layer “neural network” model for the I/O function of pyramidal neurons (514). In the first layer of this model, independent subunits represented by individual dendritic branches sum their synaptic inputs before applying a nonlinear thresholding operation, which could be implemented by a local dendritic spiking mechanism (see sect. 1B2). The outputs of the first layer are in turn summed approximately linearly before the I/O function of the second layer is applied at the soma (284, 514). This abstract two-layer model has been verified to predict the output firing rate of a detailed compartmental model of a hippocampal CA1 pyramidal neuron in response to different patterns of synaptic inputs to a high degree of accuracy (604). The two-layer model provides a larger storage capacity (given the same number of synaptic weights) than a model in which all synaptic inputs are summed linearly (605). Thus, together with synaptic properties and connectivity, the I/O functions of the individual neurons determine which computations a given network can perform.

For example, particular forms of I/O functions of neurons have recently been used in a rather ingenious way in a simple network model of working memory and decision-making (458). In a network of two neurons which mutually inhibit each other, the output of the first is subtracted from constant excitatory input to the second neuron, which then applies its I/O function to generate an output that will in turn form the inhibitory input to the first neuron, which then applies its own I/O function and so on. If the form of the I/O functions of both neurons has a particular symmetry, the symmetry of the circuit causes the reverberating activity to stabilize at a large number of fixed points forming a “line attractor” (691). Each of these fixed points is characterized by its particular ratio of firing frequencies of the two neurons. Machens et al. (458) suggest that this ratio can serve as a “register” into which the network can load and store the value of a continuous variable associated with a stimulus, and later compare it with a different value associated with a second stimulus.

A useful way of adding a temporal dimension to the I/O function of a neuron is to examine firing phase. In neurons which fire periodically, a small synaptic input can delay or advance the phase of the next spike depending on the time within the cycle of firing at which the input occurs. If an excitatory input comes very late, i.e., when the neuron is going to fire anyway, then it can shift the time of the next spike only by a small amount. Conversely, if the synaptic input arrives right after a spike, its effect is also small because it is masked by the intrinsic conductances associated with the generation of the spike and the reset of the membrane potential (283). If the input arrives near the middle of the interval between two spikes, however, it can significantly affect the timing of the next spike. This dependence of the shift in the output phase as a function of the input phase is called a phase-resetting curve (PRC) (for review, see Ref. 327), which characterizes the response of the neuron to transient inputs (267). PRCs are linked to the bifurcation type (741) underlying the onset of repetitive firing (203, 771) and can predict the conditions under which coupled neurons in a network can synchronize. However, the influence of dendritic mechanisms on the exact shape of the PRC and synchrony in neuronal populations is only beginning to be understood (594). Combining the exploration of the temporal dimension of I/O functions and their spatial dimension, the dependence on the dendritic location of synaptic inputs will be a fruitful avenue for future research (146).

Most neurons transform a large number of synaptic input signals into a single output signal, encoded as a train of action potentials that are transmitted via the axon to downstream synaptic targets. However, the dendrites of some types of neurons act as a network that transforms multiple inputs into multiple output signals. Individual dendritic branches of starburst amacrine cells in the retina, for example, contain both input and output synapses

and can compute direction-selective signals that are transferred to downstream neurons via dendritic transmitter release (205, 206, 281). Multiple outputs from a single neuron can also be communicated by electrical synapses. The dendritic trees of two types of interneurons in the fly visual system, which are topographically connected by gap junctions, create a circuit that performs a spatial low-pass filter operation on the retinotopic input signal (157). These examples, as well as the two-layer model discussed above, indicate that the I/O functions of single neurons represent computations performed due to the interaction of different functional compartments.

## B. Generation of Functional Dendritic Compartments

What are the functional compartments of a neuron? The complex treelike architecture of the dendrites can provide the anatomical substrate for multiple interconnected signal processing units. The first requirement for the generation of multiple functional compartments within a single dendritic tree is sufficient electrical segregation, which is determined by its passive electrotonic properties. Second, mechanisms for nonlinear interactions between neighboring synapses are required, which are provided by voltage-dependent conductances. A third prerequisite is a means for efficient and modifiable communication and interaction between different compartments. The stage on which such interactions between functional compartments are played out is the dendritic morphology of the neuron. It partly determines the size, number, and spatial arrangement of functional compartments. Here, we briefly discuss the mechanisms that underlie dendritic compartmentalization; these are well known and have been described in detail elsewhere (see, e.g., Ref. 687). We also examine fast signaling between compartments, via back- and forward-propagating APs as well as via more local interactions, such as local dendritic spikes.

### 1. Backpropagating action potentials

Propagation of electrical signals between functional compartments is described by the cable equation (381, 687). This mathematical model approximates the flow of electric current and accompanying voltage along dendrites (see sect. II B3) as well as axons by treating them as cylinders composed of segments endowed with electrical capacitances and resistances. In the simplest case, voltage deflections progressively decay, and transient signals are smeared out as they spread along a passive cable (e.g., Ref. 616), due to the filtering that is imposed by the cable itself. However, dendrites typically express many types of voltage-gated ion channels (442, 464, 521), which may actively boost electrical events. In the case of the axon,

for example, it has been known for decades that an AP propagates actively (300). This means that to a first approximation the AP appears rather stereotyped as it propagates along the axon (e.g., Refs. 682, 743), since the AP is continuously maintained by voltage-gated ion channels (although recent research has emphasized axonal AP variability and modulation, see Refs. 22, 54, 169, 364, 386, 534, 707). The degree to which APs backpropagate reliably into the dendritic arbor, however, was not examined quantitatively until relatively recently. Stuart and Sakmann (748) reported that in neocortical L5 neurons, somatic APs backpropagate into the apical dendrite, with their amplitude boosted by activation of dendritic voltage-gated sodium channels. When dendritic Na<sup>+</sup> channels were blocked, backpropagation was dramatically reduced, demonstrating that dendritic AP backpropagation is at least in part an active process maintained by activation of voltage-gated Na<sup>+</sup> channels. In striking contrast, in the highly branched dendritic tree of Purkinje cells, Stuart and Häusser (742) showed that the AP is reduced by 50% in as little as 50 μm, and backpropagation is essentially passive. This failure of active backpropagation is due primarily to the extensive dendritic branching (802) and low dendritic voltage-dependent Na<sup>+</sup> channel density in Purkinje cells (742; cf. sect. II, B3 and C). Subsequent studies examined dendritic AP backpropagation in other cell types (71, 124, 288, 682, 728) and under other conditions (64, 405, 406, 882), revealing that the remarkable diversity of neuronal types is paralleled by a similar range in the reliability of AP backpropagation (254, 682, 745, 820) (Fig. 5). For example, in substantia nigra dopaminergic neurons, APs backpropagate into the primary axon-bearing dendrites with virtually no attenuation (240, 288), although backpropagation into the contralateral dendrite is not always reliable (240). Between the two extremes of the substantia nigra dopaminergic neurons and the cerebellar Purkinje cells, there exists a range of efficacies of AP backpropagation. Pyramidal cells from neocortical L5 (748), L2/3 (819), the hippocampal CA1 pyramidal neurons (254) and interneurons (288, 500) as well as spinal neurons (401) all show intermediate degrees of attenuation along the main dendrite.

Most of these early studies on AP backpropagation were carried out on the larger, primary dendrites, such as the apical dendrites of L5 pyramidal neurons. Do the thin and more finely branched dendrites, which often comprise a substantial fraction of the surface area of neurons, backpropagate APs as well as the typical apical dendrite? This has been a difficult question to address given that recordings from such dendrites are considerably more challenging (162). Mitral cells (Fig. 5), whose apical dendrite supports nondecremental backpropagation (71, 124), have relatively thin lateral dendrites that typically show marked attenuation (137, 492, 820; but see Ref. 853). Direct electrophysiological recordings from the thin

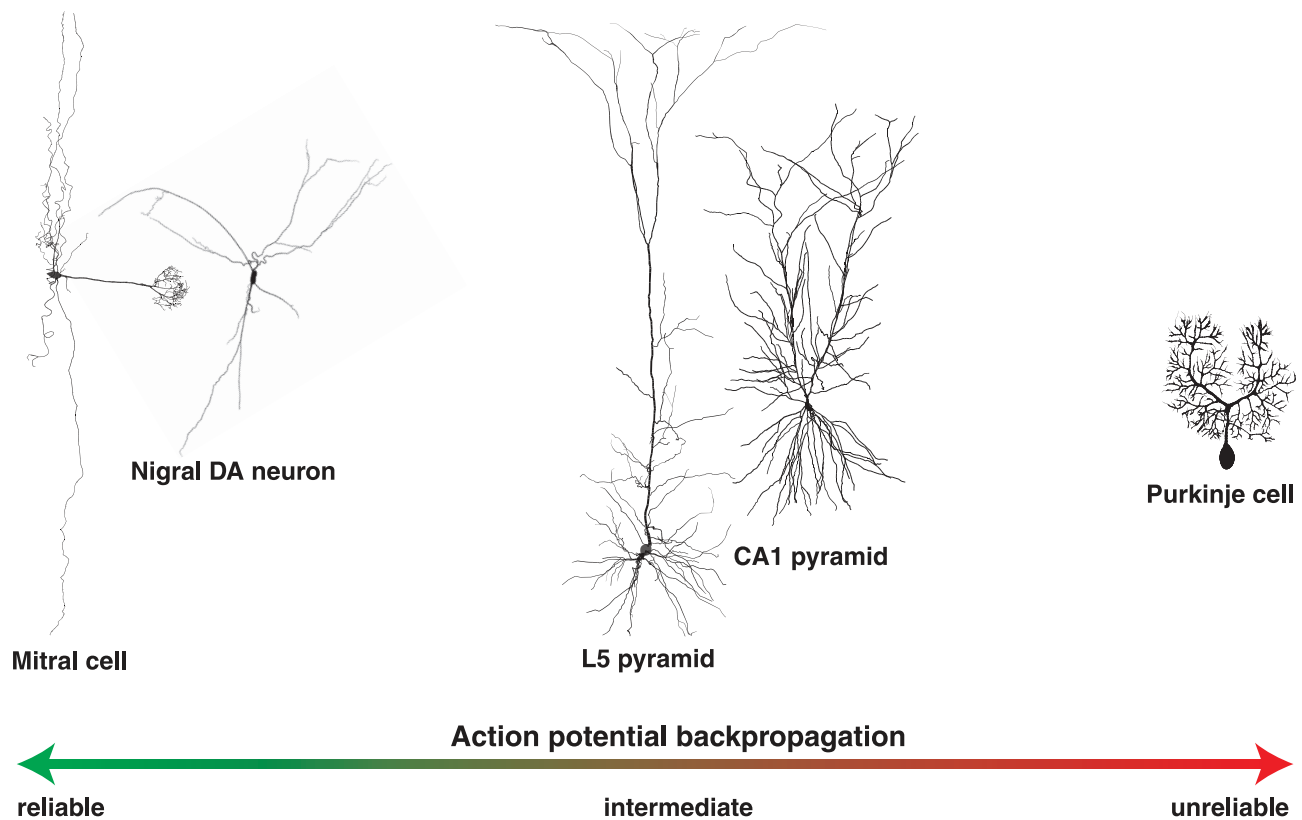


FIG. 5. The reliability of AP backpropagation spans a wide range in different cell types. In mitral cell apical dendrites (71, 124) as well as in the axon-bearing dendrite of substantia nigra dopaminergic neurons (*left*) (240, 288), APs backpropagate at nearly full amplitude. At the other end of the range are cerebellar Purkinje cells (*right*), whose dendrites do not support propagation well (442, 742). The apical dendrites of neocortical L5 (406, 747, 748) and hippocampal CA1 pyramidal neurons (254, 303, 728) actively support AP backpropagation (*middle*), although bAPs are known to fail in the distal dendrites depending on various factors such as animal age, activity patterns, and neuromodulation. Note that the lateral dendrites of mitral cells do not typically support reliable AP backpropagation (137, 492, 820), even though the apical dendrites do (71, 124).

oblique and basal dendrites of neocortical pyramidal cells have not been possible until recently, although optical methods using voltage-sensitive dyes have been used to measure spikes (28, 32, 564, 583). Using simultaneous two-photon and infrared scanning gradient contrast microscopy (844) to provide visual guidance, Nevian et al. (551) recently demonstrated that whole-cell recordings from the thin basal dendrites of L5 pyramidal neurons are possible. They found that AP backpropagation in basal dendrites was decremental and, surprisingly, mirrored that in the apical dendrite; when taking into account the differences in length and caliber, a single, relatively short and thin basal dendritic branch exhibited attenuation comparable to that of the considerably longer and thicker apical dendrite (551). Imaging of AP-evoked  $\text{Ca}^{2+}$  signals also indicates that backpropagation occurs into the thin dendrites of neocortical interneurons (251). Dendritic backpropagation of somatically initiated APs is thus a well-established feature of both primary and secondary dendrites in many neuronal types, though it exhibits considerable diversity. This diversity is due to differences in the geometry of the dendritic tree (802; sect. II B3), in

concert with the complement of voltage-gated channels expressed in dendrites (sect. II C).

Backpropagation depends critically on the location and the availability of different ionic conductances (67). Dendritic voltage-gated  $\text{Na}^+$  channels are primarily responsible for active backpropagation in all cell types studied thus far (745). The differential somato-dendritic distribution of these channels is in good (though not perfect) agreement with the varying extent of backpropagation in different neuronal types (521, 745), with some of the discrepancies attributable to additional differences in dendritic geometry (802). The activation and deactivation kinetics of  $\text{Na}^+$  channels, which are modulated by different subunit distributions and intracellular second messengers such as protein kinase C (PKC) (140), can thus profoundly change the efficacy of backpropagation. VDCC are also activated by bAPs (470), though they generally do not significantly boost the peak amplitude of the bAP.  $\text{K}^+$  channels are also critical in determining the spread of bAPs. Transient A-type  $\text{K}^+$  channels have been shown to be present in dendrites of CA1 and neocortical pyramidal cells (57, 303, 389). In cerebellar Purkinje cells,

they not only enhance the already strong attenuation of bAPs, but also play an important role in regulating the functionally homologous dendritic CF response (501). Repetitive somatic AP backpropagation into the dendrites can produce a build-up of inactivation of dendritic  $\text{Na}^+$  channels (141, 345) resulting in increased attenuation of bAP trains in CA1 pyramidal neurons. However, increasing frequencies not only recruit  $\text{K}^+$  channels, but because of the broadening of bAPs (due to dendritic filtering) can also result in summation of backpropagating APs in distal dendrites, leading to supralinear events mediated primarily by VDCC (400, 405). AP backpropagation is also sensitive to the local dendritic resting potential: more depolarized membrane potentials enhance backpropagation (254, 406, 468, 747, 818), while hyperpolarization or synaptic inhibition can reduce it (785). The somatic AP waveform, naturally, also influences the bAP (254), and depending on slight differences in  $\text{Na}^+$  and A-type  $\text{K}^+$  channel distributions and their kinetics, relatively strong or weak backpropagation can be present in subsets of hippocampal CA1 pyramidal cells (254). However, the way in which the interplay of different channel types contributes to regulating backpropagation is profoundly affected by the morphology of the dendritic tree (sect. *II B 3*), even down to quite subtle differences in dendritic diameter and branching patterns among individual pyramidal neurons (254, 667, 802).

An important question is the extent of AP backpropagation *in vivo*. Continuous synaptic barrage as well as  $\gamma$ -aminobutyric acid (GABA)-mediated inhibition has been shown to reduce AP backpropagation (735, 785). Initial studies concluded that in L2/3 pyramidal cells there is a smaller degree of backpropagation *in vivo* than *in vitro* (755, 756). Using combined patch-clamp and optical methods both *in vivo* and *in vitro*, Waters and colleagues (818, 819) subsequently showed more robust backpropagation in L2/3 pyramidal cells *in vivo*, as had been shown previously in L5 pyramidal cells (294) and CA1 pyramidal cells (348). Using less direct extracellular recording methods, other studies have also provided evidence for robust backpropagation in pyramidal cell dendrites in awake animals (62, 103).

What is the function of bAPs? The most obvious role is to signal axonal output back to the synapses located in the dendrites, enabling the association between synaptic input and the role this input played in firing the cell. Since the depolarization provided by the bAP can relieve the  $\text{Mg}^{2+}$  block of NMDA channels, STDP partly emerges through this association due to the action of the spine coincidence detector (Fig. 3). As a corollary, the distance-dependent attenuation of backpropagation in neocortical pyramidal cells should enable different synaptic plasticity rules for different dendritic locations (sect. *III E*) (230, 413, 664, 712). Given that the backpropagation of APs also depends on frequency and depolarization, bAPs can signal

to the synapse more graded and diverse aspects of somatic spike output rather than to simply inform the synapse that an AP was fired. Since sufficiently strong depolarization can boost and even rescue failing bAPs (712, 747, 835), the amplitude of bAPs may carry contextual information to distal synapses. Similarly, there is either more marked bAP attenuation (728, 835) or  $\text{Ca}^{2+}$ -spike-mediated boosting (64, 400) depending on frequency. The coincidence of strong distal synaptic input with bAPs has been shown to change the output spike pattern of pyramidal cells through a “ping-pong” interaction between the soma and dendrites (405). In this case, the bAP helps the synaptic depolarization to reach threshold for dendritic calcium spikes, resulting in a brief burst of high-frequency axonal AP output (Fig. 9). To conclude, the functional role of the bAP is to transmit information into the dendrites to impact synaptic plasticity, dendritic integration, and ultimately axonal spike output.

## 2. Local dendritic spikes

As we have discussed, the dendritic membrane abounds with different voltage-gated ion channel types. As many of these ion channels open upon depolarization and in turn cause more depolarization, they provide a positive-feedback mechanism to increase the membrane potential in a regenerative manner. With sufficient depolarization, dendritic spikes are triggered, resulting in a nonlinear I/O relationship of the dendritic region where they are initiated (Fig. 10). Dendritic spikes were first observed in cerebellar Purkinje cells (440, 442) and in hippocampal pyramidal cells (848) and have since been observed in many other cell types, such as olfactory bulb mitral cells (124) as well as hippocampal (500) and cortical interneurons (251). In Purkinje cells, whose dendrites lack voltage-gated  $\text{Na}^+$  channels (742), VDCC generate dendritic spikes (442, 620). In hippocampal pyramidal cells, dendritic spikes are produced by  $\text{Na}^+$  (255) and  $\text{Ca}^{2+}$  (253) conductances in concert (together with activation of the highly nonlinear NMDA currents; see below). In neocortical pyramidal cells there seems to be a location dependence in the conductances underlying dendritic spikes. Proximal dendrites are more prone to  $\text{Na}^+$  channel-mediated dendritic spikes (403, 551, 745) (Fig. 10C), while VDCCs contribute relatively more to distal dendritic spikes (400, 405, 674). A special case is the ligand- and voltage-gated NMDA receptor, which in addition to being a key candidate for a spine coincidence detector can also produce local dendritic spikes in the basal dendrites of pyramidal cells (551, 671) (Fig. 10B) and in multi-tufted accessory olfactory bulb mitral cells (795).

The threshold of dendritic spikes is set by the density and activation properties of the local ion channels and the excitability of the dendrite (237). Branch-specific, local modulation of excitability (228, 475) may thus make some

parts of the dendritic tree more prone to dendritic spikes. This could lead to unbalanced dendritic trees (249), but could also allow the mapping of temporarily contiguous memory traces onto dendritic branches (513).

By definition for a local dendritic spike, the depolarization produced by the regenerative activity remains confined. To some degree, this confinement is dependent on the passive electrotonic structure of the dendritic tree, governed in part by the local dendritic morphology (802). However, active processes, in particular the many types of voltage-gated  $K^+$  conductances, have also been shown to play a role in determining the spatiotemporal extent of dendritic spikes (204, 239, 253, 366).  $K^+$  conductances activated by intracellular  $Ca^{2+}$  entering through VDCCs can also have an important limiting role by setting the spatial and temporal extent of regenerative dendritic activity (105, 253, 620). Although these mechanisms are considered primarily homeostatic, keeping dendritic excitability under control, recent reports have shown that they can be modulated by neuronal activity (228, 475). Indeed, a recent study has demonstrated that dendritic spikes in oblique apical dendrites of hippocampal pyramidal cells are highly plastic and subject to neuromodulation (475), providing a novel mechanism for memory storage.

A key issue in understanding the role of dendritic spikes is to determine under what conditions they are triggered in vivo (155, 348, 819). Strong synaptic input, artificially activated with electrical stimulation, is known to produce dendritic spikes in cerebellar Purkinje cells, both in vitro (442) and in vivo (439), as well as in vitro in neocortical (674) and hippocampal pyramidal cells (255). Spatial clustering of inputs is clearly an important factor because of the distance-dependent attenuation (238, 239). A similarly important factor is temporal clustering (238, 450). In general, the closer the inputs are in time and space, the lower the threshold for triggering a dendritic spike. Thus dendritic spikes can be considered as spatio-temporal coincidence detectors. An example of this phenomenon is the time window in which coincident bAPs and EPSPs (403, 405, 747) or separate EPSPs (836) can evoke regenerative dendritic events. Another determining factor in dendritic spike generation is synaptic inhibition, which can block VDCC-mediated supralinearity of high-frequency bAPs (400) and suppress local regenerative events in an  $\sim 10$ -ms-long time window (839). This is similar to the coincidence-detection time window of regenerative dendritic spikes (403, 405, 747) and to the timing window of STDP (see sect. *iH*) (2, 158, 159).

A study by Jarsky et al. (335) shows a heterosynaptic regulation of dendritic spike propagation in hippocampal CA1 pyramidal cells. Dendritic spikes evoked in distal apical dendrites by synaptic stimulation generally fail to propagate to the soma. However, when synapses that are more proximal are also activated, the depolarization en-

ables forward propagation towards the soma. This is especially interesting as the two locations are innervated by functionally different inputs: a direct input from the entorhinal cortex to the distal apical dendrites and the Schaffer collateral input to the more proximal apical regions (861). Gasparini and Magee (238) further elucidate this picture by showing that network activity in different functional states (theta activity versus sharp waves) determines the mode of dendritic integration, thus enabling or disabling the propagation of dendritic spikes to the soma. Dendritic spikes thus start as local regenerative events which, depending on neuronal morphology, distribution of ion channels and the functional state of the neuron can propagate further, and may even reach the soma. The interaction between local spikes and bAPs can also extend the effect dendritic spikes have on somatic output (405) or increase the local effect of dendritic spikes. Naturally, in dendritic compartments electrotonically very distant from the soma, backpropagation has little or no impact (256).

Functionally, dendritic spikes can fulfill various roles. They detect synchronous activity by providing a nonlinear response. Depending on cell type and functional state of the neuron, this signal can have global effects on neuronal output and enhance somatic spike precision (34, 155, 255). It may also enable otherwise undetectable distal events to be boosted to increase their amplitude at the soma (238, 405, 834). Even if they do not forward-propagate reliably and therefore fail to contribute directly to axonal output, they can trigger local synaptic plasticity (256, 276, 310, 620, 626) and dendritic release of neurotransmitters (541, 620). In section *III D*, we revisit this local role of dendritic spikes in the induction of synaptic plasticity.

Overall, the existence of local dendritic spikes makes a neuron a more powerful computational unit, not only because the locality of spikes goes hand in hand with the degree of compartmentalization, but also because initiation and propagation of dendritic spikes is modulatable and state-dependent. The number, size, and function of compartments can thus be regulated dynamically and be continuously modified by ongoing activity. Next, we review in more detail two important determinants of dendritic excitability: the geometry of dendrites and the distribution of voltage-gated ion channels.

### 3. Importance of dendritic morphology

Neurons and their dendrites come in various shapes and sizes (Figs. 1 and 5). While the different branching patterns of dendrites allow specific patterns of synaptic connections to be made as neural circuits are wired up (733) (cf. sect. *III A1*), they also have direct consequences for the intrinsic properties of the neurons themselves. As touched on in section *II B1*, the long and thin dendrites of

neurons are cablelike structures, consisting of a conducting core (the dendritic cytoplasm) and a surface area (the plasma membrane), which has both a resistance and capacitance. Their electrical properties are described by the cable equation (328, 381, 617, 687), which links the flow of currents along the cable and across the membrane to the voltage drop across the membrane, the membrane potential. With appropriate boundary and initial conditions, the solution of the cable equation gives the membrane potential as a function of time and position along the dendrite. Thus the cable equation allows the impact of the dendritic tree on the electrical properties of a neuron to be modeled. Experiments, in particular using dendritic recordings, have been used to verify and calibrate such models, which have shown that dendritic morphology has a strong influence on the passive and active electrical properties of neurons. Below, we discuss several important functional implications that are directly due to dendritic morphology.

