Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons

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We have used Golgi-impregnated tissue to demonstrate that exposure to excess glucocorticoids alters dendritic morphology in a specific population of neurons in the adult rat hippocampus. Daily injection of 10 mg of corticosterone for 21 days resulted in decreased numbers of apical dendritic branch points and decreased total apical dendritic length measured in a 100-μm-thick section in CA3 pyramidal cells compared to sham-injected and non-injected controls. In contrast, no changes were observed in CA3 pyramidal cell basal dendritic morphology. Furthermore, no changes were observed in the dendritic morphology of CA1 pyramidal cells or granule cells of the dentate gyrus. Cross-sectional cell body area of any of the 3 cell types examined in this study was unaffected by corticosterone treatment. Finally, qualitative analysis of Nissl-stained tissue from the same brains revealed increased numbers of darkly staining, apparently shrunken CA3 pyramidal cells in corticosterone treated compared to control brains. The changes in dendritic morphology we have observed may be indicative of neurons in the early stages of degeneration, as prolonged exposure to high levels of corticosterone has been shown by others to result in a loss of CA3 pyramidal cells. Additionally, these results suggest possible structural alterations which may occur under physiological conditions in which corticosterone levels are chronically elevated such as in aged animals.

INTRODUCTION

As early as 1969, Aus Der Muhlen and Ockenfels demonstrated that elevated levels of glucocorticoids, the adrenal steroids secreted in response to stress, are toxic to neurons in the adult guinea pig hippocampus. Since then, numerous studies have sought to understand this neurotoxic phenomenon and its implications for hippocampal function under physiological conditions in which glucocorticoids levels are elevated, e.g. in aged or stressed animals. Landfield et al. have demonstrated a role for glucocorticoids in the progressive loss of hippocampal neurons with age in the rat as mid-life adrenalectomy attenuates the decrease in hippocampal neuron number normally observed in aged animals. In addition, Uno et al. have found that hippocampal neuronal loss occurs in vervet monkeys subjected to severe chronic social stress.

The damaging effects of chronic glucocorticoid exposure in the hippocampus are of particular interest as this neural structure has been proposed to be involved in cognitive processes such as learning and memory, as well as in aspects of neuroendocrine control. As elevated glucocorticoid levels have been implicated in hippocampal neuron loss and such hippocampal neuron loss has been linked to both cognitive and neuroendocrine impairments in aged animals, a better understanding of glucocorticoid-induced neuronal damage may shed light on the processes which contribute to alterations in brain function observed with aging and chronic stress.

The cellular mechanisms underlying the effects of chronic glucocorticoid exposure in the hippocampus are not well understood. While it seems likely that glucocorticoid-induced neuronal damage stems from a variety of biochemical and/or other factors, alterations in neuronal morphology may also be involved in the response of the brain to chronically elevated glucocorticoid levels. A number of studies have suggested neuronal morphology, particularly dendritic architecture, to be a modulator of neuronal physiology and thereby to influence brain function. As adult hippocampal neurons have been shown to be morphologically sensitive to low glucocorticoid levels induced by adrenalectomy, it seems quite possible that elevated levels of glucocorticoids may also result in an altered neuronal morphological profile. As such, excess glucocorticoids may exert negative effects on hippocampal function not only by reducing the absolute number of hippocampal neurons, but by altering the morphology of surviving neurons as well. To date, no...
study has examined the effects of chronic glucocorticoid administration on the morphology of hippocampal neurons. In order to determine whether excess glucocorticoids alter the structure of hippocampal neurons, we have performed a quantitative morphological analysis of the dendritic architecture of Golgi-impregnated hippocampal CA3 pyramidal cells, CA1 pyramidal cells and granule cells of the dentate gyrus from corticosterone-injected, sham-injected and non-injected control animals. Qualitative assessment of Nissl-stained tissue was also performed.

MATERIALS AND METHODS

Animals treatments and histological procedures

Male Sprague-Dawley (Charles River) rats (250–300 g) were subjected to one of the following treatments: (1) subcutaneous injection of 10 mg corticosterone in 250 μl sesame oil once daily for 21 days