First, dendrites typically attenuate voltage. In particular, long thin dendrites that have large axial resistance give rise to severe voltage attenuation in the subthreshold regime (see, e.g., Ref. 551). For example, the attenuation of the peak amplitude of EPSPs as they spread from their site of origin to the soma can be more than 100-fold for the most distal synapses in neocortical L5 pyramidal neurons (744). In part, this is due to the low-pass filtering experienced by rapid voltage transients in dendrites, which can also lead to substantial conduction delays. However, the attenuation of synaptic charge, which is equal to the steady-state voltage attenuation, is less severe.

Because of this dendritic voltage attenuation, synapses at different dendritic locations are not necessarily equally effective in influencing axonal spike output. This observation has given rise to the concept of “dendritic democracy” (282), which is the degree to which all synaptic inputs of any given neuronal type are equally heard at the soma. The charge attenuation in the long and thin dendrites of pyramidal cells significantly reduces the somatic amplitude of EPSPs originating at synapses in distal dendritic locations, compared with EPSPs generated by proximal synapses with the same synaptic conductance, thus rendering these cells rather “dendritically undemocratic.” This is in contrast to the situation in the cerebellar Purkinje cell, whose spiny branchlets are relatively short and directly connected to the thick main dendrites (168, 645). Equal synaptic conductances on distal and proximal Purkinje cell spiny branchlets therefore give rise to very similar somatic EPSP amplitudes (168, 645). Thus the dendritic geometry of cerebellar Purkinje cells is intrinsically more “democratic” than that of pyramidal neurons (467, 836). The “democracy deficit” of pyramidal neurons is in part compensated by distance-dependent scaling of synaptic conductances in the apical dendrite of CA1 neu-

rons (467). However, this type of compensatory synaptic scaling has not been found in the basal or apical dendritic trees of neocortical L5 neurons (551, 836). Regardless, plasticity mechanisms that can promote distance-dependent compensatory scaling of synaptic conductances and equalization of synaptic efficacy will be discussed in section III, *E* and *F*.

However, morphology renders the situation still more complex than this, because voltage attenuation is not identical in all directions. The structure of dendritic trees is typically functionally asymmetric, because voltage attenuation from the soma to the dendritic tips and vice versa is not the same (686). Voltage attenuation from the central location of the soma via the thick main dendrites to the distal dendritic tips is usually much weaker than voltage attenuation from the thin dendritic tips towards the soma. This asymmetry affects not only the transient and steady-state attenuation of subthreshold voltage signals, it also results in an asymmetry of active back- and forward-propagation of spikes (see below, and sect. II B, 1 and 2).

If we view the dendritic tree on a small scale, it is worth noting that voltage attenuation may isolate relatively small individual dendritic branches from the rest of the tree. Voltage attenuation from individual dendritic branches to the rest of the dendritic tree is a prerequisite for localized interactions between synapses via the dendritic membrane potential. The space constant for the attenuation of the effect of one synaptic conductance on another is even smaller than the space constant for voltage attenuation (834). Dendritic geometry thus determines the number and hierarchical arrangement of functional compartments in the neuron at the subthreshold (328, 382) as well as the suprathreshold level (604).

If, on the other hand, we view the dendrites on a much larger scale, we note that relatively global properties of a neuron often depend directly on cell morphology. These cell-wide properties include input resistance, cell capacitance, voltage and current thresholds of somatic AP initiation, *f/I* curve (58), and firing pattern (472, 599). By their mere existence, dendrites act as a resistive and capacitive load on the site of spike initiation in the axon (58), thus rendering AP initiation more difficult. Under certain conditions, however, dendrites promote spiking by providing additional inward current via the activation of dendritic voltage-activated conductances. Thus dendritic morphology exerts a powerful influence on the global I/O function of a neuron.

Finally, properties and densities of voltage-gated conductances (see sect. II B 4) along with the neuronal morphology (257, 802) jointly determine the rules for active signaling in dendrites. The influence of dendritic morphology has been demonstrated directly in numerical simulations that isolate neuronal morphology as the only variable by keeping the kinetics and densities of voltage-gated

channels constant (472). Using this approach, Vetter et al. (802) showed that dendritic trees with a large number of branch points and a large increase in dendritic membrane area as a function of distance from the soma tend to be poor substrates for AP backpropagation. The large increase in membrane area presents a large capacitive load, which severely attenuates the amplitude of fast voltage transients, thus causing the AP to quickly drop below threshold for active propagation. One prominent example having these dendritic characteristics is the cerebellar Purkinje cell. Dendritic trees with the opposite characteristics provide the best conditions for AP backpropagation. One good example here is the substantia nigra dopaminergic neuron (240, 288).

Interestingly, the pattern of AP backpropagation observed experimentally in these two cell types, as well as others (see sect. *1B1*), matches the pattern predicted from the simulations of Vetter et al. (802). AP backpropagation in dendritic trees with intermediate properties, e.g., in hippocampal pyramidal neurons, is particularly sensitive to modulation of channel densities (Fig. 5). This sensitivity adds additional flexibility, by allowing AP propagation in these neurons to be regulated. That dendritic morphology is a critical factor to a neuron was highlighted by a recent study (660), which demonstrated that hippocampal CA1 and CA3 pyramidal neurons appear to homeostatically regulate the spatial extent of the dendritic arbor.

Rules similar to those of AP backpropagation also govern forward propagation of dendritically initiated spikes. By changing AP backpropagation and forward propagation of dendritic spikes, dendritic morphology also changes the coupling between somatic and dendritic spike initiation sites in the neuron (667). Dendritic morphology therefore determines which associations, between different inputs as well as between input and output, can occur during synaptic integration and plasticity.

#### 4. *Nonuniform distribution of conductances*

In addition to dendritic morphology, the kinetics, density, and spatial distribution of various voltage-gated conductances present in dendrites are important determinants of the spread of synaptic potentials, backpropagation of APs, and the conditions for initiation and forward propagation of dendritic spikes. Regulation of channel properties and densities, as well as control of spatial gradients in these variables, endow neurons with additional degrees of freedom to shape their functional characteristics (521). Two prominent examples are the gradient of  $I_A$  in hippocampal CA1 neurons (303) and the gradient of  $I_h$  that exists in hippocampal CA1 pyramidal

cell dendrites (465, 466) as well as in neocortical L5 pyramidal cells (63, 385, 448, 521, 744). The increase of  $I_A$  density with distance from the soma, and the shift of the activation curve of the distal  $I_A$  channels towards more hyperpolarized potentials, increases threshold for initiation of dendritic spikes, reduces AP backpropagation, and also influences subthreshold synaptic integration (303). In particular, it may render summation of EPSPs on the main apical trunk sublinear (114). Similarly, the high density of  $I_h$  in the distal apical dendrite of L5 pyramidal cells acts to disconnect somatic and dendritic spike initiation zones (64). However, the influence of  $I_h$  on the backpropagation of individual APs is weak (64, 465), because  $I_h$  both shunts and depolarizes the dendrite, with little net effect on backpropagation (406, 747), and because  $I_h$  is kinetically slower than  $I_A$ . Thus different kinds of voltage-gated conductances placed at different locations in the dendritic tree can selectively tune various aspects of the excitability of different neuronal types.

Interestingly, Purkinje cells possess a relatively uniform dendritic density of  $I_h$  (27), whereas the dendritic  $I_h$  gradient of hippocampal stratum radiatum pyramidal-like principal neurons (98) is more or less the inverse of that of CA1 (465, 466) and L5 (63, 838) pyramidal neurons. In both the case of Purkinje cells (27) and stratum radiatum pyramidal-like principal neurons (98),  $I_h$  still appears to subservise the normalization of temporal summation. This suggests that the dendritic expression of  $I_h$ , but not its spatial gradient, is important for such normalization (27, 466). Neocortical L2/3 pyramidal neurons, on the other hand, appear to express relatively little dendritic  $I_h$  (403), showing that this current is specific to certain subpopulations of neurons.

Several important hyperpolarization-activated cyclic nucleotide-gated type 1 channel (*hcn1*) gene knock-out or knockdown studies also demonstrate critical roles for dendritic  $I_h$  in prefrontal cortical L5 neurons and working memory (807), in hippocampal CA1 pyramidal neurons and spatial memory (560), and finally also in Purkinje cells and motor learning (561). In these studies, the regulation of HCN1 gene and of the  $I_h$  channel appears to be a prime candidate for the control of network activity and certainly seems pivotal for the proper storage of information in the brain.  $I_h$  may in fact provide a rare case of a direct link from genes and molecules to memory formation (560, 561, 807).

Although their functional roles remain to be elucidated, dendritic gradients of ion channel densities are relatively common. What causes and maintains these dendritic gradients in channel densities? This is very much an open question. Possible mechanisms, for example, an activity-dependent regulation of channel densities, will be discussed in the following sections.



### C. Mechanisms for Regulation of Specific Dendritic Channels

The active conductances of dendrites are subject to modulation. The simplest modulator is the membrane potential itself, since it opens and closes voltage-gated ion channels. In addition, the history of the membrane potential also influences ion channel state, especially when channel kinetics are relatively slow. Neurotransmitters can activate diverse second messenger pathways, thus leading to a change in the phosphorylation state of ion channels and thereby affecting their voltage dependence, speed of gating, or opening probability. On a longer time scale, changes in the expression levels of ion channel subunits can also profoundly alter the excitability of dendrites.

#### 1. Regulation by neurotransmitters and neuromodulation

A wide variety of neurotransmitters and modulators affect dendritic ion channel properties. Monoamines, acetylcholine, glutamate, and neuropeptides all have modulatory effects through phosphorylation or dephosphorylation of various ion channels (109, 165, 416, 776).

Different phosphorylation levels of dendritic  $\text{Na}^+$  channels seem to underlie the difference in their activation curves (237). Muscarinic activation of PKC leads to a decrease in the slow inactivation of  $\text{Na}^+$  channels (140) and the increase of persistent  $\text{Na}^+$  current (40). The metabotropic glutamate receptor mGluR1 similarly acts through PKC to downregulate neuronal excitability by controlling both persistent and transient  $\text{Na}^+$  channels (112). Dopamine decreases  $\text{Na}^+$  currents in hippocampal neurons (110) and striatal neurons (669) through the D1 receptor-mediated activation of protein kinase A (PKA). By inhibiting adenylyl cyclase through D2 receptors, however, dopamine can also increase the amplitude of  $\text{Na}^+$  currents in the basal ganglia (19). In substantia nigra dopaminergic neurons, dopamine acts on a voltage-activated  $\text{K}^+$  channel with  $I_A$ -like characteristics to gate AP propagation from the axon-bearing dendrite, in which propagation does not fail (240, 288), to the contralateral dendrite by enhancing AP propagation failures (240). In CA1 pyramidal cells,  $\beta$ -adrenergic stimulation also results in PKA activation (301), which, together with PKC, is reported to shift the activation curve of A-type  $\text{K}^+$  channels (303) through a constitutively active extracellular receptor kinase (ERK) pathway (14, 865), making them less likely to open.

Serotonin, on the other hand, activates inward-rectifying  $\text{K}^+$  conductances in the soma and dendrites of neocortical pyramidal cells and hyperpolarizes the cell (456, 766). GABA<sub>B</sub> receptor activation was shown to increase the activity of constitutively active G protein-coupled inward rectifying  $\text{K}^+$  (GIRK) channels (125) as well

as to directly block dendritic  $\text{Ca}^{2+}$  channels and block bAP-evoked  $\text{Ca}^{2+}$  spiking (BAC; cf. sect. III C) (591). Big  $\text{K}^+$  (BK) channels in Purkinje cells are also controlled by multiple kinases and phosphatases (829).  $\text{Ca}^{2+}$  channels are modulated directly by G protein-coupled receptors of epinephrine, endorphins, GABA, and adenosine, to name a few (for review, see Ref. 116), resulting in a slower activation rate (53). Interestingly, PKC activation can revert these modifications (760). L-type  $\text{Ca}^{2+}$  channels can also be potentiated by  $\beta$ -adrenergic stimulation through PKA in a spine-confined manner (313). It has also been demonstrated that  $I_h$  is modulated by serotonin in cerebellar Purkinje cells (420), and dendritic  $I_h$  in Purkinje cells have been shown to be critically involved in motor learning (561). Interestingly, critical roles for dendritic  $I_h$  in spatial memory has also been discovered in hippocampal CA1 neurons (560) as well as in working memory in prefrontal cortical L5 pyramidal neurons (807).

The functional role of changes in dendritic excitability via ion channels modulation has been most extensively studied in CA1 pyramidal cells regarding the backpropagation of somatic APs into the dendrites (for review, see Refs. 341, 784). By changing  $\text{Na}^+$  channel inactivation (140) or reducing  $\text{K}^+$  channel opening (698, 699), acetylcholine can increase the amplitude of dendritic bAPs. Norepinephrine, by its effect on A-type  $\text{K}^+$  channels, also enhances backpropagation (301) and could function as a coincidence detector: a relatively weak synaptic stimulus paired with norepinephrinergic input, which increases bAP amplitude, could promote removal of the  $\text{Mg}^{2+}$  block of NMDA receptors and thus trigger long-lasting synaptic plasticity (815). Acetylcholine decreases  $I_A$  to enhance bAPs (302). Similarly, epinephrine can increase the  $\text{Ca}^{2+}$  entry to spines following bAPs, by potentiating T-type channels (313). Serotonin, on the other hand, hyperpolarizes the dendrites, thus limiting the extent of backpropagation and reducing  $\text{Ca}^{2+}$  influx (661). Dopamine enhances  $I_h$  and reduces dendritic excitability in layer 5 pyramidal neurons in the entorhinal cortex (643), but has no apparent effect on backpropagation in prefrontal cortical pyramidal cells, although it changes input resistance and excitability (263). The regulation of dendritic  $\text{Na}^+$  and  $\text{K}^+$  channels, along with  $\text{Ca}^{2+}$  and  $I_h$  channels, can thus also play a crucial role in defining local interactions between synapses and in the generation of dendritic spikes, highlighting another niche for future research.

Given the discovery that STDP (sect. I H) depends critically on neuromodulatory background (149, 690), the impact of neuromodulators on dendritic excitability, AP backpropagation, and local dendritic spikes is all the more intriguing. It is especially interesting to consider the spatial aspects of such modulation: local modulatory synaptic input, which may up- or downregulate excitability in different dendritic branches, may set different rules for plasticity in different dendritic compartments (228).

## 2. Regulation by calcium and other readouts of postsynaptic activity

One possible readout of postsynaptic activity is the level of intracellular  $\text{Ca}^{2+}$ , which can be elevated by various mechanisms: metabotropic and ionotropic neurotransmitter receptors convey information from the input; postsynaptic depolarization acting through VDCCs converts information about the excitability state of the neuron to  $\text{Ca}^{2+}$  levels. To start with, VDCCs are subject to modulation by  $\text{Ca}^{2+}$  itself. Acting through calmodulin, a  $\text{Ca}^{2+}$ -binding protein (852),  $\text{Ca}^{2+}$  enhances P/Q-type channel inactivation and increases recovery from inactivation (408), leading to facilitation and then inactivation of presynaptic  $\text{Ca}^{2+}$  channels during trains of APs (84). Interestingly, calmodulin can both up- and downregulate P/Q-type  $\text{Ca}^{2+}$  channels depending on the kinetic profile of  $\text{Ca}^{2+}$  signals (177). The C-lobe of calmodulin responds best to local, rapid changes in intracellular  $\text{Ca}^{2+}$  concentrations ( $[\text{Ca}^{2+}]_i$ ), whereas the N-lobe averages the signal more slowly and over space. Since the C-lobe promotes but the N-lobe inhibits P/Q-type channel opening, calmodulin is neatly poised to decode local  $\text{Ca}^{2+}$  signals in differential manner, by bifurcating the same signal into effects of opposing signs. Thus, as with synaptic plasticity (sect. IIIA4), it may not be the bulk  $[\text{Ca}^{2+}]_i$  levels that control intrinsic excitability, but  $[\text{Ca}^{2+}]_i$  in local microdomains generated by different sources of  $\text{Ca}^{2+}$  influx.

L- and T-type  $\text{Ca}^{2+}$  channels are modulated by calmodulin-dependent kinase II (CaMKII; Refs. 827, 884), a kinase which plays a central role in LTP (432). CaMKII-mediated phosphorylation has also been shown to increase BK channel activity (436). Conversely, CaMKII blockade leads to downregulation of BK channels in vestibular nucleus neurons (548).

LeMasson et al. (411) have proposed a very attractive model, in which  $[\text{Ca}^{2+}]_i$  controls the sum conductance of several voltage-gated conductances. Depending on the target  $[\text{Ca}^{2+}]_i$ , the model neurons showed different firing properties (silent, continuously firing, bursting). More importantly, these properties could be recovered after disturbances, leading to neurons having remarkably similar firing properties with different distributions of ion channels. Several experiments have provided support for such activity-dependent tuning of cellular excitability (184, 258, 787) (sect. ID). One attractive example is from the vestibular nucleus, where intracellular  $\text{Ca}^{2+}$  levels control BK channel activity via CaMKII, as discussed above (548). Activation of CaMKII can also directly increase cell-surface expression of Kv4.2, the subunit underlying the A-type  $\text{K}^+$  current  $I_A$ , leading to long-term decrease of excitability in CA1 pyramidal neurons (800). Finally,  $\text{Ca}^{2+}$  entry can activate phosphatases, such as calcineurin. Kv2.1, which underlies a delayed rectifier  $\text{K}^+$  current in CA1 pyramidal neurons, has been shown to form clusters

in dendrites. Calcineurin activation due to neural activity can break up these clusters and cause a hyperpolarizing shift of the activation curve of the channels, upregulating this current in response to epileptic seizures (527). Such activity-dependent regulation can be finely graded due to variable phosphorylation of Kv2.1 at a large number of sites (526, 586).

Other readouts of postsynaptic activity include numerous signals up- and downstream of intracellular  $\text{Ca}^{2+}$ . One such readout is membrane potential. By relieving  $\text{Mg}^{2+}$  block from NMDA channels, depolarization can enable  $\text{Ca}^{2+}$  influx in more ways than just opening VDCCs. In addition, slowly activating and inactivating channels provide a mechanism for storing a history of membrane potential. Trains of bAP thus can be attenuated by slowly inactivating  $\text{Na}^+$  channels (140), but can also be boosted by slowly activating  $\text{Ca}^{2+}$  channels. Increase of intracellular  $\text{Ca}^{2+}$  levels leads to the recruitment of  $\text{Ca}^{2+}$ -dependent  $\text{K}^+$  channels, which can set the spatial extent of local dendritic spikes (105, 620), but also unleashes many intracellular messengers different from CaMKII or calcineurin. For example, the effect on ion channels of unsaturated fatty acids, also produced upon mGluR activation (461), received increased attention recently (796). Arachidonic acid (AA), which acts by blocking A-type  $\text{K}^+$  channels at the same time as potentiating a sustained outward current, has been shown to affect excitability and backpropagation (142).

Functionally, few studies have addressed the dendritic aspect of activity-dependent modulation of ion channels. Change in intrinsic excitability by a theta-burst protocol (also producing LTP if paired with presynaptic activity) was shown to require AP backpropagation and CaMKII-dependent modulation of  $I_h$  (207). Spatial dendritic integration was also shown to change following LTP (813). Localized changes in dendritic excitability were first discovered by Frick et al. (228). They found that, following theta-burst pairing in CA1 pyramidal cells, the activation curve of  $I_A$  was shifted to more hyperpolarized potentials, but the effect was localized to the dendritic compartments innervated by the synapses activated during the induction (Fig. 6). This modulation of  $I_A$  was also found to require NMDA receptor activation, raising the possibility of CaMKII involvement (800). Additional studies are needed to further establish the local interactions of synaptic plasticity pathways with ion channels.

## 3. Regulation by changes in gene expression

Dendrites are equipped with protein synthesis capabilities, which are regulated through neuromodulation and neuronal activity, allowing more local control of the type and amount of proteins expressed in dendrites (88, 752). Alternatively, signals may travel from synapses to the nucleus and back again, eventually resulting in long-

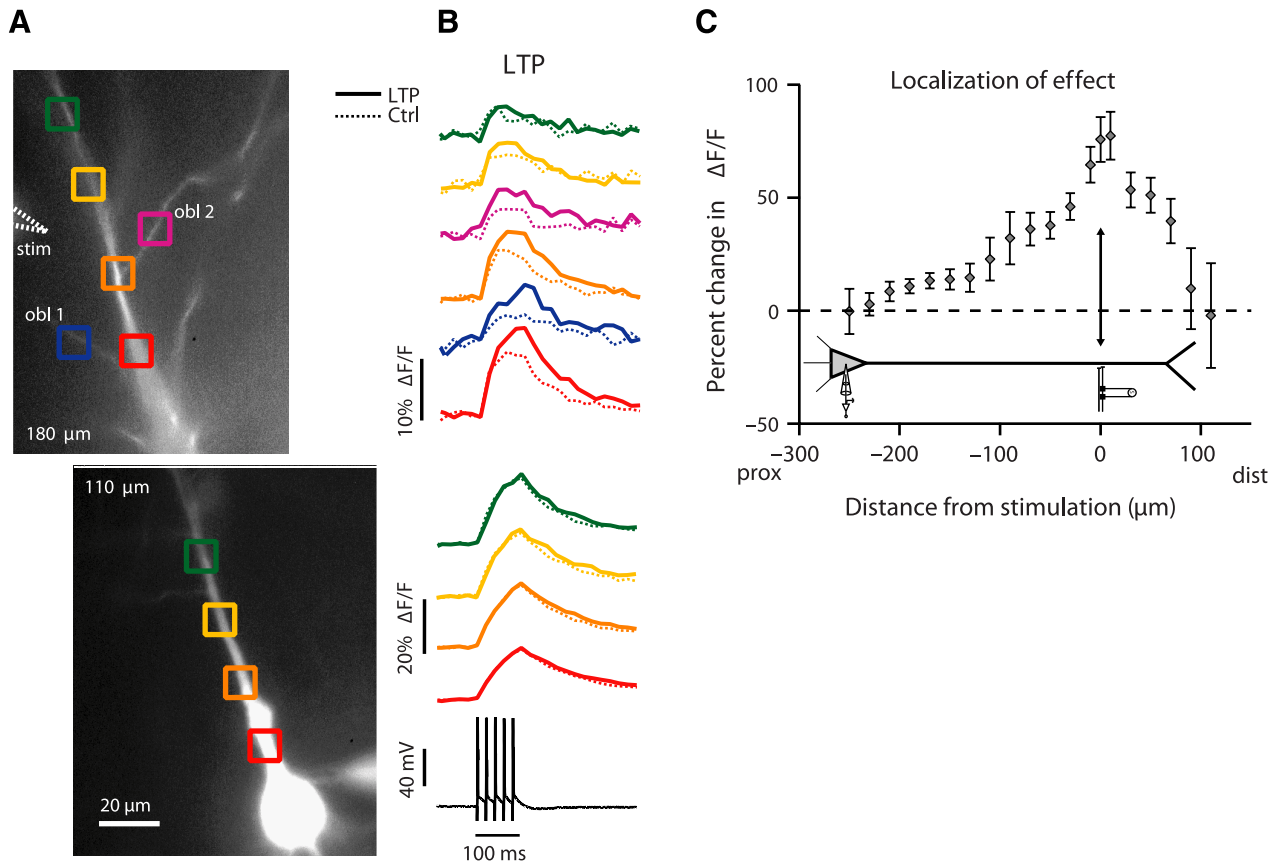


FIG. 6. LTP can locally alter dendritic excitability. *A*: fluorescence image of the main apical dendrite schematically illustrates the position of the stimulation electrode. *B*: traces represent bAP-evoked  $\text{Ca}^{2+}$  responses before (dotted) and after (solid) LTP induction. Colors correspond to regions of interest marked in *A*. Note how bAP-evoked  $\text{Ca}^{2+}$  responses increase after LTP induction in distal but not proximal dendritic regions (228). *C*: the increase in dendritic excitability is localized and maximal at the point of synaptic stimulation during LTP induction. Normalized bAP-evoked  $\text{Ca}^{2+}$  signals are plotted against the distance from the site of synaptic stimulation (228). [From Frick et al. (228), with permission from Macmillan Publishers Ltd, copyright 2004.]

term plasticity of “synaptically tagged” inputs (226, 260, 536). Recent results show that such molecular tags are even specific for different dendritic compartments (659). To date, little direct evidence, however, has been published on similar dendritic changes in ion channel composition or density. An elegant study conducted by Fan et al. (207) was the first to show increased expression of the HCN channels in CA1 pyramidal cell dendrites following theta-burst-induced LTP. This form of dendritic plasticity was dependent on presynaptic glutamate release, NMDA receptors, intracellular  $\text{Ca}^{2+}$  elevation, CaMKII, and protein synthesis.

The activity-dependent control of signaling to the nucleus and gene expression in neurons is manifested in many temporally and spatially different mechanisms (for review, see Ref. 176). It is increasingly evident that the  $\text{Ca}^{2+}$ - and cAMP-dependent mechanisms reach further than the control of transcription, playing part also on a posttranslational level (233, 377). Depending on the various voltage- and ligand-gated  $\text{Ca}^{2+}$ -permeable channels expressed in the dendrites, different signals can be transformed into elevation of  $\text{Ca}^{2+}$  levels. For example,  $\text{Ca}^{2+}$

signals evoked by EPSPs rather than APs are more effective in cAMP response element binding protein (CREB) phosphorylation, due to the slow kinetics and low voltage activation of L-type  $\text{Ca}^{2+}$  channels (518). In addition, calcineurin-mediated regulation of nuclear factor of activated T cells (NF-AT) transcription factors is critically dependent on L-type  $\text{Ca}^{2+}$  channels (261). One main pathway seems to be the mitogen-activated protein kinase (MAPK)/ERK activation by PKC or PKA leading to CREB phosphorylation (for review, see Ref. 15). Brosenitsch et al. (94), however, argues that with physiological activation of neurons, N-type  $\text{Ca}^{2+}$  channels play the main role in activating gene expression through a non-MAPK but PKA- and PKC-dependent mechanism, producing transient CREB phosphorylation.

Local translation and de novo protein synthesis can thus be recruited by many activity-dependent intracellular pathways in neurons, ultimately leading to a change in excitability via ion-channel composition of the cell membrane. Perhaps in part because of the relatively long time needed for these changes to manifest, no studies have

been done to directly map the whole pathway. Future research on the targeting of ion channels to different compartments will shed more light on long-term regulation of excitability in different parts of neurons.

In this section, we have described some key examples of modulation of ion channels, such as changes of dendritic excitability by neurotransmitters, neuromodulators, and other readouts of pre- or postsynaptic activity. As we have seen, many diverse mechanisms shape dendritic function in a cell-type and compartment-dependent manner.

#### D. Triggers for Long-Term Plasticity of Dendritic Excitability

In the previous section, we reviewed several different ways in which dendritic ion channels are directly regulated by neuromodulators, neurotransmitters,  $\text{Ca}^{2+}$ , and genes. In section 1E, we introduced the concept of long-term plasticity of intrinsic excitability. Here, we combine these concepts, to examine how plasticity of dendritic excitability might be triggered (for a review, see Ref. 227). We begin with activity-dependent changes in general (sect. 1D1), subsequently touching on EPSP-spike potentiation (sect. 1D2) and STDP of dendritic excitability (sect. 1D3). Finally, we discuss changes in excitability that occur during development (sect. 1D4).

##### 1. Are there local activity-dependent changes in dendritic excitability?

Several studies have reported that the excitability of a neuron can be altered by activity (cf. sect. 1E). Unfortunately, the information available on excitability changes that are specifically dendritic is scarce. Here we examine studies reporting activity-dependent changes in overall intrinsic excitability and discuss the possibility that dendritic changes of excitability could be involved. We will also describe evidence supporting local dendritic alterations in excitability and discuss the functional implications.

In 2000, Aizenman and Linden (17) published an influential study describing a novel form of intrinsic excitability of neurons in the deep cerebellar nuclei. By briefly applying 100-Hz tetanization trains to the nearby white matter while inhibition was blocked, they found that the number of spikes due to a brief depolarizing somatic current injection was persistently increased. This NMDA receptor-dependent form of plasticity was, perhaps surprisingly, also evoked by brief postsynaptic depolarization in the absence of synaptic activation. Whether this change of intrinsic excitability involves dendritic changes is unclear.

Desai et al. (184) found that by reducing the activity in a network of cultured cortical neurons for many hours, the intrinsic excitability of cells was upregulated in a

compensatory manner, thus resulting in a homeostatic type of plasticity (sect. 1D). This plasticity is expressed through the modulation of a fast  $\text{Na}^+$  current and a subset of  $\text{K}^+$  channel types. Cudmore and Turrigiano (156), on the other hand, found that brief high-frequency firing in a single neocortical L5 neuron in the acute slice resulted in a persistent increase in its intrinsic excitability. This mechanism depended on postsynaptic  $\text{Ca}^{2+}$  influx and PKA activation. Cortical neurons are thus sensitive to rapid as well as prolonged changes in activity and may respond with alterations in intrinsic excitability that results in either positive or negative feedback. In both cases, however, it remains unclear to what extent specifically dendritic changes are brought about by induction of plasticity.

In neurons of the vestibular nucleus, hyperpolarization by somatic injection of negative current or by recruiting synaptic inhibition brings about a long-lasting increase in intrinsic excitability (549), thus resulting in a negative-feedback loop. This mechanism is expressed through the regulation of BK-type  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels, and its induction relies on  $\text{Ca}^{2+}$  influx and CaMKII activation (548, 549). Interestingly, the sign of this rapidly induced plasticity rule is opposite to the one found by Cudmore and Turrigiano (156) in neocortical L5 neurons. Intrinsic excitability of granule cells is also persistently increased by brief depolarization, either through current injection or through excitatory synaptic activation, in an NMDA receptor-dependent manner (35). Similarly, prolonged visual stimulation of *Xenopus laevis* tadpoles produced a  $\text{Na}^+$  channel-based persistent increase in the intrinsic excitability of the primary dendrite in optic tectal neurons, although this effect was not NMDA receptor dependent (16). The difference in sign of these forms of plasticity is probably a reflection of the role played by these cell types in their respective circuits. In general, positive-feedback mechanisms probably underlie memory storage (sect. 1E), whereas negative feedback is substrate for homeostasis (sect. 1D).

In Purkinje cells, Smith and Otis (720) found that transient application of a nitric oxide (NO) donor caused a persistent upregulation in spontaneous firing rates. More importantly, brief 20-Hz PF activation could substitute for the NO donor, even during blockade of all principal synaptic transmission, presumably because PF stimulation directly elicits NO production (701) by NO synthase located in PF terminals (90). Since PFs synapse onto dendrites but not the soma of Purkinje cells (582), the observation that PF activation can increase Purkinje cell firing rates most likely means there is a dendritic component to the expression of this form of plasticity. However, in the actual in vivo situation, where PF synaptic transmission is not blocked, it is quite likely that PFs recruit interneurons that then help produce NO (639, 703) and thereby contribute to the regulation of Purkinje cell

spontaneous firing rates. Nevertheless, the putative dendritic component of this learning rule definitely deserves further investigation.

In hippocampal CA1 pyramidal neurons, van Welie et al. (799) found a homeostatic downregulation of intrinsic excitability due to enhancement of synaptic drive. By this mechanism, the hyperpolarization-activated  $I_h$  current is increased on a time scale of tens of minutes, which is relatively rapid for a negative-feedback learning rule (cf. sect. 1D). Although the authors only examined the  $I_h$  conductance measured at the soma, these results are suggestive, as CA1 pyramidal neurons are known for expressing a very steep somatodendritic gradient of this conductance type, such that the dendritic current density is fivefold that in the soma (465, 466, 607). In fact, lamotrigine, a drug for treating epilepsy, has been shown to specifically boost dendritic but not somatic excitability, by enhancing this  $I_h$ -based gradient (607). Although this line of reasoning is circumstantial, it is tempting to speculate that the homeostatic learning rule of van Welie et al. (799) preferentially acts on the dendrites of CA1 cells. In fact, in another recent study by Aptowicz et al. (30), it was reported that 2-day-long activity deprivation in a hippocampal slice culture preparation resulted in a compensatory enhancement of neuronal activity as well as in increased expression of voltage-gated  $\text{Na}^+$  currents specifically in the dendrites. Although the target current types are different in these different reports, one emerging principle is that specifically dendritic currents are regulated to control intrinsic excitability.

In a study by the Johnston lab, Fan et al. (207) discovered a mechanism for changes in intrinsic excitability of CA1 pyramidal neurons that is particularly intriguing, because it relied on a theta-burst type of postsynaptic spiking pattern as well as on NMDA receptor activation, yet surprisingly evoked presynaptic activity was not actually needed. Spontaneous neurotransmitter release, however, was required. Furthermore, the postsynaptic APs needed to backpropagate into the dendrites and produce NMDA receptor-mediated  $\text{Ca}^{2+}$  signals. On the expression side, this form of plasticity relies on increasing  $I_h$  in the dendrite and/or the perisomatic region, thus providing a form of negative feedback to synaptic strengthening as well as to brief periods of heightened synaptic drive. Given the fact that this learning rule appears to form a negative feedback loop, the function of the mechanism of Fan et al. (207) may be to provide stability by producing a form of metaplasticity. Fan et al. (207) did however find that synaptic strengthening by theta-burst-induced LTP did not necessarily produce increased postsynaptic firing rates. Perhaps, then, this cellular learning rule acts similar to the activity-dependent sliding threshold of the BCM rule (sect. 1D) (70).

Hoffman's group (370) recently reported that LTP induction in CA1 neurons resulted in rapid clathrin-mediated

endocytosis of the  $I_A$  channel subunit Kv4.2. This NMDA receptor and  $\text{Ca}^{2+}$ -dependent downregulation of  $I_A$  in effect contributes to LTP (370) and presumably to learning, since it functionally acts in synergy with the insertion of AMPA receptors in the spine head (also see Refs. 452, 482, 565). Interestingly, the internalization of Kv4.2 subunits was synapse-specific, in the sense that  $I_A$  was only effectively removed from spines that had experienced synaptic stimulation during LTP induction (370). The functional impact of spine-restricted removal of  $I_A$ , however, need not be limited to individual synapses (see sect. 1E). Regardless, this is a clear case of a spatially very restricted mechanism for the altered excitation of dendritic compartments.

Of the above examples, only a few provide evidence, even indirect, for dendritic components of the expression or the induction mechanisms (16, 207, 370, 546, 720). The question of whether such dendritic components are involved is very important, since they would alter the balance of synaptic weights in the dendritic tree (249), although this is presumably less relevant in the case of the electrically compact granule cells (35). In addition, given the relatively recent evidence for sequences of differential somatic-dendritic activation of inhibition in CA1 pyramidal neurons (608), the relative excitability of these two regions is probably of prime importance for proper brain functioning. Although we have discussed above a few clear-cut examples of specifically dendritic changes in intrinsic excitability (16, 207, 370), more work is clearly needed to elucidate how common such changes are, what their mechanisms and functional implications are, and to what extent they underlie pathology.

## 2. Changes of dendritic excitability may underlie EPSP-spike potentiation

In Bliss and Lømo's (76) first report on LTP (cf. sect. 1B), they reported that, concomitant with potentiation of synaptic responses, there was an increase in the population spike. This phenomenon, termed EPSP-spike (E-S) potentiation (73, 76, 877), is suggestive of a lower threshold for spiking postsynaptically. Although some have suggested that this effect is due to an altered balance of excitation and inhibition subsequent to LTP induction (7, 123), others have argued that this is a result of changes in intrinsic excitability (for a brief historical overview, see Ref. 877). Some have found that the balance of excitation and inhibition should actually be preserved rather than altered after LTP, since inhibition is also potentiated (398). In addition, E-S potentiation can be induced in the absence of inhibition (41, 297, 338), strongly suggesting that it must at least in part be due to changes in excitability. The converse reduction in E-S coupling upon the induction of LTD has also been discovered, and this mechanism does not rely on synaptic inhibition either

(161). Although in principle these changes could also be presynaptically located (234, 510), it has been theorized for some time that local dendritic changes may be the main culprit (821).

Indeed, Wang et al. (813) recently discovered that, in hippocampal CA1 pyramidal neurons, a persistent increase in supralinear summation of two separate pathways was brought about by LTP induction via an STDP-like experimental paradigm, that is, via repeated pairing of presynaptic activity just before postsynaptic spiking (see sect. *iH*). Wang et al. (813) found that this increased supralinearity was due to a downregulation of dendritic  $I_h$  channels. Interestingly, LTD induced by inversely timed post-leading-presynaptic pairings gave rise to the opposite reduction in supralinearity, perhaps by the converse upregulation of  $I_h$  in the dendrites, although Wang et al. (813) did not investigate this possibility. While the authors also discovered a potential involvement of NMDA receptor channels in the expression of this form of dendritic plasticity, it is at present unclear whether the role of NMDA receptors is in the induction process or in the expression of the changes in supralinearity (813). Regardless of the mechanistic details, Wang et al. (813) provide strong support for the notion that E-S potentiation may at least in part be due to synaptically induced activity-dependent changes in dendritic excitability. Functionally, the mechanism of Wang et al. (813) may thus boost LTP, since any individual potentiated input is not only strengthened through LTP but also sums to relatively larger compound EPSPs when activated in synchrony with other inputs. The overall impact on axonal spike output is thus doubly enhanced through the synergistic workings of LTP and of the mechanism discovered by Wang et al. (813).

Interestingly, recent results demonstrate that the mechanism described by Wang et al. (813) may also enhance the ability of distal dendritic inputs of CA1 neurons to detect coincidences on a 5-ms time scale (855). This means that this form of dendritic plasticity does not merely alter synaptic efficacy but also dramatically changes the impact of dendritic computations on axonal spike output. It is tempting to speculate that such plasticity of distal dendritic coincidence detection may also exist in neocortical L5 neurons (836).

The findings of Wang et al. (813) may seem contradictory to those of Fan et al. (207) (see sect. *IID1*); the former group found that LTP upregulates presumably dendritic  $I_h$  currents, whereas the latter group found precisely the opposite. Also, Wang et al. (813) proposed that their mechanism may act in synergy with LTP and that there may be a link to E-S potentiation, whereas Fan et al. (207) argued that, upon LTP induction, their form of plasticity may promote network stability through normalization of neuronal firing rates. How can these studies be reconciled? Campanac and Debanne (107, 108) reveal an elegant resolution to this discrepancy by finding that near-

maximal LTP induced by theta-burst pairing produces an apparently homeostatic upregulation of the  $I_h$  conductance in CA1 pyramidal dendrites. This is similar to what Fan et al. (207) described, but in contrast, Campanac and Debanne have also found that eliciting more moderate levels of LTP, for example, through STDP, triggers E-S potentiation through downregulation of  $I_h$  (108), in agreement with the findings of Wang et al. (813). In other words, all these results are consistent with a scenario in which several opposing mechanisms are at play simultaneously: depending on the stimulation strengths used in the experimental paradigm, either negative-feedback homeostatic mechanisms or positive-feedback Hebbian-like learning rules are recruited. The emerging principle is that dendritic excitability is differentially regulated both to ensure efficient learning and to help maintain stability.

In another study from the Johnston group, Frick et al. (228) found an increase in dendritic excitability upon LTP induction that was dependent on NMDA receptor activation (Fig. 6). In this case, however, the altered excitability was not due to regulation of the  $I_h$  current, but rather of the A-type  $K^+$  current  $I_A$  by a hyperpolarized shift of its inactivation curve. Interestingly, the authors demonstrated that the altered excitability was spatially restricted to a region of the dendritic tree no larger than a couple of hundred micrometers (Fig. 6C). This beautiful study thus provides us with the first clear-cut example of a localized dendritic change in excitability produced upon the induction of synaptic plasticity. As the shift of the  $I_A$  inactivation curve promoted AP backpropagation, this form of plasticity is very likely to impact subsequent induction of plasticity at nearby synapses, thus producing a form of heterosynaptic metaplasticity (cf. sect. *iD*). Consistent with an involvement in E-S potentiation (e.g., Ref. 338), Frick et al. (228) found that the increased dendritic excitability had a slower time course than that of LTP, beginning with no effect and gradually building up over several tens of minutes before plateauing at a maximal level that appears to persist in the long term.

In a more recent study, Xu et al. (854) report an analogous mechanism, also in hippocampal CA1 neurons, although one that depends on the upregulation of  $Na^+$  channels rather than a suppression of the  $I_A$  current. Xu et al. (854) also find that the expression is gradual, with a time course slower than that of LTP, and, interestingly, the locus of expression appears to be more dendritic than somatic. Given their NMDA receptor dependence and slow time course, the mechanisms of Xu et al. (854) and of Frick et al. (228) are thus ideal candidates to explain E-S potentiation. The reasons for the different targets of expression ( $Na^+$  versus A-type  $K^+$  currents) are unclear but may depend on subtle differences in experimental conditions; *in vitro* preparations are infamous for their experimental variability. Regardless, the more important take-home message is that a localized upregulation in

dendritic excitability convincingly accounts at least in part for the E-S potentiation phenomenon that Bliss and Lømo described in 1973 (76), although a contribution from inhibition can at present not be entirely ruled out.

### 3. STDP of dendritic excitability

In the previous two sections (sect. II, *D1* and *D2*), we described how activity-dependent mechanisms that induce synaptic plasticity may also alter intrinsic excitability in general and local dendritic excitability in particular. All mechanisms mentioned were triggered by altering firing rates, albeit on time scales ranging from seconds to several days. Over recent years, there has been a tremendous interest in STDP (sect. *IIH*). Typically, STDP refers to spike-timing-dependent changes of synaptic rather than intrinsic excitability. There is no a priori reason, however, to believe that plasticity of intrinsic excitability, just as with synaptic plasticity (sect. I, *G* and *H*), depends on rate but not on timing. This suggests that there may exist timing-dependent intrinsic excitability rules, in particular for those that may specifically regulate dendritic compartments in a relatively local manner.

The existence of STDP of dendritic excitability is indirectly supported by several studies demonstrating changes in presynaptic intrinsic excitability concomitant with the induction of STDP. For example, Ganguly et al. (234) found that repeated spike pairings, consisting of a presynaptic spike evoked  $\sim 10$  ms before a postsynaptic spike in paired recordings, gave rise to both LTP of synaptic currents and long-term enhancement of presynaptic excitability, with a follow-up study demonstrating a corresponding decrease in presynaptic excitability induced with spike pairings of the opposite temporal order (419). These studies clearly demonstrate that induction of STDP can regulate intrinsic excitability, albeit on the presynaptic side of the synapse. On the postsynaptic side, the papers of Wang et al. (813), Xu et al. (854), Frick et al. (228) (Fig. 6), and Fan et al. (207) suggest that there may be corresponding STDP of dendritic excitability, since they demonstrate that the induction of synaptic plasticity using an STDP-like protocol can have direct effects on the intrinsic excitability of dendrites (sect. II, *D1* and *D2*). This possibility has recently received strong support from the work of Campanac and Debanne (108) (see sect. *IID2*), who have demonstrated bidirectional changes in dendritic integration of EPSPs following STDP protocols in CA1 pyramidal neurons. These changes were input-specific, suggesting that the underlying changes in dendritic excitability are likely to be local. We anticipate that much future work will address the mechanisms responsible for this crucial link between STDP and local changes in dendritic excitability.

### 4. Changes of dendritic excitability during development

The growth of dendritic trees during development is accompanied by dramatic changes in their excitability. For example, somatic input resistance decreases far more strongly than expected from the morphological changes alone (508, 882). This is due to a general increase in the densities of many types of channels ( $I_{Na}$ ,  $I_K$ ,  $I_{Ca}$ ,  $I_h$ ) during development (318, 447, 568, 630; for review, see Refs. 189, 638). Little is known how this general upregulation of channel densities is triggered, i.e., how much of it is due to an intrinsic genetic program in each cell or cell type, how much is dependent on pre- or postsynaptic activity, and how much is due to changes in neuromodulation.

Functionally, as input resistance decreases and cell capacitance increases due to dendritic growth, cells would be expected to generate less output for a given level of synaptic input; neuronal gain is reduced (243). However, as dendritic surface area increases during development, so do the number of synaptic inputs, and, with the assumption of constant synapse density, synaptic strength, and mean presynaptic activity levels, this increase in the number of synaptic inputs would largely compensate the decrease of input resistance due to dendritic growth. At the same time, a number of other changes are taking place, which tend to at least partially compensate each other's effect on overall excitability of the neuron. First, the somatic resting membrane potential becomes more depolarized, as does the voltage threshold for evoking  $Na^+$  APs in the axon. Second, somatic input resistance decreases due to additional leak and  $I_h$  channels, as does the threshold for evoking  $Ca^{2+}$  spikes in the dendrites, which in L5 pyramidal neurons can cause bursts of  $Na^+$  APs to be evoked in the axon. Finally, in perhaps the most important and sensitive balancing act,  $Na^+$  and  $K^+$  conductance densities in the axon and soma are upregulated in a concerted way that allows continuous generation of  $Na^+$  APs while their width markedly decreases, and their somatic amplitude increases with development (508, 882).

Therefore, while somatic input resistance markedly decreases, this does not lead to an overall decrease in excitability of the neuron. On the contrary, the appearance of local  $Ca^{2+}$  spikes in dendrites indicates that in a sense, dendrites become more excitable during development, and consequently neurons acquire firing patterns that are more complex (472, 508, 599, 882).  $Na^+$  APs become narrower and temporally more precise. Dendritic AP backpropagation becomes more dependent on dendritic voltage-gated conductances, and thus more susceptible to modulation (see sects. *IIIC* and *IIIE*).

The characteristics of a neuron such as its firing pattern,  $f/I$  curve, somatic AP waveform, or the spatial profile of AP backpropagation into dendrites are depen-

dent on neuron type and can even be considered to define it. Underlying these characteristics are the morphology of the neuron (sect. *II B3*) as well as the specific types and spatial distributions of different ion channels in its axon, soma and dendrites (sect. *II B4*). How do neurons “learn” to acquire those characteristics specific to their type and function in the network? Whatever the details of the regulatory and compensatory mechanisms involved, it is already clear that there are often multiple solutions to this problem. Different combinations of channel densities have been shown to generate very similar neuronal behavior in experiments (679, 761) and in simulations (12; for review, see Ref. 486). Given the multitude of mechanisms for the regulation of channels and different triggers for plasticity of intrinsic excitability, it is not too surprising that different neurons of the same type can attain the typical phenotype via different mechanisms.

In summary, during development, small neurons that are effectively represented by a single compartment become large, complicated structures that can accommodate multiple functional compartments (400, 606, 671, 674, 868, 882). These changes may lead to better pattern discrimination and more complex rules for mapping of synaptic input to neuronal output (see sect. *II, A* and *B* above, and sect. *II G* below) (514, 604, 667) as well as for synaptic plasticity (see sect. *III* below) (230, 413, 712).

### E. Differences Between Local and Global Regulation of Dendritic Excitability

Using a theta-burst pairing protocol in adult hippocampal CA1 pyramidal neurons, Frick et al. (228) described a localized increase in the amplitude of bAPs, accompanied by an increased AP-triggered  $\text{Ca}^{2+}$  influx in a  $\sim 100\text{-}\mu\text{m}$  stretch of dendrite around the stimulated synapses (Fig. 6). With the same pairing protocol, Fan et al. (207) found a global decrease in neuronal excitability, represented by a lower somatic input resistance and rightward shift of the  $f/I$  curve. The increase in local AP amplitude (228) was mediated by a hyperpolarizing shift in the inactivation curve of local A-type  $\text{K}^+$  currents in the dendrite receiving synaptic stimulation, while the reduction in somatic input resistance (207) was due to an upregulation of  $I_h$  in presumably a large part of the neuron. This example shows that the same plasticity protocol can trigger both local and global changes in dendritic excitability via divergent mechanisms. Interestingly, the full theta-burst protocol including synaptic input was required for the localized increase in AP backpropagation, whereas the postsynaptic APs alone were sufficient to trigger the upregulation of  $I_h$  and the decrease in somatic input resistance.

How local can changes in channel densities or properties induced by synaptic input be? They can be limited

to a single spine (370), thus rendering them highly input specific (cf. sect. *III A1*), in analogy with classical synaptic plasticity (sect. *I B*). But, even if changes in intrinsic properties are very spatially restricted (cf. Ref. 370), their impact may be quite nonlocal and may, depending on their location in the neuron, extend well beyond the region where regulation of dendritic conductances occurred (e.g., sect. *III A1*). Effects analogous to shunting inhibition on subthreshold synaptic potentials may be quite restricted in spatial extent (e.g., Ref. 435). However, boosting of bAPs by extra inward current, even if that current is very localized, may have rather nonlocal effects as the boosted AP continues to propagate actively, recruiting additional inward current along the way (747). Thus dendritic structure and excitability, as well as the type of signal to be modified, determine how local the effect of a change in local dendritic excitability can be.

This nonlocality has direct consequences for memory storage; nonlocality suggests that the storage capacity of intrinsic plasticity is less than that of synaptic plasticity, but perhaps it is inappropriate to focus on raw storage capacity in this case. Intrinsic plasticity might, for example, be used as a teacher signal for synaptic plasticity, in which case its own memory capacity is not what matters (334, 763). Using a computer model with an unsupervised learning rule for self-normalization, Stemmler and Koch (731) found that, by keeping the output firing rate normalized in a useful range, global intrinsic plasticity could help the neuron to be maximally informative about the different input stimuli that it has learned to represent. Local intrinsic plasticity, on the other hand, could apply such normalization at a more fine-grained level of dendritic subunits on parts of the dendritic tree or even individual dendritic branches (514, 604, 667), where it could also influence subsequent local intrinsic and synaptic plasticity. These possibilities will be discussed in the following sections. Regardless of how local intrinsic excitability changes are, it seems safe to conclude, however, that their effects can never be entirely input specific.

### F. Intrinsic Excitability Changes: Helping Homeostasis or Helping Hebb?

In section *I, A–C*, we discussed how Hebbian synaptic plasticity, a form of positive feedback, is one of the best candidate mechanisms for learning and memory (455). In section *I D*, on the other hand, we considered the need for negative-feedback mechanisms, such as synaptic scaling (791), to maintain stability and proper neuronal functioning. We subsequently discussed briefly (sect. *I E*) the evidence for global changes in intrinsic excitability as a mechanism for memory storage (877), and we touched on the observation that changes in intrinsic excitability can lead to both positive feedback (e.g., Ref. 17) or negative



feedback (e.g., Ref. 184). In section  $\Pi E$ , we also discussed Stemmler and Koch's model (731), which shows how unsupervised normalization of firing rates can maximize information encoded in neuronal firing rates. Here we ask the question: Are activity-dependent changes in intrinsic dendritic excitability likely to be the result of negative or positive feedback? In other words, do such dendritic changes contribute to homeostatic or to Hebbian-like mechanisms?

As discussed in section  $\Pi D2$ , LTP is sometimes associated with a lowered threshold for synaptically driven AP generation, a phenomenon termed E-S potentiation (7, 41, 76, 123, 161, 297, 821, 877). We also discussed the finding of Wang et al. (813) that LTP induction resulted in a long-lived increase in supralinearity of EPSP summation, as well as the findings of Frick et al. (228) and of Xu et al. (854), which demonstrate a similar upregulation of dendritic excitability with the induction of LTP. These changes in intrinsic excitability of the dendritic arbor would appear to contribute to Hebbian plasticity by providing an additional positive feedback, rather than negative stability-promoting feedback that underlies homeostasis of synaptic gain and of intrinsic excitability (sect.  $\Pi D$ ).

As mentioned previously in section  $\Pi D1$ , a later study from the Johnston lab, however, demonstrated a presumably stability-promoting form of plasticity of intrinsic excitability. Fan et al. (207) found a mechanism that relied on NMDA receptor activation and postsynaptic (but not presynaptic) firing. This form of plasticity would thus be induced simultaneously with LTP, but it would result in a negative-feedback loop through the global upregulation of the  $I_h$  current (also see sect.  $\Pi D2$ ). Similarly, LTD is accompanied by a downregulation of  $I_h$ , which thus also acts in a negative-feedback manner to maintain excitability (85).

Can any overarching organizing principles be identified? At first glance it appears that local changes in dendritic excitability go hand in hand with Hebbian plasticity and with positive-feedback loops, while global changes of dendritic excitability may be more involved in promoting stability and providing negative feedback. The problem with this view is that such local positive-feedback mechanisms are likely to spatially destabilize the dendritic tree, just as STDP and local dendritic spikes should destabilize the dendrites (249) (see sects.  $\Pi D$  and  $\Pi B2$ ). In addition, there are clearly several cases of cell-wide upregulation of intrinsic excitability due to activation of excitatory synaptic currents (e.g., Ref. 17) (see sects.  $\Pi E$  and  $\Pi D1$ ), but some of these results might be possible to interpret as negative feedback once the local neuronal circuitry is taken into account (877). Alternatively, there may be "an embarrassment of riches" regarding mechanisms involved in the plasticity of intrinsic excitability, just as there is for synaptic plasticity (477). Thus both positive- and negative-

feedback mechanisms may exist for the regulation of intrinsic excitability, which vary widely with cell type, brain region, induction protocol, age, and so on. Clearly this is a field where more studies are needed.

### G. Consequences of Changes in Dendritic Function for Neuronal Output

If dendritic mechanisms such as those described in section  $\Pi$ ,  $A$  and  $B$ , can be modulated by intrinsic plasticity mechanisms, so can the I/O functions of the neurons concerned. Here we list a few examples. First, changes in somatic input resistance will change the  $f/I$  curve of the neuron (207, 798, 799). Second, changes in the degree of summation of subthreshold EPSPs due to local dendritic modifications of  $I_h$  channels (813) will change the combinations of synaptic inputs that can generate spike output, as will the modulation of any other channel type that influences EPSP summation. Finally, several mechanisms have been described that modulate BAC firing in L5 pyramidal neurons (cf. sect.  $\Pi C$ ) (405). Each of them affects the nonlinear coupling between  $\text{Na}^+$  APs originating in the axon and  $\text{Ca}^{2+}$  spikes initiated in the dendrites and, therefore, the rules for transforming synaptic input into spike output. GABA<sub>B</sub> receptor-mediated modulation of dendritic  $\text{Ca}^{2+}$  channels effectively shuts down the BAC firing mechanism in L5 pyramidal neurons for hundreds of milliseconds (591). On a longer time scale, BAC firing is also modulated by changes in dendritic morphology (667) and by neuromodulators such as neuropeptide Y (W. F. Colmers and M. E. Larkum, unpublished data). The coupling between somatic and dendritic spike initiation sites, which underlies BAC firing (sect.  $\Pi C$ ; Fig. 9), is also likely to be changed by the modulation of other voltage-gated channels, such as  $I_h$  (64). Thus a large number of mechanisms are available by which intrinsic plasticity can change different aspects of the I/O functions of neurons.

### III. HOW DO DENDRITIC PROPERTIES AFFECT SYNAPTIC PLASTICITY?

In this section, we discuss how dendrites influence synaptic plasticity rules. The dendritic tree determines the electrical and chemical signals available at the synapse. Its morphology and its biophysics compartmentalize chemical and electrical signals, thus impacting the synapse specificity and cooperativity of synaptic learning rules (sect.  $\Pi A$ ). The biophysics of the dendritic arbor, e.g., the types and densities of voltage-gated ion channels, also provide for dendritic coincidence detection mechanisms that underlie the induction of some forms of plasticity (sect.  $\Pi B$ ). Distal dendritic regenerative  $\text{Ca}^{2+}$  bursts, a supralinear dendritic event with cell-wide repercussions, strongly impact both somatic spike output and

induce some forms of synaptic plasticity (sect. III C), whereas local dendritic spikes may be critical for rapid induction of synaptic plasticity, yet only have a minute effect on the soma membrane potential (sect. III D). The filtering and voltage dependence of dendrites render synaptic plasticity location-dependent (sect. III E). Such spatially skewed positive-feedback synaptic plasticity rules destabilize the distribution of synaptic efficacies in the dendritic tree, which makes it important that synapses are somehow normalized across dendritic space (sect. III F). Dendritic properties thus affect synaptic plasticity in multiple different ways. It is an oversimplification, therefore, to regard synaptic plasticity in isolation without its dendritic context (cf. sect. I A). Encouragingly, there has been a substantial improvement in recent years of our understanding of dendritic function and its contribution to synaptic plasticity rules.

### A. The Impact of Dendritic Compartmentalization on Synaptic Plasticity

Before we embark on a discussion of compartmentalization in dendrites (sect. III, A2 and A5), we need to first examine the complicated matter of the function of spines (sect. III A1). Spines cover many dendritic trees and exhibit a range of morphologies (215, 273, 502). While spines can be remarkably motile (154, 504, 570), they typically consist of an approximately micrometer-wide spine head and a narrower spine neck. Since the discovery of spines by Santiago Ramón y Cajal (for a historical review, see Ref. 235), the function of these enigmatic structures has been the subject of considerable debate. For example, spines are the target of the majority of excitatory synapses (86, 557), but why is this the case?

#### 1. A thorny issue: what is the point of spines?

What function do spines serve? In pyramidal neurons, spines probably serve in part to enhance the number of possible connections and, therefore, the potential for plasticity, between axons and dendrites (130, 734). Because synapse density is nearly maximal in cortical tissue (86), spines may also allow axons and dendrites to pursue cost-effective straight routes (762), although if this were the only reason for their existence, spines could equally well sit on axons as on dendrites. However, the induction of LTP can result in the growth of new spines (199, 480, 777), and spine growth appears to precede the formation of a new synapse (378). Perhaps all this makes sense since plasticity is typically induced on the postsynaptic side (73, 455) (sect. I, I–K) (although see Ref. 191). Even though the majority of cells possess spines (383), not all neurons do. In particular, interneurons tend not to have spines (150, 250, 346, 383, 398, 506, 579). Since some synapses form directly onto the dendritic shaft, even in

neurons that do possess spines (346), one has to conclude that the function of spines is probably not merely to connect the pre- to the postsynaptic side, at least not in all cell types. The hypothesis that spines only serve to connect thus seems unlikely (383).

Chang (121) suggested already in 1952 that spines might reduce synaptic strength through electrical attenuation of EPSPs. Rall and Rinzel, however, were the first to point out, in 1971, that altering spine neck resistance would be a way of changing the weight of a synapse (for a historical note, see Ref. 618). This is the “spine resistance hypothesis,” or the notion that the neck of the spine can significantly attenuate synaptic potentials (reviewed in Ref. 383). In fact, Bliss and Lømo (74) proposed that changes in spine structure could underlie LTP by reducing spine resistance.

However, the spine resistance hypothesis was later questioned. Electrical flow can be viewed similar to biochemical diffusion (sect. III A2 below), which means it is possible to use diffusion to estimate the electrical resistance of the spine neck (383, 557). Indeed, experimental measurements of dye diffusion across the spine neck (758) as well as electron-microscopic serial reconstructions combined with computer simulations (274, 275) gave relatively low estimates for the spine neck resistance, with an upper bound of 150 or 400 M $\Omega$  depending on the method. Although these approaches are somewhat indirect, low electrical resistance in the spine neck, at least in combination with relatively small synaptic conductances, suggests that changes in neck length cannot significantly alter synaptic weight (383), which makes spine resistance an implausible substrate for LTP and LTD.

Yuste and colleagues, however, have argued for strong voltage attenuation across the spine neck (31, 32, 781; although see Ref. 564). For example, they found that glutamate uncaging evokes EPSPs that are inversely correlated with spine neck length (32), although perhaps this is due to overly long and strong glutamate uncaging pulses that lead to unrealistically high synaptic conductances (compare, e.g., Ref. 551). High synaptic conductance means low spine head resistance and consequently greater attenuation of voltage across the spine neck resistance. In other words, only if the synaptic conductance is sufficiently high will the spine resistance appreciably reduce the synaptic driving force and consequently the somatic EPSP amplitude (383). This means the range of physiologically relevant synaptic conductances is critically important for the potential contribution of spine neck resistance to synaptic plasticity. Using voltage-sensitive dye imaging in neocortical neurons, Palmer and Stuart (583) estimated an average spine neck resistance of merely 170 M $\Omega$ , implying only the very tail end of the distribution of synaptic conductances (493) would be sufficiently large to allow for a noticeable voltage drop

across the spine. Interestingly, Bloodgood and Sabatini (77) found evidence for the sporadic high spine neck resistance in organotypic culture of CA1 neurons, occasionally approaching  $\sim 1 \text{ G}\Omega$  (cf. Ref. 758). In conclusion, the spine neck resistance hypothesis does not appear relevant for the expression of LTP and LTD (654).

Even though the balance of opinion is currently not in favor of the spine neck resistance hypothesis, spine morphology may still be altered during synaptic plasticity. It is, for example, well established that several parameters reflecting synapse size (274, 275, 502, 565, 597, 670, 739, 767, 768) are correlated with synaptic strength (although see Refs. 683, 810). Spine neck length (274), however, is not (although see Ref. 502). In addition, synaptic strengthening is at least under some circumstances associated with increased spine volume (387, 503, 573, 577, 587). Conversely, synapse weakening may evoke the opposite decrease in spine volume (573, 879). Although it appears not to be the case for Purkinje cells (683), it is fair to say that synapses generally grow and shrink with LTP and LTD (for a review, see Ref. 764). Presumably, spines grow in part because the postsynaptic density becomes larger as more AMPA receptors are being inserted after LTP induction (452, 482, 565) and perhaps also because molecular machinery such as ribosomes is transported into spines (576).

Nevertheless, the sole function of spines cannot be to provide space for receptor insertion during LTP. After all, there are plenty of examples of synapses without spines that undergo LTP (e.g., Refs. 23, 150, 398, 579; for a review, see Ref. 396). Still, there is probably some additional as yet unknown elusive structural role to spines, especially considering the fact that spines are incessantly and actively twitching (154, 504, 570). Interestingly, spine size is directly controlled during LTP and LTD through actin polymerization and depolymerization (573). Perhaps this structural change indirectly underlies synaptic plasticity, by providing a “scaffold of scaffolds” for various postsynaptic proteins that help anchor AMPA receptors, such as PSD-95 and Shank (361). In fact, actin polymerization does underlie the remodeling of postsynaptic density proteins (397). Larger spines also contain more polyribosomes (576), suggesting a connection with localized protein synthesis (see sect. IIIA2). Although the mechanistic details and functional implications of spine size change during plasticity still remain largely unknown, we conclude that these rapid morphological changes probably have little to do with altering the voltage drop across the spine neck, because spines are probably not well isolated electrically (see above and Refs. 77, 274, 286, 383, 583, 654, 758).

The spine also impacts the biophysics of the parent dendrite (618, 686, 781). To begin with, spines add a substantial amount of surface area to the dendritic arbor, which means that total capacitance and the electrotonic

length, as perceived from the somatic recording electrode, are increased (383). Similarly, the overall input resistance is decreased by the addition of spines. In fact, in multicompartmental computer models of reconstructed neurons, spines are sometimes accounted for simply by increasing dendritic membrane capacitance and conductances (305, 696, 712). The addition of spines therefore increases the impedance load posed by the dendritic tree on the soma, thus rendering AP backpropagation less reliable (802) (see sect. II B). Moreover, the addition of spines reduces the length constant, which diminishes the amplitude of EPSPs at the soma as well as the degree of spatial summation (336). This scenario changes, however, if spines contain active conductances (reviewed in Refs. 618, 686, 781), in which case spines may promote AP backpropagation (44, 336). Also, if spines are electrically isolated from the parent dendrite and at the same time contain voltage-dependent ion channels, spikes that are spatially confined to the spine may even be evoked (686). Indeed, hippocampal pyramidal neurons (78, 656, 685, 867), neocortical pyramidal neurons (552), as well as Purkinje cells (179) are known to contain VDCCs in spines. There is also evidence for  $\text{K}^+$  (78, 554) and  $\text{Na}^+$  channels in spines (642, 781). Recently, Bloodgood and Sabatini (78) estimated that synaptic input locally depolarizes the spine, along with its parent dendrite, several tens of millivolts relative to the soma. Their results demonstrate that synaptic stimulation can be enough to activate voltage-dependent ion channels in spines (cf. Ref. 552).

Finally, another possible function of spines is that they serve as biochemical compartments, which remain diffusively relatively isolated from the parent dendrite (252, 292, 383, 557, 758, 869, 871). As we shall see in the next section, this view is well supported, although there are also other ways than using spines to biochemically compartmentalize the dendrite (252, 292).

## 2. Biochemical compartmentalization by spines

As we discussed in section IB, LTP typically relies on postsynaptic  $\text{Ca}^{2+}$  influx as a signal for coincident pre- and postsynaptic activity. This also holds true for STDP (sect. IH). In particular, the postsynaptic spine appears to be the ideal location of the coincidence detection machinery (sect. I; Figs. 3 and 4). It contains the NMDA receptor as well as other  $\text{Ca}^{2+}$  sources (sect. IK) that are known to be involved in inducing synaptic plasticity (sect. I, B and H) as well as in determining its sign (sect. IJ).

Direct experimental measurements of diffusion in spines using fluorescence recovery after photobleaching (FRAP) or photoactivatable fluorophores have demonstrated that spines are chemically isolated (77, 286, 654, 758). In addition, the existence of active extrusion mechanisms in spines helps localize  $\text{Ca}^{2+}$  signals (449, 473, 655,

668). A spine may therefore constitute a protected micro-environment, for  $\text{Ca}^{2+}$ , cAMP, and other second messengers. These findings help explain why synaptic stimulation results in  $\text{Ca}^{2+}$  signals that are confined to the spine and that do not enter the parent dendrite (867) (Fig. 4), unless a large number of neighboring spines are activated concurrently (675). However, it is important to note that not all signaling molecules are restricted by the spine. Ras activation, for example, occurs both in the activated spine and in the parent dendrite, albeit to a lesser degree in the dendrite (860).

In addition, not only diffusion of second messengers may be restricted by the spine. The kinase CaMKII, which has been hypothesized to underlie memory storage (430, 432), is actively transported into spines after LTP induction, where it is incorporated into the postsynaptic density (577, 697). Similarly, a subset of mRNAs is specifically transported to the dendrites, and protein synthesis may occur right next to activated spines (50, 88, 751, 752). In particular, CaMKII $\alpha$  mRNA is targeted to dendrites, and this targeting is essential for CaMKII $\alpha$  translation, CaMKII $\alpha$  incorporation into the postsynaptic density, synaptic plasticity, and behavioral learning (525). Translation probably even takes place in spines (88). The Harris group (576) found that LTP induction gave rise to translocation of polyribosome from dendrites into spines, and Yoshimura et al. (863) discovered that short-range transportation of mRNAs into spines was facilitated by the actin-based motor myosin Va in a calcium-regulated manner. Although processes such as these do not depend on diffusion, but on active transport (525, 577, 697, 751, 752, 863), the physical compartmentalization provided by spines may endow neurons with a privileged environment that is important for controlling a subset of biochemical processes specific to synaptic plasticity.

Biochemical compartmentalization by spines depends on spine morphology. As mentioned earlier, spines are continuously motile and they undergo rapid and essentially incessant morphological changes (504, 570). Majewska et al. (474) have demonstrated that such changes in spine morphology also alter the parameters of diffusion. Elongation of the spine neck makes the spine more diffusively isolated from the parent dendrite, whereas shortening makes it less compartmentalized (cf. Ref. 388). Using a low-affinity  $\text{Ca}^{2+}$  indicator and two-photon laser scanning microscopy (2PLSM) imaging, Noguchi et al. (559) also showed that thin spine necks concentrate NMDA receptor-mediated  $\text{Ca}^{2+}$  signals in the spine more than do thick spine necks. Given the role of  $\text{Ca}^{2+}$  in synaptic plasticity (sect. 1J), such morphological changes may thus impact the balance between LTP and LTD and/or the threshold for induction of plasticity.

Interestingly, Bloodgood and Sabatini (77) discovered the converse form of regulation: synaptic plasticity impacts diffusion between the spine to the parent den-

drite. They found that long-term manipulation of activity, a protocol that is often used to induce homeostatic synaptic plasticity (789) (sect. 1D), resulted in altered diffusion across the spine neck (77). Intriguingly, Bloodgood and Sabatini (77) also showed that reduced diffusion could only be partially explained by, e.g., spine neck constriction, as spines of comparable morphologies still had different diffusive properties. There may thus exist additional mechanisms that control diffusion in spines. Findings such as the ones of Bloodgood and Sabatini (77) and of Noguchi et al. (559) suggest a possible reciprocal interaction between synaptic plasticity and biochemical compartmentalization. In other words, morphological concentration of spine  $\text{Ca}^{2+}$  may reduce the threshold for LTP (388, 559), while synaptic plasticity may alter the morphology (387, 503, 573, 577, 587, 879) and diffusive properties of spines (77), thereby resulting in a closed loop (compare sect. IV).

That a spine provides a biochemical compartment separate from its parent dendrite is thus well established. Santamaria et al. (662) recently described how the mere existence of spines also affects the overall diffusion inside the parent dendrite. To address this issue, the authors studied the cerebellar Purkinje cell, which has dendrites that are spiny as well as those that are not. They found that an inert fluorophore, fluorescein dextran, diffused more slowly in spiny dendrites. This, they discovered, was due to the repeated trapping inside spines, resulting in a phenomenon known as "anomalous diffusion." Intriguingly, Santamaria et al. (662) found that  $\text{Ca}^{2+}$  and  $\text{IP}_3$  molecules were differentially affected, with the latter being trapped and thereby slowed down significantly more. This intriguing property of spinous dendrites is likely to affect considerably the signaling transduction cascades that exist in spines as well as dendrites.

The biochemical compartmentalization by spines need not only act on molecules and proteins inside the cell, however. In a recent study, Ashby et al. (39) found that spine morphology also affected lateral diffusion in the cell membrane. Using fluorescence photobleaching of membrane-targeted green fluorescent protein, they discovered that lateral diffusion was restricted in the membrane of spines compared with neighboring spine-free dendritic regions. Furthermore, the degree to which lateral diffusion was diminished in spines correlated well with the spine neck restriction. Given that membrane-targeted green fluorescent protein is for the purposes of lateral diffusion presumably a biologically inert molecule in rat hippocampal cultures, the study of Ashby et al. (39) convincingly demonstrates that the morphology of spines directly compartmentalizes lateral diffusion in the cell membrane.

Yet, the morphology of spines does not alone determine their biochemical compartmentalization. The proteins themselves of the postsynaptic density may help

compartmentalize the spine through the juxtaposition and organization of  $\text{Ca}^{2+}$  sources, sensors, and effectors (reviewed in Ref. 42). In addition,  $\text{Ca}^{2+}$  is also actively pumped out of the spine and into the smooth endoplasmic reticulum (449, 473, 655, 668). This active process, along with constrained diffusion, explains why synaptic stimulation evokes more-or-less spine-restricted  $\text{Ca}^{2+}$  signals (42, 384, 552, 867). Bloodgood and Sabatini (78) recently described yet another mode of  $\text{Ca}^{2+}$  compartmentalization in hippocampal pyramidal CA1 spines. They found that synaptic stimulation sufficiently depolarizes spines to activate VDCCs (see previous section). The authors found that VDCC-mediated  $\text{Ca}^{2+}$  influx in turn triggers small-conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels, which further confines  $\text{Ca}^{2+}$  transients to the spine by rapidly repolarizing and closing NMDA receptors (also see Refs. 65, 554). In addition, Bloodgood and Sabatini (78) propose that this mechanism may form a novel substrate for LTP and LTD, since it suggests synaptic strength theoretically can be regulated independently of either AMPA receptor regulation (193, 368, 415, 424, 452, 482, 700, 812) or presynaptic changes in neurotransmitter release (82, 83, 132, 133, 321, 497, 556, 575, 624, 715, 716, 794).

### 3. Compartmentalization and synapse-specific plasticity

According to the Hebbian postulate (sect. 1A), only activated synapses ought to be potentiated. This synapse specificity of LTP (sect. 1B) is an important and central property that has been attributed to  $\text{Ca}^{2+}$  compartmentalization, in particular by spines (479). In this view, cooperativity (see sect. 1L for a definition) occurs because strong activation of a set of synaptic inputs sufficiently depolarizes an entire dendritic branch, whereas weak activation does not (73, 479). Although input specificity is not necessary for information storage per se (e.g., Ref. 877), it has been argued that synapse specificity increases the memory storage capacity of a neuron (471, 479). To a first approximation, it appears that LTP of the typical excitatory synapse is indeed input specific (73, 97, 479). There are some reports, however, showing that input specificity breaks down for synapses that are on the order of tens of microns apart, most likely due to lateral spread inside the dendritic branch of some messenger molecule (200, 277), or due to presynaptically expressed LTP mediated by nonspecific diffusion of a retrograde messenger (200, 680). Similar findings demonstrating spreading plasticity exist for cerebellar PF LTD (809). As with DSI and DSE (sect. 1F), presynaptically expressed LTP or LTD that relies on a freely diffusible retrograde messenger cannot be truly input-specific unless there exist a presynaptic mechanism that restricts plasticity to only those terminals that were repeatedly active during the induction of plasticity (61, 191, 716). Here, we shall avoid the topic of

retrograde messengers and presynaptically expressed plasticity and instead limit ourselves to breakdown of synapse specificity that arises on the postsynaptic side, in the dendrite. To begin with, we shall investigate the proposal that input specificity is due to  $\text{Ca}^{2+}$  compartmentalization by the dendritic spine (479).

As mentioned in section IIIA1, inhibitory interneurons tend not to have spines (150, 250, 346, 383, 398, 506, 579), at least not to the same degree that excitatory neurons do (86, 557). To examine the hypothesis that synapse specificity arises due to the localization of  $\text{Ca}^{2+}$  to the spine (180, 479), it therefore seems like a good starting point to examine long-term plasticity at synapses onto aspiny inhibitory interneurons. However, synaptic plasticity is not readily evoked at such synapses. To begin with, it appears that some of these synapse types are deficient in long-term plasticity altogether. Ouardouz et al. (579), for example, found that the same induction protocol resulted in LTP of excitatory inputs onto stratum oriens/alveus interneurons but not onto lacunosum moleculare interneurons in the CA1 region of the hippocampus. In fact, McBain et al. (506) argued in 1999 that inhibitory interneurons lack synaptic plasticity for a reason: they mainly serve to maintain oscillations and are in effect the brain's chronometers. In other words, it would appear nonsensical for these synapses to be plastic, when synaptic stasis would appear paramount for correct time keeping (although see Ref. 355). Kano (353), on the other hand, had pointed out in 1995 that plasticity at inhibitory synapses was overlooked, that it did in fact exist, and that it was synapse-specific. McBain et al. (506), however, proposed that the spine served as plasticity apparatus, perhaps by compartmentalizing and concentrating  $\text{Ca}^{2+}$  (180) (cf. sect. IIIA2), so without spines it is reasonable to expect little or no plasticity. Some of the discrepancies and disagreements no doubt boil down to technical issues. Lamsa et al. (398), for example, recently demonstrated that LTP of inputs onto aspiny stratum radiatum interneurons of the hippocampal CA1 region could only be reliably evoked when using the perforated-patch technique to ensure that the integrity of the postsynaptic intracellular milieu was preserved. Thus, the hypothesis that inhibitory interneurons are not plastic is incorrect; today there exist many studies demonstrating synaptic plasticity in inhibitory interneurons (23, 52, 127, 150, 371, 396, 398, 399, 517, 719, 722). Here we shall examine a subset of these as well as other studies in more detail, to see what we can learn about  $\text{Ca}^{2+}$  compartmentalization in dendrites and its impact, if any, on synaptic plasticity.

Cowan et al. (150) found LTP at synapses onto aspiny stratum pyramidale interneurons in the hippocampal CA1 region. The authors discovered that, upon the induction of LTP via tetanization, either LTP or LTD of the control pathway was evoked. This heterosynaptic plasticity, whether LTP or LTD, could be blocked by internal  $\text{Ca}^{2+}$

chelation, suggesting it was due to the induction protocol and not some unspecific rundown or run-up of the untetrazined control pathway. Furthermore, the authors verified that they could evoke pathway-specific plasticity at inputs onto spiny pyramidal neurons. This study would thus seem to suggest that input specificity is indeed lost at synapses onto spiny neurons.

On the other hand, Nishiyama et al. (558) found that, although hippocampal CA3-CA1 LTP is input specific, partial NMDA receptor blockade transforms LTP into LTD. In addition, this led to a breakdown of input specificity so that heterosynaptic LTD was also evoked (also see sect. 1K). Nishiyama et al. (558) found that spine RyR receptors control homosynaptic long-term plasticity, whereas IP<sub>3</sub> receptors regulate heterosynaptic LTD (558). Intuitively, this makes good sense, given the respective spine and dendrite localization of these two receptor types. However, the physiological relevance of these results has been questioned (845), since Nishiyama et al. (558) induced long-term plasticity with K<sup>+</sup> channels blocked by internal Cs<sup>+</sup>. K<sup>+</sup> channel activation normally regulates AP backpropagation (303) (sect. 1B1) and thus normally prevents massive Ca<sup>2+</sup> influx that may have led to CICR in the study of Nishiyama et al. (558). Regardless, since the CA1 pyramidal neuronal type is obviously spiny, these results suggest that spines per se do not render plasticity input specific. Rather, input specificity is actively brought about through some downstream signaling mechanism.

Indeed, Miyata et al. (531) also found a critical role in synaptic plasticity for internal stores that are specifically located in the spines of cerebellar Purkinje cells. In the cerebellum, PF LTD is evoked by repeated pairing of CF activation at the end of PF bursts. This combination evokes supralinear spine Ca<sup>2+</sup> responses, which in turn rely on mGluRs and IP<sub>3</sub>-sensitive internal Ca<sup>2+</sup> stores (216, 765, 808; cf. sect. 1K). However, the IP<sub>3</sub>-sensitive internal stores are absent from the Purkinje cell spines of the mutant mice and rats that Miyata et al. (531) investigated, because these animals carried a spontaneous mutation in the myosin Va motor protein that presumably normally drives IP<sub>3</sub>-sensitive stores into spines. In the mutant animals, PF-triggered and IP<sub>3</sub>-mediated spine Ca<sup>2+</sup> signals were not comparable to those of control animals, nor could PF LTD be evoked. Yet, IP<sub>3</sub>-sensitive internal stores were still present in the dendritic shaft of mutant Purkinje cells, approximately one micron from the PF spines. If, however, spine Ca<sup>2+</sup> levels were artificially brought to PF-CF pairing levels by the photolysis of a caged compound, PF LTD was rescued in mutant animals. In conclusion, although dendritic compartmentalization is obviously critical for properly functioning synaptic plasticity, the role of spines is probably not only to concentrate Ca<sup>2+</sup>, but also to house specific components of a complex molecular machinery.

Furthermore, when Lamsa et al. (398) (see above) examined LTP at synapses onto hippocampal CA1 aspiny stratum radiatum interneurons, they found it was indeed pathway specific. Although the pathway specificity concept determines the synapse specificity issue with a spatial resolution that is much too poor to resolve spines or even individual dendritic branches (cf. Refs. 200, 277), this study clearly demonstrates that spines are not necessary for LTP or for input specificity.

In agreement, Soler-Llavina and Sabatini (722) examined LTD at PF synapses onto cerebellar stellate cells, an aspiny inhibitory interneuron type, and found that plasticity was in fact input specific, at least on a spatial scale of tens of microns. They also investigated Ca<sup>2+</sup> diffusion in the postsynaptic dendrite using 2PLSM of a Ca<sup>2+</sup>-sensitive dye and discovered that it was severely restricted due to interactions with dendritic molecules such as parvalbumin. Interestingly, synaptically evoked Ca<sup>2+</sup> transients mediated by Ca<sup>2+</sup>-permeable AMPA receptors were limited to a region extending only a micron or so on either side of the synapse. This finding is particularly striking, as the PF-evoked Ca<sup>2+</sup> signals of Soler-Llavina and Sabatini (722) were very long-lived compared with the Ca<sup>2+</sup>-permeable AMPA receptor-mediated Ca<sup>2+</sup> transients that Goldberg et al. (250) had found earlier in dendrites of aspiny neocortical interneurons. Soler-Llavina and Sabatini (722) demonstrated that the main reason is a nearly 100-fold retardation of diffusion rates compared with the aspiny neocortical interneuron. Interestingly, Goldberg et al. (250) had also discovered very spatially restricted Ca<sup>2+</sup> transients. In the aspiny neocortical interneuron, however, Goldberg et al. (250) revealed that this was largely attributable to the rapid kinetics of Ca<sup>2+</sup>-permeable AMPA receptors along with a Na<sup>+</sup>/Ca<sup>2+</sup> exchanger that efficiently pumps out Ca<sup>2+</sup>. Although Goldberg et al. (250) did not examine plasticity, the spatial degree of Ca<sup>2+</sup> compartmentalization in aspiny neocortical interneurons shows a striking resemblance to that of cerebellar stellate cells (722), even if the underlying mechanisms are quite distinct.

In another elegant study, Kaiser et al. (346) investigated Ca<sup>2+</sup> transients evoked at unitary connections between neocortical L2/3 excitatory pyramidal neurons and somatostatin-positive bitufted interneurons. Although this inhibitory interneuronal type is spiny, the spine density is considerably lower and also more variable than that of L2/3 pyramidal neurons. Yet, most of the connections that Kaiser et al. (346) found were on the dendritic shaft. Perhaps consistently with this observation, synaptically evoked Ca<sup>2+</sup> responses extended several microns on either side of the synapse itself, almost 10-fold larger than the typical spine. Although the authors did not examine LTP at inputs onto the dendritic shaft of this interneuronal type, it is tempting to guess that, if it exists at all, it is at best input specific on a spatial scale of ~10 μm.

To conclude, these studies demonstrate that  $\text{Ca}^{2+}$  compartmentalization using spines is not necessary for LTP or for synapse specificity, nor are spines sufficient for input specificity. In addition, it is clear that one must exercise caution when using the concept of input specificity, as it is a matter of gradation. Furthermore, the degree of input specificity may depend on the details of the induction protocol (276). Given the perhaps surprising absence of input specificity on a spatial scale of tens of microns for hippocampal CA1 LTP (200, 277, 680) and for cerebellar PF LTD (809), it is not particularly surprising that synapse specificity in aspiny cerebellar stellate cells (722) may break down for inputs that are immediately next to each other. It would be interesting to know the impact of such relatively mild breakdown of synapse specificity on the upper limit of the information storage capacity of neuron (801). Perhaps there are also advantages to less than perfect synapse specificity. For example, maybe nearby synapses would be primed by the resulting local heterosynaptic LTP, leading to dendritically clustered storage of similar memory traces (compare with Refs. 515, 605, 606). Conversely, it is conceivable that local heterosynaptic LTD, a spatially shrunken version of what Royer and Paré found in intercalated neurons of the amygdala (647), would help stabilize the dendritic tree (249). Regardless, a principle that emerges from this section is that  $\text{Ca}^{2+}$  compartmentalization is indeed important for pathway-specific synaptic plasticity. This biochemical dendritic compartmentalization can be achieved in different ways in different cell types, with both spines and restricted diffusion in dendrites being effective (though over different spatial scales).

#### 4. Realms smaller than a spine: $\text{Ca}^{2+}$ domains

As we saw in the previous section, biochemical compartmentalization can in fact occur without spines (e.g., Refs. 250, 346, 722). In addition, spines are not necessarily even small enough to explain some properties of plasticity. In section 1J, we discussed how in the consensus view, the sign of plasticity is largely determined by the level and duration of postsynaptic  $\text{Ca}^{2+}$  influx; brief, strong  $\text{Ca}^{2+}$  elevations evoke LTP, whereas weaker and relatively more prolonged  $\text{Ca}^{2+}$  transients result in LTD. A recent and very interesting study by Nevian and Sakmann (553), however, found in neocortical L2/3 neurons that both the temporal and the quantitative match between dynamics of spine  $\text{Ca}^{2+}$  responses and the outcome of synaptic plasticity is in actuality quite poor, suggesting that bulk  $\text{Ca}^{2+}$  dynamics in the spine head alone does not determine plasticity. Similar types of criticism have been made before (292, 550; although see Ref. 857). In particular, Helmchen (292) has pointed out that it seems paradoxical that

NMDA receptor-mediated spine  $\text{Ca}^{2+}$  influx can result in LTP, when bAP-mediated spine  $\text{Ca}^{2+}$  accumulations of a similar order of magnitude do not evoke plasticity.

A comparable conundrum has existed on the presynaptic side: at the squid giant synapse, correlations between amplitudes of presynaptic  $\text{Ca}^{2+}$  transients and postsynaptic response amplitudes were sometimes weak and exhibited poorly understood nonlinearities (122, 522, 710). Llinás and colleagues helped resolve this puzzle by showing, through simulations (710), direct measurements of presynaptic  $\text{Ca}^{2+}$  currents (441), and  $\text{Ca}^{2+}$ -sensitive protein fluorescence imaging (443), that  $\text{Ca}^{2+}$  transients could reach concentrations of 100–300  $\mu\text{M}$  immediately adjacent to the open channels of presynaptic VDCCs. With a spatial extent of only 10–100 nm, these  $\text{Ca}^{2+}$  micro- or nanodomains, which may exist for a millisecond or even less, activate the  $\text{Ca}^{2+}$  sensors that only 200  $\mu\text{s}$  after the presynaptic spike elicit neurotransmitter release (42, 547, 677, 710). If such  $\text{Ca}^{2+}$  microdomains exist postsynaptically in the spine and if they indeed trigger the relevant  $\text{Ca}^{2+}$  sensors for LTP and LTD, they may help explain discrepancies such as those found by Nevian and Sakmann (553), since even 2PLSM  $\text{Ca}^{2+}$  imaging would not sufficiently resolve in space or time such  $\text{Ca}^{2+}$  domains. Indeed, there are reports suggesting the existence of postsynaptic  $\text{Ca}^{2+}$  domains at VDCCs (65, 72, 174, 175) and NMDA receptors (271). In fact, Hoffman and Sakmann (304) concluded, using a theta-burst protocol and internal  $\text{Ca}^{2+}$  chelation with either BAPTA or EGTA, that there is a mere 30- to 350-nm distance between the  $\text{Ca}^{2+}$  source and the  $\text{Ca}^{2+}$  sensor for hippocampal synaptic potentiation, which is strongly indicative of a postsynaptic  $\text{Ca}^{2+}$  microdomain in LTP. Thus, in this view, it is not simply  $[\text{Ca}^{2+}]_i$  that determines the sign and amplitude of plasticity; it is also the precise location of  $\text{Ca}^{2+}$  transients.

Another possible and quite straightforward explanation for some of Nevian and Sakmann's (553) results as well as for Helmchen's (292) paradox (see above), however, is simply that spine  $\text{Ca}^{2+}$  transients do not alone control the magnitude and sign of synaptic plasticity. After all, several recent studies point in the direction of considerably more convoluted mechanisms for LTP and LTD induction. In addition to the typical need for NMDA receptor activation (sect. 1K), these mechanisms include the need for, e.g., mGluR activation (61, 553),  $\text{Ca}^{2+}$  release from internal stores (558), or transsynaptic signaling (61, 191, 658, 703, 714, 716). What is clear is that the simple version of the  $\text{Ca}^{2+}$  hypothesis for LTP and LTD (sect. 1J) cannot account for all the available results, as demonstrated in particular by Nevian and Sakmann (553) as well as others, and that further studies are needed to determine how it should be modified, or whether it should be abandoned.

### 5. Biochemical compartmentalization of dendrites and cooperativity

Thus far, we have discussed how spines form biochemically but probably not electrically isolated compartments (sect. III, A1 and A2) and how this may impact plasticity (sect. IIIA3). In addition, we discussed how there exist  $\text{Ca}^{2+}$  compartments that are actually smaller than the confines of a spine, which may help explain some puzzling properties of synaptic plasticity (sect. IIIA4). Here, we shall investigate briefly how the dendrite is biochemically compartmentalized on a relatively larger scale, on the order of tens and hundreds of microns, and how this may impact synaptic plasticity. This discussion is not exhaustive; it leaves out e.g.,  $\text{Ca}^{2+}$  waves (543–545). For a detailed review, we refer the reader to Augustine et al. (42).

In 1992, Jaffe et al. (332) published one of the first studies to investigate dendritic  $\text{Ca}^{2+}$  influx in hippocampal CA1 pyramidal neurons. As subsequent studies would show in CA1 (728) as well as neocortical L5 neurons (495, 748), decrementally backpropagating APs recruit VDCCs to evoke  $\text{Ca}^{2+}$  transients in the apical dendrite that diminish with distance from the soma (sect. II B1). In fact, at the distal portions of the CA1 apical dendrite, Jaffe et al. (332) observed little or no signal. Yet, under conditions resulting in strong dendritic depolarization, distal dendritic  $\text{Ca}^{2+}$  signals were larger than those closer to the cell soma. Jaffe et al. (332) thus demonstrated two important features of both the CA1 and L5 pyramidal neurons: unreliable backpropagation of APs compartmentalizes the soma from the distal dendrite (sect. II B1), and the distal dendrite is capable of local regenerative events (sect. II B2). As a corollary, dendritic  $\text{Ca}^{2+}$  transients are compartmentalized into two regions: one proximal to the soma and another one that is more distal. Thus the chemical compartmentalization was a consequence of compartmentalization of electrical signals (see sect. IIIA6).

Jaffe et al. (332) correctly speculated that their observations would have important functional consequences for synaptic plasticity. Indeed, Golding et al. (256) demonstrated 10 years later that plasticity of distal dendritic CA1 synapses does not depend on bAPs, but on local dendritic spikes, whereas more proximal synapses can rely on bAPs for the induction of LTP (sects. II B2 and III D). Although Golding et al. (256) focused on the biophysics and on the regenerative voltage-dependent events underlying the phenomenology, it remains possible that the  $\text{Ca}^{2+}$  transients resulting from local dendritic spikes form an important contribution to the resultant plasticity rules. The form of cooperativity (sect. I L) at distal inputs described by Golding et al. (256) may thus not only be defined by local dendritic spikes, but also by the resulting

$\text{Ca}^{2+}$  influx and downstream signaling mechanisms. Since LTP depends on sufficiently high  $\text{Ca}^{2+}$  levels (sect. I, J and K), the cooperativity of LTP that is restricted to the distal inputs may in effect be a result of the distal dendritic compartmentalization produced by the local spike itself.

Indeed, a similar scenario may also exist in the apical dendrite of neocortical L5 neurons, since these neurons too have distal regenerative  $\text{Ca}^{2+}$  spikes (674), a form of a cooperativity that is restricted to distal inputs (712) and that may be triggered by the local regenerative zone (413) (cf. sect. II B). Again, that the membrane biophysics and voltage-dependent regenerative events are critical is clear, but the potential involvement of the resulting  $\text{Ca}^{2+}$  signals has not been investigated in detail. Also, it remains unknown if such distal dendritic regenerative events underlie the form of cooperativity described in classical papers on LTP (51, 372, 417, 509; see sect. I L). Furthermore, given the results of Nevian et al. (551) (cf. sect. II B1) showing that the L5 basal dendrites are remarkably similar to “shrunk versions” of the much longer apical dendrite in terms of reliability of AP backpropagation, it is tempting to speculate that a similar form of cooperativity exists in L5 basal dendrites (717).

Purkinje cells, however, are quite dissimilar to the CA1 and the L5 neurons in terms of reliability of AP backpropagation (sect. II B1) (Fig. 5). AP backpropagation in this cell type is strikingly poor, failing completely and propagating passively within a few tens of microns from the soma (742). Although the low densities of dendritic  $\text{Na}^+$  channels contribute (sect. II B1), dendritic morphology is the critical factor (sect. II B3). However, voltage-dependent dendritic  $\text{Ca}^{2+}$  channels allow local regenerative events in Purkinje cell dendrites, which trigger spatially restricted  $\text{Ca}^{2+}$  transients (196). Although Eilers et al. (196) dubbed these subthreshold since there were no somatic APs, they may have been suprathreshold to local dendritic spikes (sect. II B2), as has been found by others (e.g., Refs. 620, 808). That locally restricted  $\text{Ca}^{2+}$  signals such as these underlie a form of unspecific heterosynaptic LTD has been demonstrated (809) (sect. IIIA3); it would be interesting to know if there is a corresponding cooperativity effect in cerebellar PF LTD. Marcaggi and Attwell (484) recently made a closely related observation; they demonstrated that DSE of PFs (sect. I F) only occurs if spatially clustered PFs are recruited. Although this phenomenon does not constitute a form of cooperativity in the classical definition (sect. I L), such a mechanism of spatially defined cooperation may act in cerebellar PF LTD as well. Considering the recent report by Safo and Regehr (658), which demonstrates that PF LTD, like DSE and DSI (sect. I F), requires endocannabinoid signaling, this is not implausible.

To conclude, the role of supralinear dendritic  $\text{Ca}^{2+}$  signals in cooperativity, if any, is at present unclear. It is, however, not far-fetched to suspect a direct link between



the massive  $\text{Ca}^{2+}$  influx generated by such supralinearities and the resulting synaptic plasticity (sect. I, *I–K*), but few studies to date have directly attempted to address this possible link.

### 6. Electrical compartmentalization of dendrites

This section aims to demonstrate how the main features of dendritic excitability can be harnessed to provide mechanisms for regulating the induction of synaptic plasticity. As described in section *II B*, the dendritic morphology of many types of neurons, acting in concert with nonuniform spatial distributions of various voltage- and calcium-dependent conductances, provides space for linear and nonlinear interactions among different synapses or different groups of synapses, and between synaptic input and neuronal output. The strong voltage attenuation from individual dendritic branches to the rest of the dendritic tree limits the spatial scale on which subthreshold electrical interactions between synapses can occur. Dendritic geometry can thus determine the number and hierarchical arrangement of functional compartments in the neuron at the subthreshold level (328, 382, 615). However, electrical compartmentalization at the subthreshold level also influences the rules for compartmentalization at the suprathreshold level (450, 604, 606, 615). These rules, in turn, determine the grouping of synapses that can undergo cooperative synaptic plasticity mediated by dendritic spikes (256, 310, 515, 605, 626) (see sect. III, *C* and *D*) or synaptic plasticity mediated by backpropagating APs (see sect. III, *B* and *E*).

Electrical compartmentalization tends to operate on a larger spatial scale and faster time scale than chemical compartmentalization. The most global electrical signal in the typical dendritic tree is the bAP, which can inform within milliseconds a large number of inputs that threshold was reached, an AP was fired, and that information was transmitted via the axon. However, as seen in section *II B1*, the reliability of backpropagation varies widely between cell types (Fig. 5). In addition, it is modulated by ongoing activity in the network as well as by intrinsic plasticity mechanisms. Depending on where spikes are initiated and on which ionic conductances are involved, the spatial extent of dendritic spikes varies considerably. For  $\text{Ca}^{2+}$  spikes in the main apical dendrite of L5 pyramidal neurons, a large fraction of the dendritic tree is involved (674). For nonpropagating NMDA spikes in the basal dendrites of these cells, as little as a single dendritic branch is depolarized (606, 671). Single spines act as chemical but probably not as electrical compartments, since the spine neck resistance is small compared with the membrane resistance of the spine, even during activation of a synapse on the spine head (583, 758).

## B. Backpropagating Action Potentials as Triggers for Plasticity

The evidence for the existence of an NMDA receptor-dependent coincidence detector in the spine is overwhelming and generally accepted (Fig. 3 and sect. *II D*). In addition, the active properties of dendrites provide additional mechanisms for coincidence detection which permit individual dendritic branches, or even the entire dendritic arbor, to act as coincidence detectors in Hebbian plasticity (468, 747). Using a few examples, we outline below how such dendritically based coincidence detection can be brought about mechanistically. To understand how this may happen, let us take an AP-centric view and follow the AP as it invades the dendritic arbor.

Our starting point is in the axon, where the bAP is typically initiated (138, 288, 386, 682, 729, 743). It then spreads into the soma and then into the dendritic arbor (sect. *II B1*), where it may provide one of the two components needed to trigger the spine coincidence detector (sect. *II D*), the other component arising from the synaptic input. As detailed in section *II B1*, however, the efficacy of AP backpropagation spans a wide range in different neuronal types (Fig. 5) (287, 745, 802). In particular, AP backpropagation in neocortical L5 and hippocampal CA1 pyramidal neurons is of an efficacy intermediate (Fig. 5) to the two opposite extremes of the cerebellar Purkinje cells (442, 742) and the substantia nigra dopaminergic neuron (287, 745). One could say that the L5 and the CA1 pyramidal cell types are just on the cusp of unreliable AP backpropagation (Fig. 5), because AP backpropagation in these cell morphologies is relatively sensitive to changes in the distribution of dendritic ion channels (254, 302, 745, 802). This means that the bAP will under certain circumstances fail to invade the distal dendrites of both neocortical L5 pyramidal (406, 747) and hippocampal CA1 neurons (254, 728). Coincident presynaptic activity and postsynaptic spiking may thus fail to trigger the spine coincidence detector at a distal synapse, since failing bAPs may not sufficiently depolarize distal NMDA receptors (Fig. 3). Seemingly paradoxically, conditions that may appear to satisfy the Hebbian postulate, such as high-frequency correlated pre- and postsynaptic firing in STDP (712, 717), may thus fail to induce LTP.

Because AP backpropagation into the distal dendrites of L5 and CA1 neurons is on the verge of being reliable, the bAP not only carries information to the synapse about whether the postsynaptic cell fired or not. In addition, the bAP provides the synapse with contextual information regarding the conditions that promoted reliable AP backpropagation. What these exact conditions are and what they tell the synapse depend on the type of neuron. Johnston and colleagues (303), for example, discovered that in hippocampal CA1 pyramidal neurons, the spike typically fails to invade distal dendrites chiefly be-

cause there is a steep somatodendritic gradient of  $I_A$  that renders AP backpropagation inefficient. Without this  $K^+$  channel gradient, backpropagation would be far more robust, as dendritic  $Na^+$  channel densities are in fact comparable to those of the soma (468, 469). These dendritic  $I_A$  channels, however, are rapidly inactivated by moderate depolarization near resting membrane potential (Fig. 7A), which means that appropriately timed EPSPs of sufficient amplitude can briefly inactivate  $I_A$  channels and thereby rescue AP backpropagation into apical and radial oblique dendrites (236, 303, 520). These dendritic  $I_A$  channels can therefore be viewed as part of a “plasticity gating mechanism,” with appropriately timed dendritic depolarization of sufficient amplitude being the key to boosting bAPs and enabling LTP (303, 342, 468, 520, 816).

Neocortical L5 neurons possess a similar AP boosting mechanism (Fig. 7B) (747). AP backpropagation into distal dendrites is also insecure in L5 neurons (406, 747, 835), even though dendritic  $I_A$  density is much lower in L5 neurons than in CA1 pyramidal cells (57, 389). Rather, the lack of reliable AP backpropagation into the distal dendrites of neocortical L5 neurons is probably due to the combination of insufficiently high densities of dendritic voltage-gated  $Na^+$  conductances (748) and the branched dendritic morphology (802). In distal dendrites exhibiting strongly attenuated backpropagating APs, pairing EPSPs with bAPs trigger a highly supralinear boosting of the bAP

(747). The timing relationship required for the coincidence detection is similar to that for STDP resulting from EPSP-AP pairing in the same neurons. Interestingly, this coincidence detection mechanism relies on recruitment of voltage-gated  $Na^+$  channels (747). The subthreshold depolarization recruits additional voltage-gated  $Na^+$  channels, which results in more reliable AP backpropagation (Fig. 7B) (747). It should be noted that a similar contribution of voltage-gated  $Na^+$  channels to the  $I_A$ -dependent plasticity gating mechanism of Johnston et al. (303) is difficult to exclude.

We have recently found evidence that such AP amplification may underlie a cooperative dendritic switch for distal inputs onto neocortical L5 neurons (712). Using paired recordings of L2/3 and L5 neurons, we discovered a progressive gradient between LTP and LTD as the distance of the synaptic contacts from the soma increased (Fig. 8). At synaptic inputs far from the soma, cooperativity among synapses or direct dendritic depolarization switched plasticity between LTD and LTP (Fig. 8C) by boosting backpropagation of APs (Fig. 8, A and B). This demonstrates that the sign of plasticity is regulated by the spread of the bAP to the synapse. Presumably, this is because failing bAPs do not unblock NMDA receptors to allow sufficient amounts of synaptic  $Ca^{2+}$  influx to induce LTP, but amplified bAPs do (cf. sect. 1J). Importantly, dendritic depolarization boosts bAPs across the distal

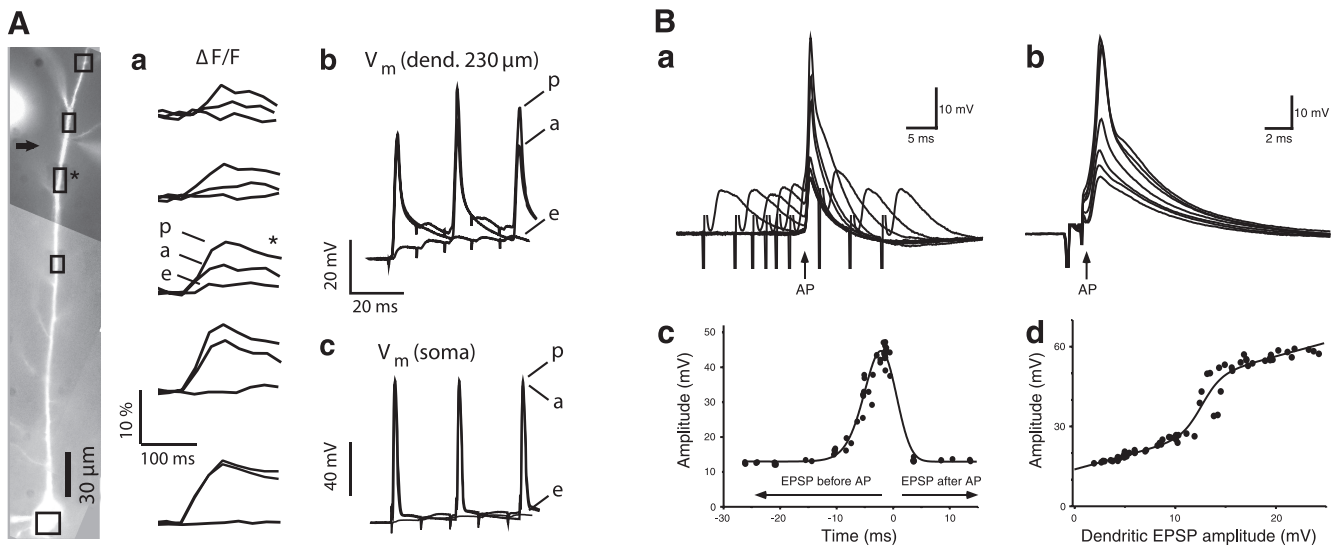


FIG. 7. The dendritic tree can act as a coincidence detector in synaptic plasticity. *A*: in CA1 pyramidal neurons, pairing (“p”) of somatic APs (“a”) and excitatory postsynaptic potentials (EPSPs) (“e”) results in supralinear  $Ca^{2+}$  (*Aa*) and voltage signals (*Ab*) throughout large portions of the apical dendrite, although no such voltage supralinearity is observed at the soma (*Ac*) (468). This form of dendritic supralinear summation comes about because EPSPs depolarize and inactivate transient A-type  $K^+$  channels, which renders AP backpropagation more reliable (303, 520). The net result is thus a dendritic detector of coincident pre- and postsynaptic activity. [From Magee and Johnston (468), with permission from AAAS.] *B*: a similar type of supralinear dendritic summation exists in neocortical L5 neurons (747). Here, coincidence of an appropriately timed EPSP (*a*, *c*) of sufficient amplitude (*b*, *d*) and a decrementally backpropagating AP results in AP amplification. This mechanism does not rely on A-type  $K^+$  channel inactivation, however, but on depolarization-dependent recruitment of voltage-gated  $Na^+$  channels (747). Recent results suggest that a mechanism similar to, or maybe even identical to, AP amplification underlies a dendritic switch between LTD and LTP in the apical dendrite of neocortical L5 neurons (712) (also see Fig. 8). [From Stuart and Häusser (747), with permission from Macmillan Publishers Ltd, copyright 2001.]

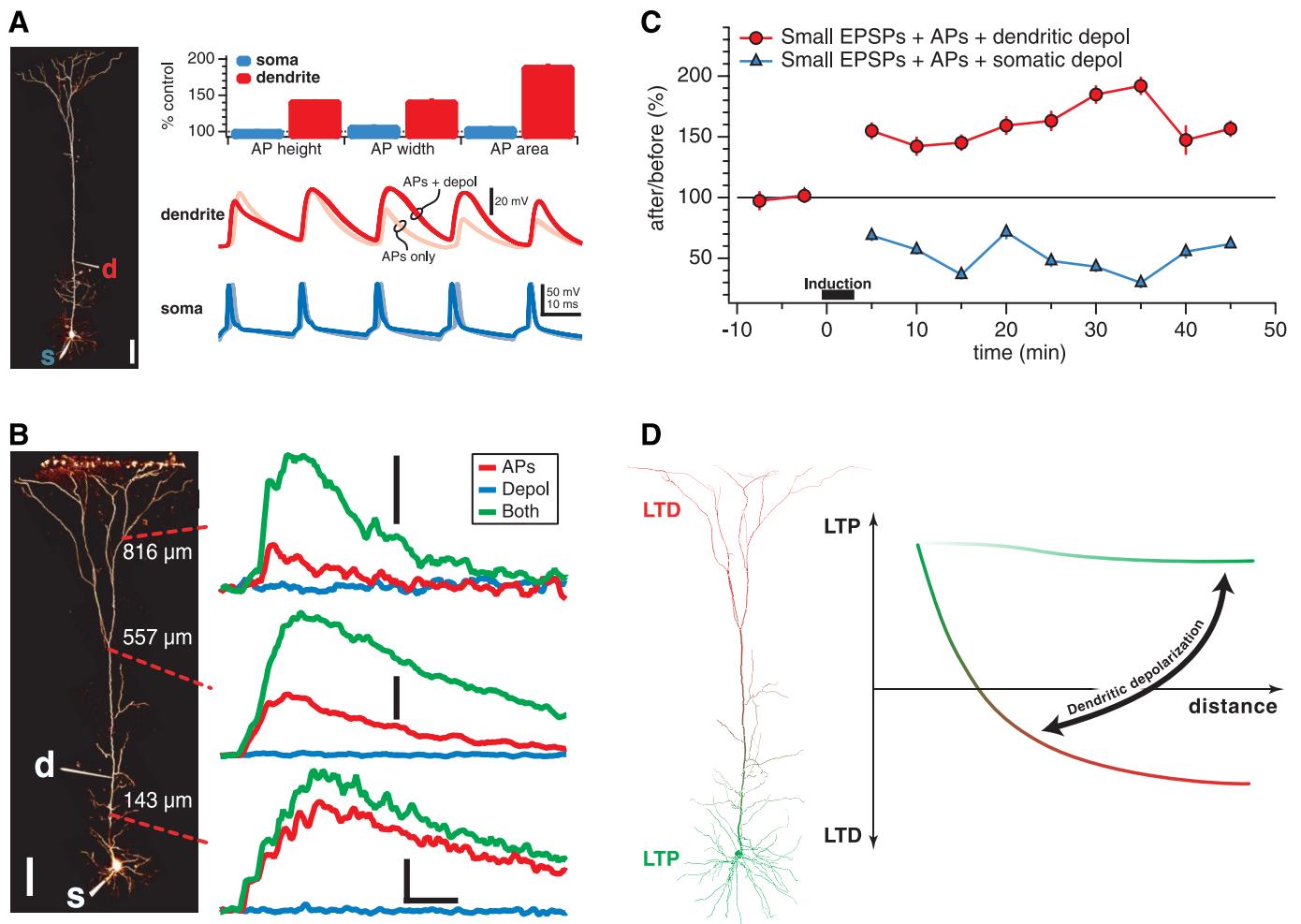


FIG. 8. A dendritic switch controls the sign of plasticity of distal inputs onto neocortical L5 neurons. *A*: a dual somatic and dendritic recording demonstrates how the amplitude and width of backpropagating APs are boosted by subthreshold dendritic depolarization (712). Scale bar: 100  $\mu$ m. *B*: the same recording configuration in a Ca<sup>2+</sup>-sensitive-dye-filled neuron reveals how subthreshold dendritic depolarization results in an analogous boosting of AP-mediated Ca<sup>2+</sup> responses. Scale bars: 100  $\mu$ m, 20% dG/R, 50 ms. *C*: the same type of dendritic depolarization that boosts bAPs and concomitant Ca<sup>2+</sup> responses also results in LTP (red circles). The corresponding somatic subthreshold depolarization, however, results in LTD (blue triangles). *D*: relatively high-frequency AP-EPSP pairing evokes robust LTP of proximal inputs (green) (494, 717), but the same protocol results in LTD of distal inputs (red) (712). This graded transition from LTP to LTD is due to decremental AP backpropagation. If the apical dendrite is depolarized sufficiently, however, the bAP is boosted and the plasticity of distal inputs is “switched” from LTD to LTP. This depolarization can be provided by other synaptic inputs, resulting in a form of cooperativity for LTP of distal inputs. Importantly, this dendritic switch for distal plasticity can be triggered by relatively proximal depolarization. This novel learning rule thus permits not only within-layer but also cross-layer associative learning and may also enable the gating of plasticity by cortical states (223, 224, 818). [From Sjöström and Häusser (712), with permission from Elsevier.]

dendritic tree (Fig. 8*B*), which means that relatively proximal inputs can “gate” LTP at distal inputs (Fig. 8*D*), a novel learning rule that works as a “dendritic switch” for synaptic plasticity. This switch can therefore enable associative learning not only within but also across neocortical layers. It has previously been demonstrated that proximal inputs onto L5 neurons are mostly from neighboring neocortical cells (493, 774), whereas the most distal layer 1 inputs onto the apical tuft originate from higher cortical regions (117, 145, 339, 873). The types of information carried by these two pathways are therefore distinct from one another, suggesting that this learning

rule may also enable the neocortical storage of associations between different types of information.

Interestingly, Waters and Helmchen (818) have demonstrated that backpropagating APs in neocortical L2/3 neurons evoke relatively larger dendritic Ca<sup>2+</sup> transients during cortical up-states, suggesting that the reliability of AP backpropagation can be switched by the network state (although see Ref. 62). The results of Waters and Helmchen (818) are thus consistent with a different and more general role for our “dendritic switch” of cortical plasticity (Fig. 8*D*), one in which cortical states more globally toggle plasticity between LTP and LTD by controlling AP

backpropagation in entire assemblies of neurons simultaneously (cf. Refs. 403, 712). The fact that AP backpropagation in L5 neurons is right on the cusp of reliability (cf. Fig. 5 and sect. *nBI*) is from this point of view not a bug but a feature, as it adds flexibility by providing a mechanistic basis for the “dendritic switch” (712). In fact, our dendritic switch (712) combined with the results of Waters and Helmchen (818) may explain earlier *in vitro* findings of Frégnac et al. (223). Frégnac et al. (223) discovered that, in cat and guinea pig neocortical acute slices, repeated pairing of extracellular stimulation in the white matter with intracellular depolarization in L2/3 neurons evoked potentiation. The same pairing but with intracellular hyperpolarization, however, resulted in depression (223; cf. Refs. 36, 47). These findings may in turn help explain previous results that Frégnac et al. obtained using *in vivo* cat recordings (224), showing that repeated pairing of a preferred visual stimulation with direct visual cortical depolarization triggered a functional strengthening of the preferred response. Pairing with cortical hyperpolarization, on the other hand, resulted in functional weakening (224). The dendritic switch (712) (Fig. 8*D*), if active in the neurons of Frégnac et al. (223, 224), would promote LTP during relatively global postsynaptic depolarization while favoring LTD during hyperpolarization. However, an alternative explanation to the functional changes of Frégnac et al. (224) could be made based on STDP and the altered postsynaptic spike timings that presumably result from depolarization or hyperpolarization of cortical neurons (sect. *iH*), thus illustrating how consistency of a phenomenological observation with any one cellular learning rule does not prove a causal relationship (cf. consistency vs. necessity in sect. *iH*).

In both the CA1 case and the L5 case described above, the entire distal dendritic arbor of a CA1 or L5 pyramidal neuron acts as a coincidence detector in LTP. However, as opposed to the NMDA receptor-based spine coincidence detector that senses the coincidence of glutamate and depolarization (sect. *iI*), this dendritic mechanism detects the conjunction of a sufficiently large depolarization and a bAP. This mechanism is therefore relatively global. What general purpose does this dendritic coincidence detector serve? We already touched on the possibility that it may enable cross-layer associative learning. Since this mechanism filters out EPSP-AP pairings involving weak synapses, one additional function might be to allow only the potentiation of synapses that carry reliable information. Weak synapses not only have larger coefficient of variation due to the probabilistic nature of neurotransmitter release (493, 725), they may also just barely make a signal above the background noise. Such weak inputs may therefore carry less dependable information. Another purpose of the dendritic coincidence detector might be to ensure that spurious pairings of background EPSPs and APs are filtered out and do not

result in LTP. Otherwise unspecific potentiation of inputs with significantly higher than average background frequency could occur, even though these would not necessarily carry more information than those of low frequency.

This type of dendritic coincidence detection, however, does not have to be global. As demonstrated by Magee et al. (see Fig. 2 in Ref. 464), it can also be restricted to a single dendritic branch. In these experiments, bAP amplification similar to the  $I_A$ -dependent boosting described in CA1 neurons (303, 468, 520) was restricted to individual dendritic branches provided the source of the depolarization was at that same branch. Although a clear involvement of this more local, branch-specific bAP depolarization coincidence detection in LTP remains to be conclusively demonstrated, one advantage of such a branch-specific coincidence detector in LTP would be that synapses that carry related information are potentiated together. Theoretical studies have demonstrated that this kind of clustering of synapses may increase the information storage capacity of individual neurons (515, 605). It will be interesting to see if branch-specific cooperative LTP due to this type of mechanism indeed exists and, if so, if it is a more general phenomenon that occurs in, e.g., L5 pyramidal neurons as well.

The entire distal dendrite thus can perform an ongoing computation that determines which postsynaptic activity patterns are allowed to affect synaptic strength at distal synapses. In CA1 and L5 pyramidal neurons, this is done by gating bAPs so that the spine coincidence detector (Fig. 3) does not experience irrelevant bAPs. One of the two components needed to trigger the NMDA receptor-based spine coincidence detector, the depolarization, is thus restricted from distal synapses by the dendrite itself in an activity-dependent manner.

### C. $\text{Ca}^{2+}$ Bursts and Distal Regenerative Events in Plasticity

As the bAP invades the dendritic tree, it relies heavily on voltage-gated  $\text{Na}^+$  channels for propagation (468, 728, 748). The reliability of AP backpropagation is not static, however. It depends on the history of previous activity of the neuron. For example, during a train of spikes, APs occurring towards the end of the train will attenuate substantially more than the first spike in the apical dendrite of hippocampal CA1 pyramidal cells (728) and neocortical L5 neurons (743, 835). In CA1, this effect is due to the inactivation and slow recovery of dendritic fast sodium channels (141, 345). This slow inactivation is more marked in the more distal dendrites (519), and these sodium channels recover from inactivation faster at hyperpolarized membrane potentials (519, 728). In conclusion, AP backpropagation depends in a complicated man-

ner on the resting membrane potential and previous history of spiking (also see sect. II B).

As the frequency is increased, the last spikes in a high-frequency burst will decay relatively more compared with the first spike. This is true for both CA1 and L5 pyramidal cells (400, 728) although not for L2/3 pyramidal neurons (403), in which bAP amplitude remains relatively constant. As the frequency is increased further, however, bAPs look dramatically different in L5 (400) and in L2/3 (403) pyramidal neurons. Above a critical frequency, the bAPs are significantly amplified, due to strong distal dendritic regenerative events (400, 403) (sect. II B2). Typically, in a L5 pyramidal cell from a 4-wk-old rat, the critical frequency at resting membrane potential is  $\sim 100$  Hz (400). The critical frequency also seems to be set by the hyperpolarization-activated nonselective cation current,  $I_h$  (64). This critical frequency varies from cell to cell, raising the intriguing possibility that it too is plastic. In addition, distal dendritic regenerative events also depend on animal age (882) and the degree of dendritic depolarization (400, 835). Dendritic depolarization decreases the critical frequency dramatically, however, so the combination of high-frequency spike trains and dendritic depolarization readily produces distal dendritic regenerative events (400, 403, 835).

Failing bAPs are a prerequisite for the type of global dendritic coincidence detection mechanism that we described in section III B. If bAPs above a critical frequency do not actually fail but instead result in a distal dendritic regenerative event (sect. II B2), then one might surmise that the coincidence of EPSPs and AP bursts above the critical frequency should result in strong NMDA receptor-mediated  $\text{Ca}^{2+}$  influx and LTP at distal synapses. Letzkus et al. (413) investigated this possibility experimentally and found that suprathreshold spike trains indeed had an impact on distal synaptic plasticity (Fig. 9B). The sign of plasticity, however, depended on the relative timing of distal EPSPs and the high-frequency AP burst. If the EPSP preceded the AP burst by 10 ms, LTD was obtained. With the opposite temporal order, however, LTP was induced. The temporal requirements of this form of STDP, however, depended strongly on synapse location in the dendritic tree, a finding that we will revisit in section III E.

In an earlier study, Larkum et al. (405) found that sufficiently strong dendritic depolarization in coincidence with a single somatically evoked AP results in a dramatic burst of APs, termed a BAC (see Fig. 9) (405). This BAC spike is probably due to a distal dendritic regenerative event that is sufficiently strong to evoke additional somatic APs. So far, nobody has explicitly investigated the role, if any, of BAC firing in synaptic plasticity. It is however quite likely that the suprathreshold frequency AP bursts that Letzkus et al. (413) employ in their experiments correspond to the BAC spikes of Larkum et al. (405). Given the global nature of the BAC spike and the

large  $\text{Ca}^{2+}$  influx that it must entail, it appears likely that BAC spikes do impact plasticity.

#### D. Local Dendritic Spikes and Synaptic Plasticity

In the section III B, we discussed how global dendritic spikes act as coincidence detectors in plasticity: supralinear summation of somatically generated APs and incoming EPSPs results in a dendritic spike that is widespread in the distal dendrites (468, 712). Similarly, we reviewed in section III C how the production of distal dendritic regenerative events also can result in synaptic plasticity (256, 413). It is not clear, however, that synaptic plasticity requires dendritic spikes of such global character. In fact, some argue that somatically initiated APs are not necessary for synaptic plasticity under realistic circumstances (but see Refs. 412, 433). Given the NMDA receptor involvement in LTP, it is perhaps not so strange that postsynaptic spikes in and of themselves are not required for hippocampal LTP; depolarization sufficient to unblock NMDA receptors is likely to induce plasticity, regardless of its source (264, 265, 359, 509). The more important issue, however, is whether somatic APs typically are involved in plasticity under in vivo conditions, or if local dendritic spikes are the dominating triggering factor. No study has addressed this issue directly.

Local dendritic spikes were first described in Purkinje cells (440, 442) (sect. II B2). Here, relatively strong PF activation results in spatially restricted  $\text{Ca}^{2+}$  transients that are largely mediated by VDCCs (95, 276, 530). Hippocampal CA1 and neocortical L5 pyramidal neurons are also capable of producing local spikes in the distal apical dendrites (25, 848). In CA1 and L5 neurons, however, dendritic spikes are mediated by voltage-gated  $\text{Na}^+$  (255, 681, 684, 743) as well as  $\text{Ca}^{2+}$  channels (369, 674, 681). Similar local dendritic spikes have been discovered in L2/3 neurons (403). In general, dendritic spikes propagate decrementally to the soma and typically do not evoke axonal output (442, 674). In particular, for the purposes of the discussion in this section, we simply define local dendritic spikes as spatially restricted without concomitant somatic APs. However, we note that local dendritic spikes may be modulated by activity to generate axonal spike output under certain circumstances (335), thereby becoming nonlocal.

In pyramidal cells, local spikes are not a phenomenon exclusive to distal apical dendrites: Schiller and colleagues demonstrated that relatively strong activation of NMDA receptors on the basal dendrites of neocortical L5 pyramids results in local regenerative events, termed NMDA spikes (Figs. 10 and 11) (551, 671, 672). These findings are naturally of particular interest, given the involvement of NMDA receptors in synaptic plasticity. Similar local spikes were subsequently identified in the ter-

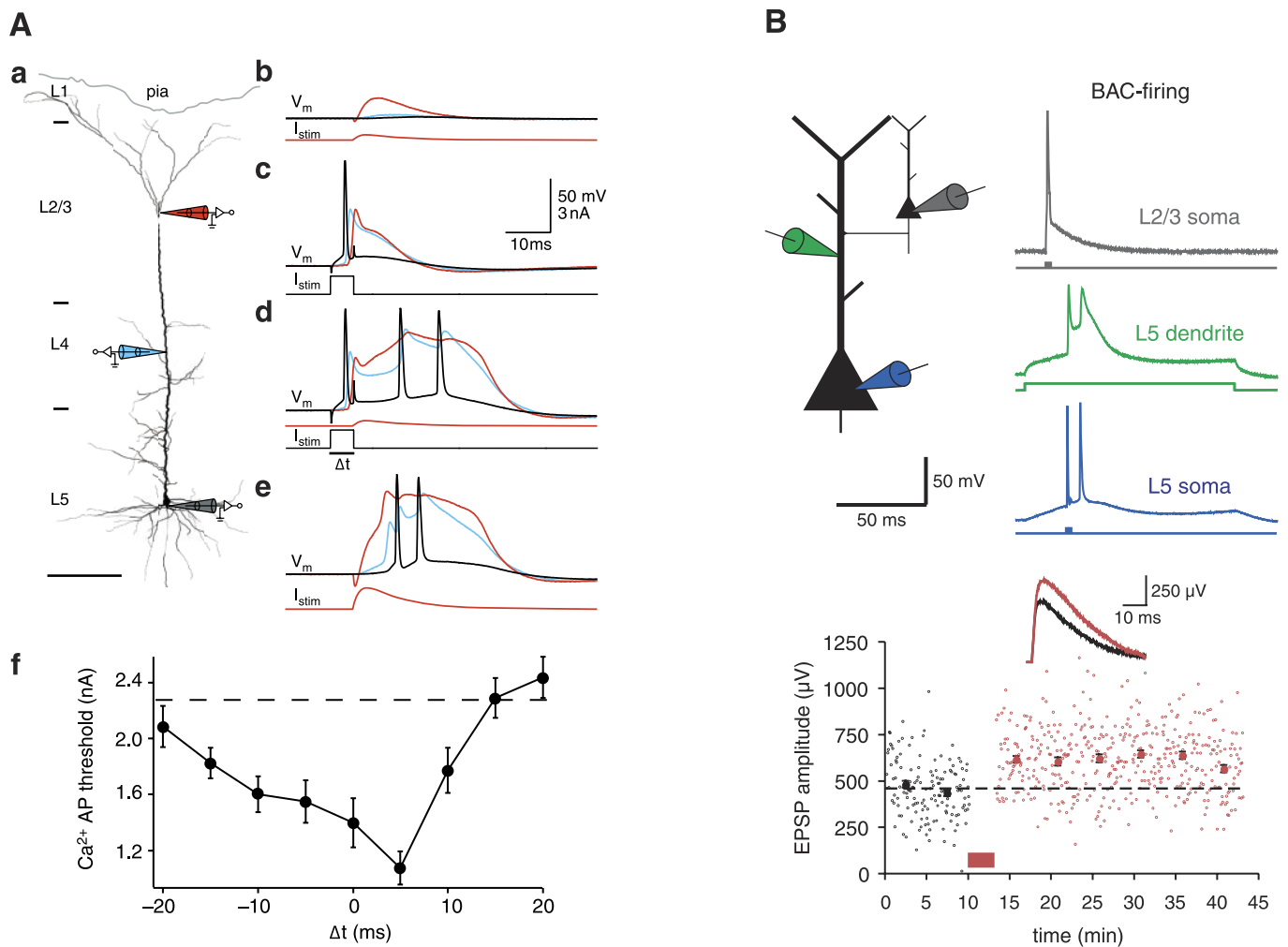


FIG. 9. bAP-evoked Ca<sup>2+</sup> spiking (BAC) firing in L5 pyramidal cells may result in LTP. *A*: BAC firing was first described by Larkum et al. (405). *a*: Schematic illustration of recording configuration, consisting of a somatic and dual dendritic recording. *b*: Distal dendritic current injection of an artificial EPSP (red) alone evokes a weak somatic response (black). *c*: Somatic current injection (black step) results in a somatic AP (black) that backpropagates decrementally into the apical dendrite (blue and red). *d*: Coincident activation of a somatic AP (black) and a distal artificial EPSP (red) results in a burst of APs, or BAC firing. This mechanism can therefore act as a coincidence detector. *e*: Sufficiently strong distal dendritic current injection on its own also evokes BAC firing. *f*: The temporal requirements for BAC firing due to coincident somatic and distal dendritic activation (bAP leading artificial EPSP for positive timings). Minimal threshold for BAC spike (left axis) illustrates optimal timing at  $\Delta t = +5$  ms. [From Larkum et al. (405), with permission from Macmillan Publishers Ltd, copyright 1999.] *B*: recent results obtained by Letzkus et al. (413) indicate that distal synaptic inputs that are appropriately timed with BAC firing undergo LTP. *Top*: schematic illustration of the recording configuration, showing a dual dendritic and somatic L5 neuronal recording in conjunction with a L2/3 recording. The L2/3 cell is synaptically connected to the L5 neuron. *Bottom*: pairing of L2/3 input with BAC firing in L5 cell results in LTP. [From Letzkus et al. (413), with permission from the Society for Neuroscience, copyright 2006.]

minimal segments of apical dendrites of CA1 neurons, although these rely not only on NMDA receptors but also on VDCCs (824). Local dendritic spikes are thus a widespread phenomenon.

The involvement of local dendritic spikes in synaptic plasticity, however, is less well studied. In CA1 neurons, nevertheless, Golding et al. (256) found that somatically initiated APs are not necessary for LTP of distal synapses. If distal synaptic activation was sufficiently strong, LTP was evoked regardless of whether the soma was spiking or not. This does of course not mean that somatic spikes

cannot possibly affect distal plasticity (e.g., if sufficiently boosted; see Refs. 303, 712, 747), but it does strongly argue for the involvement of local dendritic spikes in LTP of distal inputs onto CA1 neurons (Fig. 11*B*). Golding et al. (256) found that no distal LTP was evoked below the threshold for distal dendritic spikes. This means that this dendritic mechanism also results in a novel form of cooperativity (sect. 1*L*), which may facilitate associative learning (cf. sect. 1*J*). However, just like Hebbian plasticity is intrinsically unstable (788, 790), forms of LTP which rely on local dendritic spikes will destabilize the synaptic

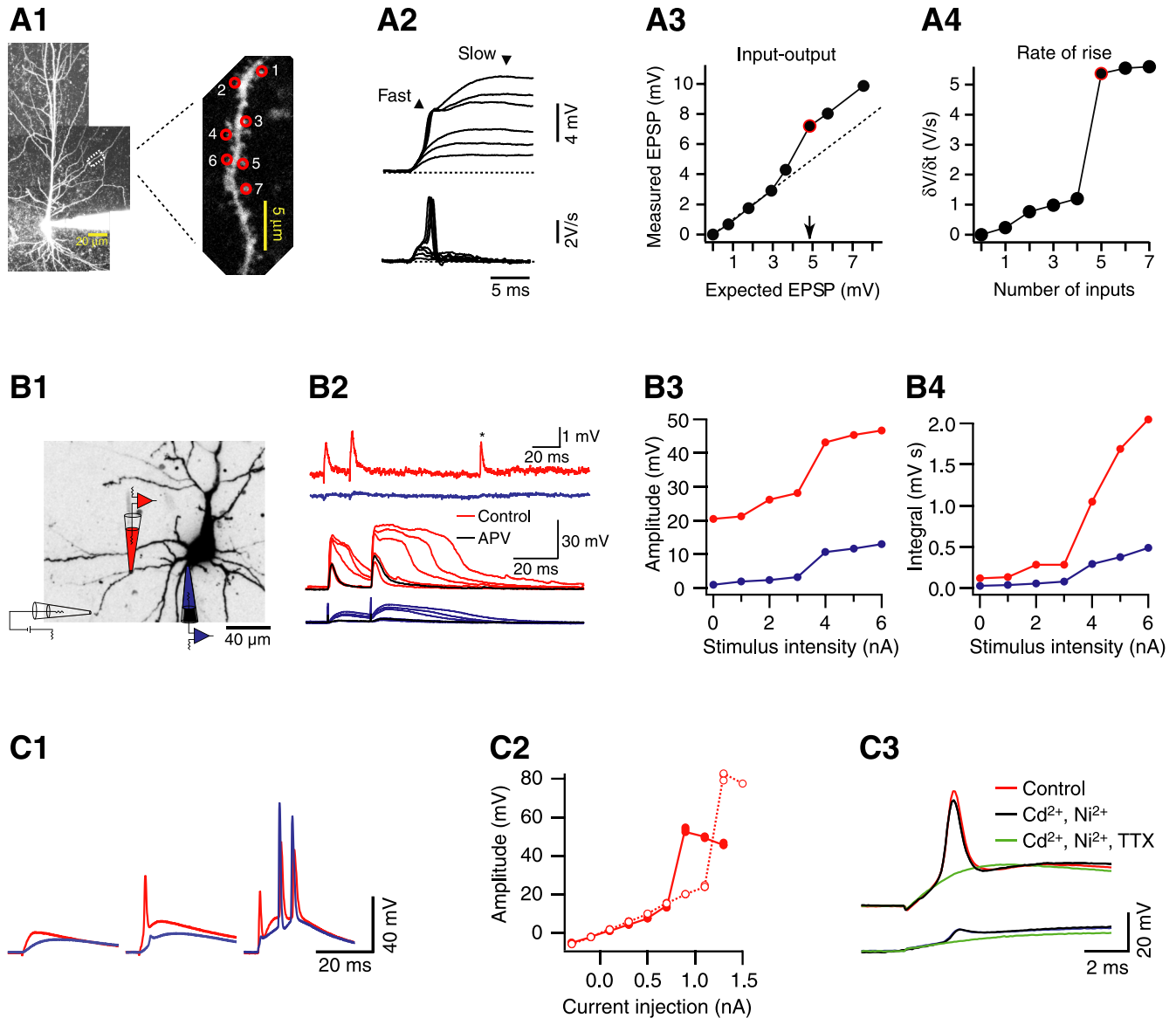


FIG. 10. Examples of local dendritic spikes. *A*: local spikes in radial oblique dendrites of CA1 pyramidal neurons evoked by multi-site two-photon uncaging of glutamate (450). *A1*: two-photon image of a CA1 pyramidal neuron (*left*) and single scan image showing seven spines selected for two-photon uncaging of glutamate. *A2*: somatic EPSPs evoked by glutamate uncaging on another oblique branch (*top*) and time derivatives of the same traces (*bottom*). Note that the supralinear responses consist of a fast and a slow component. *A3*: measured somatic EPSP amplitudes during simultaneous uncaging at multiple spines versus the arithmetic sum of somatic EPSPs measured when the same spines are activated separately. Note the deviation of the measured EPSP from the expected EPSP at threshold of the dendritic spike (arrow). *A4*: maximum time derivative of the somatic EPSP versus the number of spines stimulated. *B*: NMDA spikes evoked by synaptic stimulation, directly recorded in basal dendrites of L5 pyramidal neurons (551). *B1*: two-photon image of the basal dendrites of a L5 pyramidal neuron. Blue, somatic patch pipette; red, dendritic pipette; white, extracellular stimulation electrode. *B2*: *top traces*, two pulses separated by 20 ms were delivered to the stimulation electrode. Dendritic responses (red) show similarity to spontaneously occurring EPSP (asterisk); *bottom traces*, increasing the stimulus intensity leads to a NMDA spike. *B3*: amplitude of the dendritic (red) and somatic (blue) response as a function of stimulus intensity. *B4*: time integral of the dendritic (red) and somatic (blue) response as a function of stimulus intensity. Note the discontinuity of the slope at threshold for the dendritic spike. *C1*: local sodium spikes evoked by current injection, directly recorded in basal dendrites of L5 pyramidal neurons (551); same colors as in *B*. *C2*: current-voltage relationship of the local dendritic spike (solid circles) and the bAP (open circles). *C3*: pharmacology of dendritic spikes evoked by dendritic current injection in basal dendrites. *Top*: spikes were little affected by 50  $\mu\text{M}$  cadmium and 500  $\mu\text{M}$  nickel (black), but blocked by 1  $\mu\text{M}$  TTX, indicating that they are mediated predominantly by  $\text{Na}^+$  channels. *Bottom*: corresponding somatic recordings. [A1–A4 from Losonczy and Magee (450), with permission from Elsevier; B1–B4 and C1–C3 from Nevian et al. (551), with permission from Macmillan Publishers Ltd, copyright 2007.]

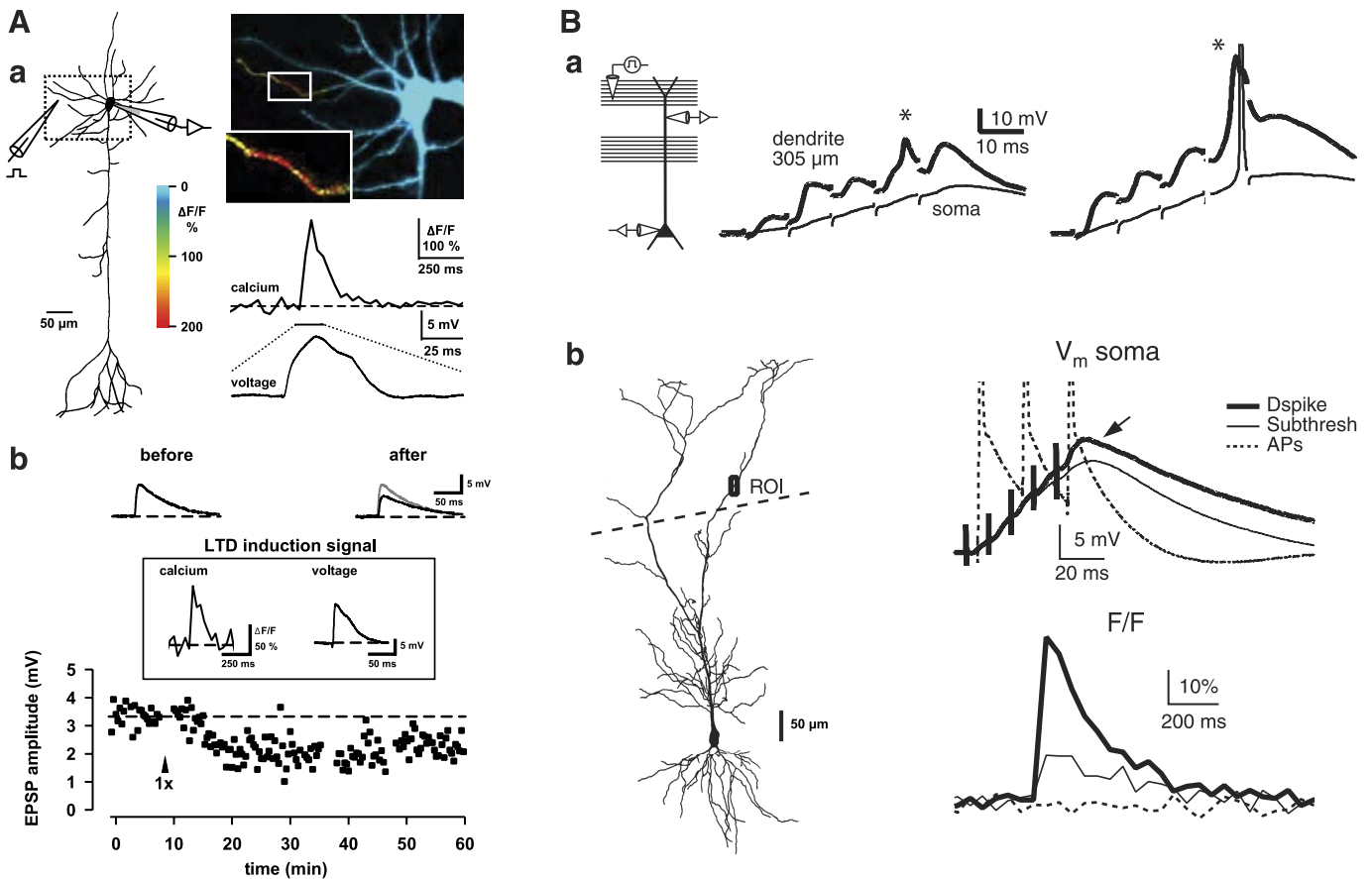


FIG. 11. Local dendritic spikes can induce synaptic plasticity. *A*: local dendritic spikes in the absence of somatic APs result in rapid induction of LTD in neocortical L5 neurons (308–310). *a*: The spikes evoked by this induction protocol are reminiscent of NMDA spikes (Fig. 10) (671, 672), in that large NMDA-receptor-dependent local calcium and voltage transients are evoked during induction (*inset right, top and bottom*). *b*: A single local dendritic spike is sufficient to produce saturating amounts of LTD (310). *Inset box* shows calcium and voltage transients during induction. [From Holthoff et al. (310), with permission from Blackwell Publishing.] *B*: distal dendritic spikes are necessary for a form of cooperative LTP in CA1 neurons (256). *a*: High-frequency stimulation of distal dendritic (stratum lacunosum-moleculare) inputs results in dendritic spikes (asterisks) that occasionally propagate to the soma. *b*: Local dendritic spikes (thick line, *inset top right*), but not weak stimulation (thin line) or somatic APs (dashed line), were associated with supralinear  $\text{Ca}^{2+}$  responses (*inset bottom right*) and LTP (not shown) (256). ROI (*left*) denotes region of interest for  $\text{Ca}^{2+}$  imaging (*bottom right*). [From Golding et al. (256), with permission from Macmillan Publishers Ltd, copyright 2002.]

weight distribution of the dendritic tree (249). How a neuron defends its dendritic arbor against such local runaway excitation remains mysterious.

Are local dendritic spikes also involved in LTD? Holthoff et al. (310) found evidence that something very similar to NMDA spikes (671) reliably results in LTD (Fig. 11A). Intriguingly, this form of LTD required only a single shot to be induced (310), although this observation may depend on brain region and/or experimental protocol (259, 320). Regardless, this one-shot synaptic learning rule is in stark contrast to classical LTD induction protocols, which typically involves hundreds of repetitions (374) (sect. 1G). Similarly, it has been demonstrated in visual cortical L2/3 neurons that at least 10 spike-EPSP pairings are required to yield noticeable levels of timing-dependent LTD (231). This suggests that the type of LTD that Holthoff et al. describe (310) depends on other mechanisms than the classical and timing-dependent forms of

LTD. Given its remarkably rapid induction (Fig. 11A), it is tempting to speculate that the putatively NMDA spike-mediated LTD of Holthoff et al. (310) serves other computational purposes than previously studied forms of LTD. One possibility is that rapid LTD is necessary for rapid, “one-shot” learning. Nevertheless, the existence of a specific function for this type of neocortical LTD remains an open question.

Interestingly, a recent study by Remy and Spruston (626) revealed the corresponding form of single-shot LTP, although in hippocampal CA1 neurons. This type of LTP required only one rapid burst of presynaptic activity (also see Ref. 317), and, like Holthoff’s neocortical one-shot LTD (310), depended critically on relatively local dendritic spikes. In Remy and Spruston’s study (626), these dendritic spikes forward propagated decrementally to the soma in the form of spikelets, and this form of LTP was partially antagonized by NMDA receptor and L-type  $\text{Ca}^{2+}$



channel blockers. The relatively large EPSPs that Remy and Spruston used in their study (626) would seem to suggest that several dozens of presynaptic CA3 pyramidal neurons would have to be simultaneously activated in vivo with quite high temporal precision, but this is in fact not an unlikely situation during, for example, hippocampal sharp waves (348). Remy and Spruston's one-shot LTP (626) thus potentially constitutes a biologically relevant, very rapid, and purely dendritic computation that results in information storage entirely in the absence of axonal spike output.

The involvement of local dendritic spikes in long-term plasticity is not restricted to neocortex and hippocampus. In the cerebellum, LTD of PF synapses onto Purkinje cells is classically evoked by repeated simultaneous PF and CF activation (326). It is possible, however, to induce PF LTD in the absence of CF activation, by substituting postsynaptic depolarization for the CF-induced complex spike (153, 299). Nevertheless, both these scenarios involve global regenerative events. Can more localized depolarization also evoke PF LTD? A decade ago, Hartell (276) discovered that localized PF-mediated dendritic spikes were also sufficient for LTD of PF synapses. His induction protocol relied on relatively strong PF activation and evoked a local  $\text{Ca}^{2+}$  spike in the dendritic arbor of Purkinje cells. The resulting LTD, however, surprisingly did not depend on NO signaling, a commonly reported feature of PF LTD (160, 414, 702), although a concomitant spreading form of PF LTD did (276). This suggests that there might be multiple pathways to induce PF LTD, one of which involves localized dendritic spikes in Purkinje cell dendrites. Given the need for relatively strong local PF activation in these in vitro experiments, Hartell's  $\text{Ca}^{2+}$ -spike-mediated LTD would seem to rely on synchronous activation of PFs that form synapses next to each other in the Purkinje cell dendritic tree. Currently, there is no evidence for or against such correlated activity of neighboring PF synapses in vivo (sect. 1G). It is therefore conceivable that other types of LTD, for example, due to weaker PF activation in conjunction with the global CF-induced complex spikes (808), dominate in vivo (cf. sect. 1I). Additional experiments are required to address this possibility.

Dendritic spikes have also been implicated in a relatively short-lasting form of synaptic plasticity, such as DSE, which is mediated by retrograde endocannabinoid signaling from the postsynaptic cell (128, 225, 394, 601, 842) (sect. 1F). This form of plasticity is  $\text{Ca}^{2+}$ -dependent, is expressed as a decrease of presynaptic transmitter release through CB1 receptor-induced inhibition of presynaptic VDCCs (96), and lasts for a few tens of seconds (sect. 1F). Recently, Rancz and Häusser (620) found that local  $\text{Ca}^{2+}$  spikes in cerebellar Purkinje cell dendrites are critically involved in DSE that is evoked by bursts of PF input. In addition, there was a strong correlation between

the number of dendritic spikes and the magnitude of the DSE (Fig. 12A). Rancz and Häusser (unpublished data) also investigated the impact of two PF bursts delivered in quick succession. They found that, owing to the suppression of PFs induced by the first burst, the second burst failed to evoke any dendritic spikes (Fig. 12B). This means that local dendritic spikes trigger a fast negative-feedback loop that renders them self-limiting; PF-evoked dendritic spikes reduce the likelihood of subsequent dendritic spikes for several tens of seconds (Fig. 12C). It is worth noting that dendritic spikes not only evoke DSE and trigger this negative-feedback loop (Fig. 12C), they also impact axonal AP output (621). This mechanism thus succinctly illustrates the multiple complex effects that local dendritic spikes may simultaneously have on plasticity, local excitability, and spike output.

Interestingly, Rancz and Häusser (620) also found that dendritic spikes evoked by other means, such as current injection or CF activation, were unable to produce DSE unless dendritic excitability was altered by blocking BK channels. It is noteworthy that BK channels are targets of endocannabinoid modulation as well (657), thus suggesting the existence of an additional feedback loop acting on dendritic excitability. This possibility, however, remains to be tested experimentally.

### E. Location Dependence of Synaptic Plasticity in Dendritic Trees

In the canonical view, synaptic plasticity depends critically on the spine coincidence detector (sect. 1I). In neocortical and hippocampal pyramidal neurons, this coincidence detector relies on the NMDA receptor. This receptor, of course, detects the coincidence of presynaptically released glutamate and postsynaptic depolarization, quite possibly due to postsynaptic spiking (Fig. 3). However, as we discussed in section 1B1, AP backpropagation into the dendritic arbor is unreliable in these cells. Depending on factors such as morphology (802), ion channel distributions (521), activity patterns (745, 835), and neuromodulation (302), bAPs may fail as they spread into the dendritic tree (sect. 1B). Ultimately, a decrementally propagating AP cannot evoke as much NMDA receptor-mediated  $\text{Ca}^{2+}$  influx in the distal as in the proximal dendrites. As a corollary, long-term plasticity should depend on the location of a synapse in the dendritic tree.

Froemke et al. (230) investigated location dependence of synaptic plasticity in L2/3 pyramidal neurons of visual cortex. By placing an extracellular stimulation electrode close to the apical dendrite at different distances from the soma, they found that the STDP timing curve depended weakly but significantly on the stimulation electrode location. In particular, the temporal window for LTD was wider and of smaller magnitude for distal than

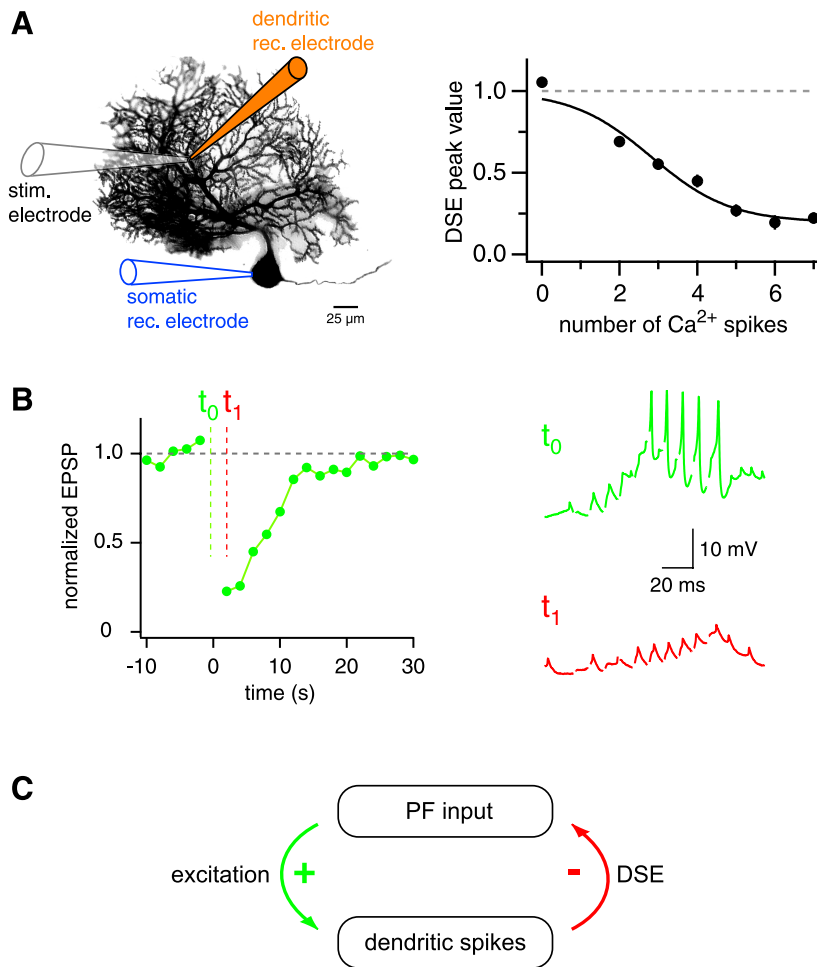


FIG. 12. Reciprocal interaction between local dendritic spikes and depolarization-induced suppression of excitation (DSE). *A*: parallel fiber (PF)-evoked local dendritic  $\text{Ca}^{2+}$  spikes are critically involved in DSE (620). *Left*: double somato-dendritic patch-clamp recordings were made from cerebellar Purkinje cells. *Right*: a train of PF stimuli evoked DSE that gradually increased with the number of dendritic  $\text{Ca}^{2+}$  spikes that were triggered. Note that without  $\text{Ca}^{2+}$  spikes no DSE was evoked. [Adapted from Rancz and Häusser (620).] *B*: A PF burst delivered at time  $t_0$  trigger local dendritic  $\text{Ca}^{2+}$  spikes (dendritic recording: green trace, *inset top right*) and DSE. An identical train of PF stimuli delivered at time  $t_1 = 2$  s does not evoke dendritic  $\text{Ca}^{2+}$  spikes (red trace, *inset bottom right*). *C*: there exists a negative-feedback loop between excitatory PF inputs and local dendritic spikes, which renders PF-evoked dendritic spikes self-limiting, since such spikes inhibit their own production for tens of seconds. Given the clamping effect of dendritic  $\text{Ca}^{2+}$  spikes on axonal AP output (621), this loop must impact information processing of Purkinje cells, the principal neuronal type and only output of the cerebellar cortex.

for proximal positions. No significant effect was reported for the LTP temporal window, but there is a trend showing less LTP for distal inputs. Given how compact L2/3 pyramidal cells are, the finding that there are small but significant proximal-distal differences in STDP timing curves is perhaps surprising; one would not necessarily expect bAPs to decay much in as little as 100  $\mu\text{m}$ . It is possible, however, that dendritic ion channel distributions and morphology are such that AP backpropagation is quite unreliable in the dendrites of this cell type (230). In agreement, Nevian et al. (551) recently found that AP backpropagation is decremental in the basal dendrites of L5 neurons (sect. *nBI*). Froemke et al. (230) argue that the location dependence of synaptic plasticity in L2/3 pyramidal neurons may enhance the computational power of these neurons, since the proximal-distal plasticity gradient may lead to differential input selectivity along the apical dendrite.

A more dramatic location dependence of synaptic plasticity was discovered by Golding et al. (256) in hippocampal CA1 pyramidal neurons. Here, it appears that AP backpropagation is so decremental that LTP of distal inputs onto the apical dendrite does not depend at all on

somatic spiking: AP-EPSP pairing evoked LTP at proximal but not at distal inputs (Fig. 11*B*). In fact, reliable LTP induction of distal inputs seemed to require relatively strong stimulation and as a result local dendritic spiking (see sect. *III D* above). It remains to be shown, however, whether or not sufficiently strong activation of distal inputs can boost the failing bAP to the point that distal LTP by AP-EPSP pairing is rescued (303, 468, 712). In addition, LTD and STDP may also depend on location in CA1 neurons. Interestingly, Golding et al. (256) found that LTP of proximal inputs could also be induced by a local dendritic spike in the absence of somatic APs (Fig. 11*B*). It follows that axonal spike output need not be inextricably linked to the induction of plasticity (433). Since spatially colocalized synaptic inputs are more likely to evoke local dendritic spikes and LTP, one important possible consequence is that synapses carrying similar information may be clustered on the dendritic tree. Such synaptic clustering has been predicted to result in improved information storage capacity (515, 605).

In L5 neurons, we recently discovered that plasticity induced through AP-EPSP pairing depended critically on synaptic location. There was a steep proximal-distal gra-

dient from LTP to LTD (Fig. 8) (712). In contrast to CA1 neurons (256), LTP of distal inputs onto L5 neurons did depend on somatic spiking, but only if distal inputs were sufficiently large (cf. sect. III B). From a functional point of view, it is presently unclear why L5 neurons would be endowed with a form of plasticity that is so apparently different from CA1 neurons in this one regard. However, from a mechanistic viewpoint, it perhaps makes sense that LTP of distal CA1 inputs does not depend on somatic spiking whereas it does in L5 neurons; there is a steep gradient of A-type potassium channel  $I_A$  in CA1 pyramids (303), but not in L5 cells (57, 389). The high density of distal  $I_A$  channels in CA1 neurons helps ensure that bAPs fail and have minimal impact on distal plasticity (521).

As discussed in section III C, Letzkus et al. (413) discovered a form of STDP in L5 neurons that depended on postsynaptic spike trains that were suprathreshold for the distal dendritic  $Ca^{2+}$  spike (sect. II B2). They found the typical form of STDP (Fig. 2A) for proximal synapses so that pre-before-post pairing evoked LTP (see Fig. 9B), whereas post-before-pre pairings resulted in LTD. Surprisingly, Letzkus et al. (413) found the opposite timing requirements for STDP of distal inputs (Fig. 2B), with a gradual switch along the apical dendrite between the two STDP timing requirement curves. As evidenced by a computer model, this location-dependent switch in the sign of STDP may depend mechanistically on the differential activation of postsynaptic NMDA receptors by AP bursts at proximal and distal synapses (413). Functionally, this study highlights how the proximal and the distal zones of L5 neurons are dissimilar. They are relatively electrically disconnected from each other (64), and each possesses its own mechanism for regenerative events (400, 405, 743) (sects. II B and III A5), and they finally also exhibit diametrically opposed synaptic learning rules. Letzkus et al. (413) propose that the distal and proximal zones therefore probably perform different computational tasks, an intriguing idea that deserves further investigation.

One intriguing aspect about the steep distance dependence of synaptic plasticity in L5 pyramidal neurons (413, 712) is that it should render the proximal-distal distribution of synaptic efficacies quite unbalanced. Since proximal inputs are more prone to LTP (712), they should grow stronger. The distal inputs, on the other hand, are more likely to undergo LTD and should therefore tend to be weakened (Fig. 8) (712). In addition, as shown by Letzkus et al. (413), the timing requirements are completely opposite for proximal and distal inputs. The former conform to the Hebbian postulate, whereas the latter do not, so strong synaptic drive may lead to strengthening of proximal inputs but weakening of distal inputs. The synaptic learning rule of L5 neurons is therefore spatially unstable (249); strong proximal synapses will get stronger, whereas weak distal inputs will become weaker and should, if anything, result in the exact oppo-

site of the “dendritic democracy” (282) found in CA1 pyramidal neurons (26, 467, 718) (see below). Indeed, Williams and Stuart (836) have provided some evidence consistent with the view that this spatially skewed rich-get-richer synaptic learning rule actually operates in L5 neurons. They found that the distribution of synaptic efficacies actually exhibits a gradient reminiscent of that described for plasticity in these cells (Fig. 8), such that distal inputs are quite weak while proximal ones are strong, as measured at the soma (836). Dendritic filtering of forward-propagating EPSPs is long known to render distal inputs weak compared with their proximal counterparts (329, 617). Given the small impact on somatic spike output of distal synapses, one may wonder what sense it makes to have a learning rule that amplifies this proximal-distal difference in synaptic efficacy. This form of synaptic inequality, however, may serve a specific function. Williams and Stuart (836) demonstrated that, in L5 neurons, distal inputs must be activated in tight synchrony to evoke somatic spike output. Functionally, the tendency of distal inputs to undergo LTD may help ensure that distal inputs remain small relative to the threshold for somatic AP generation so that distal synapses are forced to cooperate to produce axonal spike output. This learning rule may therefore help preserve the distal dendritic coincidence detector of Williams and Stuart (836).

The distribution of synaptic efficacies in CA1 pyramidal neurons is quite different compared with that of L5 neurons (467). In CA1 pyramids, synaptic weights are typically stronger distally so that the synaptic efficacy, measured at the soma, is relatively constant for inputs at different distances from the soma along the apical dendrite (467). There must therefore exist a mechanism by which CA1 neurons normalize their synaptic inputs, to provide a form of “dendritic democracy” (282). Although it is known that this equalization of synaptic weights is mainly due to increased AMPA receptor insertion with distance from the soma (26, 555, 718), it is at present unclear exactly how this normalization is brought about.

A theoretical study by Rumsey and Abbott (649) demonstrates that an STDP learning rule with inverse timing requirements could endow a neuron with such an equalization mechanism. In this model, a presynaptic spike preceding a postsynaptic spike results in synapse weakening, but since a strong synapse is more likely to evoke a somatic AP, it is also more likely to be punished by weakening. The net result is therefore self-equalization due to a combination of the electrotonic attenuation provided by the apical dendrite in combination with reverse STDP. In Rumsey and Abbott’s model, this reverse STDP rule does not provide learning; it only provides stability. The learning would have to be through another learning rule, such as the more typical STDP rule discussed in section I H. One possibility is that STDP and anti-STDP would act on different time scales (646) (sect. I D), with

the equalization rule running an order of magnitude more slowly, or at different developmental stages (650).

It should be added, however, that another explanation for the equalization found in CA1 neurons (467) is that it is not only a form of spatial normalization but also a matter of distinct excitatory pathways impinging at different locations of the CA1 pyramidal dendritic tree. There is, for example, some evidence that the distal stratum launosum-moleculare excitatory inputs originating from entorhinal cortex are simply stronger in and of themselves (511). Other possible contributions to such spatial gradients include pathway-specific molecular properties of synapses (e.g., see Refs. 280, 574). The same objection can be raised for location-dependent plasticity found in hippocampus (256) as well as in neocortex (230, 712). In particular, Holthoff et al. (311) found a spatial gradient of spine  $\text{Ca}^{2+}$  extrusion efficiency in the dendrites of neocortical L5 neurons; spine  $\text{Ca}^{2+}$  pumping mechanisms appear relatively more prominent farther away from the soma. Although the physiological relevance of these findings may be questioned (293, 655, 713), these results, if correct, imply a location dependence of synaptic plasticity that is merely due to the resulting dynamical spine  $\text{Ca}^{2+}$  gradient (cf. sect. III, A2 and A3). Indeed, quite distinct pathway-specific forms of synaptic plasticity exist even for different inputs that are intermingled on spines next to each other on the same dendritic branches (319), showing how important the molecular machinery of a synapse is for its synaptic plasticity rules. In all likelihood, future studies will enable a distinction between the contributions from synapse location and pathway-specific properties in synaptic learning rules.

#### F. Local Versus Global Balancing of Synaptic Input: Dendritic Versus Axonal Readout

As mentioned in sect. I, A and B, Hebbian plasticity and LTP are intrinsically unstable. This instability may lead to spatial destabilization of the synaptic weight distribution in the dendritic tree (sect. III D) (also see Ref. 249). In the preceding section, we discussed Rumsey and Abbott's (649, 650) elegant theoretical solution to the problem of this spatial instability. They employ anti-STDP, a form of STDP with inverted timing requirements (cf. Fig. 2 and sect. I H) that reduces the strength of inputs that frequently evoke axonal APs. Anti-STDP therefore relates the synaptic weight to its capacity for producing axonal spike output, a capacity that corresponds to the synaptic efficacy. This means anti-STDP in and of itself constitutes a robust mechanism for global equalization of synaptic inputs. In other words, Rumsey and Abbott employ the relatively global bAP to link axonal readout to local synaptic plasticity, and in doing so, they generate an equalization rule that solves the spatial instability problem across the entire dendritic tree.

Presently, Rumsey and Abbott's anti-STDP is largely a theoretical construct, although inverse STDP rules have been discovered in some neuronal types (see sect. I H), such as in the cerebellar-like electrosensory lobe of the mormyrid electric fish (59, 60, 269, 666) and at inhibitory inputs onto neocortical L2/3 pyramidal neurons (307). The existence of anti-STDP at excitatory inputs onto pyramidal neurons is therefore largely hypothetical. Letzkus et al. (413), however, recently found a reversed STDP timing rule at excitatory synapses onto the distal apical dendrite of L5 pyramidal cells (sect. III E). Whether or not the learning rule of Letzkus et al. (413) serves to equalize the synaptic efficacies of L5 neurons in a manner similar to that proposed by Rumsey and Abbott (649, 650) remains to be investigated.

An alternative solution to the spatial instability problem would be to use a local readout of synaptic strength to stabilize synaptic weights. Local balancing could be achieved by a synaptic plasticity rule that tries to maintain a target membrane potential at the location of the synapse or a target value of the postsynaptic calcium concentration (555, 615). Such a rule equalizes neither the synaptic efficacy nor the synaptic strength, but it will generate a distribution of synaptic strengths that is matched to the local input impedance and local density of other active synapses.

Another (perhaps related) approach to achieve spatial equalization of synaptic weights is based on heterosynaptic LTD (sect. I C). Since the goal is to maintain total synaptic weight approximately the same while at the same time equalizing weights across the dendritic tree, once one synaptic input is potentiated, for example, by Hebbian synaptic plasticity, a compensatory non-Hebbian heterosynaptic depression of neighboring synapses could be triggered. To produce such a learning rule, there must exist some sort of readout of synaptic strength and activity that accounts for what it means to be neighboring. The readout can, for example, be the mean local membrane potential or perhaps the local  $\text{Ca}^{2+}$  concentration. Such readouts are not set by a single synapse but rather jointly and cooperatively by a group of local synapses, and the localness is determined by the electrical and/or chemical compartmentalization of the dendritic tree. This approach is thus related to the local balancing idea discussed above. An equalizing learning rule could thus employ heterosynaptic LTD to ensure that, e.g., the mean local membrane potential remains constant. Experimental evidence supporting the notion that heterosynaptic LTD plays an equalizing role has been found by Royer and Paré (647) in the intercalated neurons of the amygdala. However, it remains unclear whether the underlying readout mechanism of Royer and Paré's equalization rule (647) is local or global. An example of a global readout mechanism for heterosynaptic LTD could be the expression of the immediate-early gene arc after LTP protocols. In-

creased Arc expression has been shown to lead to a reduction in AMPA receptor expression associated with a global decrease in AMPA-mediated synaptic currents at the nonpotentiated synapses (629).

In addition to balancing of the weights across the population of excitatory synapses, local or global regulation of inhibitory synaptic weights could be employed to avoid instability in the network. Some evidence exists supporting the idea that balancing of excitatory and inhibitory synapses arriving on individual dendritic branches can occur (435). However, again it is not clear whether the readout is local to each dendritic branch or global across the entire neuron. To prove the existence of local readout mechanisms and local feedback loops, it is necessary to first manipulate synaptic activity locally and then to test whether synaptic strengths change locally in a single dendritic branch or globally in the entire neuron.

A general problem of the mechanisms above, whether they are based on anti-STDP or on some form of local readout of synaptic strength, is that they need to coexist with other plasticity rules, such as Hebbian (sect. 1A) and intrinsic plasticity (sect. 1E). These different forms of plasticity may interfere with each other, since Hebbian learning and homeostatic stabilizing rules have opposite signs (sect. 1D). Several solutions have been suggested for this problem: there may exist different sensors or triggers for plasticity, different learning rules may act in distinct spatial regions and on separate time scales, and certain forms of plasticity may dominate at particular developmental stages (see sect. 1D). Whether the proposed solutions above solve the spatial instability problem in reality awaits experimental confirmation.

#### IV. A LOOP CONNECTING SYNAPTIC AND DENDRITIC PLASTICITY

We have discussed in section III how dendritic excitability can define the rules for the induction of synaptic plasticity. As described in section II, dendritic properties are themselves subject to regulation by synaptic input and, in particular, by patterns of synaptic activity that can themselves generate synaptic plasticity. The combination of these two observations offers the prospect of a reciprocal link between synaptic and intrinsic dendritic plasticity (Fig. 13), which raises many questions. Does this link typically represent a positive or negative feedback loop? How can it be regulated? Can disruptions in this link underlie diseases such as epilepsy?

As introduced in section I, Hebbian synaptic plasticity in itself represents a positive feedback loop, causing instability in the network if left unchecked. To compound these instability problems, intrinsic plasticity in the form of E-S potentiation, which accompanies classical hippocampal CA1 synaptic LTP (sect. II D2), acts in synergy

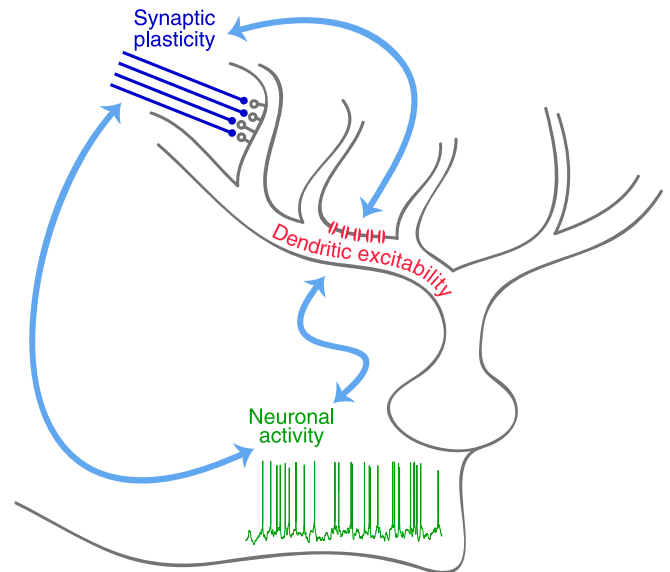


FIG. 13. Reciprocal relationships between synaptic plasticity, regulation of dendritic excitability, and activity. This schematic of an arbitrary neuronal type illustrates the complex interdependencies of the synaptic plasticity rules, the regulation of intrinsic excitability, and the activity of a neuron. Synaptic input drives the cell and activates voltage-sensitive ion channels and downstream signaling mechanisms at the synapse and in the dendrite. Thus synaptic plasticity is triggered, but the rules of plasticity are in part determined by the biophysical properties and the context of ongoing activity in the different compartments of the cell (cf. Fig. 8). The biophysical properties of the dendritic arbor, however, are in turn also regulated by the ongoing activity triggered by these same plastic synapses (cf. Fig. 6). The net result is a loop of reciprocal dependencies that determines the computations performed by an individual cell (cf. Fig. 12).

with this positive feedback loop. What is needed is an overall normalization of synaptic weights. One way to achieve this is to choose the details of the synaptic plasticity rules such that they become self-normalizing. In the case of STDP, this is dependent on subtle features of the learning rule, such as the dependence of the change in synaptic weights on their present value (sect. 1H). For independent Poisson synaptic inputs to a single-compartment integrate-and-fire neuron, a “multiplicative” STDP rule provides the desired normalization of synaptic weights (sect. 1D) (266, 648, 797; for a review, see Ref. 362). The resulting unimodal distributions of synaptic weights are indeed similar to those found experimentally (48, 210–212, 306, 325, 493, 663, 709, 725, 775). An STDP rule with a multiplicative dependence on the synaptic weight for depression and a power-law dependence for potentiation (69) was recently shown to allow stable and self-consistent operation of large random recurrent networks of integrate-and-fire neurons. The weight dynamics of recurrent excitatory synapses undergoing STDP and the network dynamics can reach a mutual equilibrium, with a unimodal distribution of synaptic weights (537).

In dendritic neurons, however, synaptic efficacy depends on the dendritic location of the synapse (446, 616,

837). Distal synapses have a smaller influence on axosomatic AP initiation compared with proximal synapses of the same strength. This puts them at a disadvantage in the competition to become potentiated by STDP. Moreover, the plasticity rules themselves are location dependent (sect. III E) (230, 256, 413, 712). This dependence of plasticity rules on location depends in part on the attenuation of the AP, which provides the feedback signal for STDP, as it propagates back into the dendritic tree. Together, these two mechanisms would cause proximal synapses to be potentiated maximally while the strength of distal synapses would be reduced to zero. Such disastrous effects, however, are not observed experimentally, since the average synaptic strength is constant or even increases with distance from the soma (272, 282, 322, 467, 551, 740, 836). Furthermore, distal synapses can be potentiated by recruitment of dendritic nonlinear mechanisms (272, 413, 712). These processes could play a role in local or global negative-feedback mechanisms that normalize synaptic weights across the dendritic tree (sect. III F).

Another layer of complexity is added by local dendritic mechanisms for plasticity of intrinsic excitability, such as those recently described in CA1 pyramidal neurons (228, 475) (sect. II E). Theta-burst pairing, a protocol that also causes synaptic plasticity, triggers a long-lasting increase in the amplitude of bAPs near the stimulated synapses (Fig. 6). Mechanistically, this is caused by a hyperpolarizing shift in the voltage dependence of inactivation of A-type  $K^+$  channels, which increases dendritic excitability locally. One consequence of the increased amplitude of the bAP is that it may provide local, and in particular more distal synapses downstream from the location of the stimulated synapse with a feedback signal for synaptic plasticity, or change the quality of this feedback signal, possibly altering the rules for synaptic plasticity at those synapses. This mechanism could therefore represent a form of metaplasticity, in which intrinsic plasticity near the stimulated synapse influences subsequent synaptic and intrinsic plasticity at neighboring synapses. Both effects would represent further examples of positive-feedback loops and of complex interactions between dendritic and synaptic plasticity. Their action would initially be spatially restricted to the dendritic region in which AP backpropagation is boosted, but this region could move and expand as the feedback loop continues to run. They might be countered by other intrinsic plasticity mechanisms representing a global negative-feedback loop (207, 546), normalizing output firing rate and enhancing the contrast between different synaptic input patterns. Localized intrinsic plasticity could also help to define sites for and regulate the threshold of dendritic spike initiation. Together with appropriate rules for cooperative synaptic plasticity (515, 605), this could be a way to establish and use multiple dendritic subunits in a neuron, allowing it to

even better discriminate and classify large numbers of synaptic input patterns.

## V. CONCLUSIONS AND DISCUSSION

This review has emphasized the importance of dendritic properties for understanding the rules governing the induction of synaptic plasticity. Rather than simply being passive conduits of synaptic activity, we have described how the structural, molecular, electrical, and chemical properties of dendrites define functional groupings of active synapses and create a bidirectional relationship between synaptic input and neuronal output. The fact that dendritic function can be modulated endows this system with enormous flexibility and power. In particular, since dendritic properties are in turn affected by activity patterns that result in synaptic plasticity, this indicates that changes in synaptic strength and regulation of dendritic excitability are therefore interdependent and are both shaped by dendritic properties (Fig. 13). This reciprocal relationship is undoubtedly important for the development of neuronal microcircuits, and for the long-term stability of synaptic strength, neuronal input-output relationships and network dynamics. These considerations have profound implications for how we view memory storage in the brain. The connection between dendrites and plasticity also has important implications for neuronal homeostasis, and its dysfunction may ultimately contribute to disease, which has recently become the subject of intense study (e.g., Refs. 66, 695, 851, 856).

As mentioned in the introduction, recent advances in technology have dramatically accelerated dendritic research, rendering even the most remote corners of the dendritic tree accessible to investigation. We predict that the combination of recently developed tools such as dendritic patch-clamp recordings (162, 746, 748), 2PLSM (178), genetically encoded sensors (532), and two-photon uncaging of glutamate (502), applied both in vitro and in vivo, will further quicken the pace of discovery. However, there is a danger that, rather than illuminating new principles, this arsenal of novel techniques will simply increase the mass of data illustrating the diversity of dendritic structure and function. Theory, particularly theoretical work that is tightly linked to experiments, will provide an important corrective to this tendency, since it can help to reveal the unifying principles underlying this diversity.

Ultimately, the message of this review is simple: synapses made onto a given neuron are not all alike, and the location of the synapse matters; it is a critical determinant of its properties and its plasticity rules. In turn, each synapse helps to define its local environment by regulating local dendritic excitability, and via cooperative and homosynaptic mechanisms, also the global excitability of

the cell. This reciprocal interdependence of synaptic and dendritic properties adds a rich new dimension to the view of synaptic plasticity that we have inherited from Hebb's visionary postulate. While the spatial dimension to plasticity is yet another variable that must be carefully controlled by the experimenter, appreciation of the role of dendrites in synaptic plasticity offers a fresh perspective on how the intricate three-dimensional forest of synaptic connections is formed and maintained. We expect that dendrites will become the meeting ground of a new generation of neuroscientists interested in understanding how structure, connectivity, synaptic strength, and excitability are regulated in concert, on a local and global scale, to optimize the performance of neural circuits.

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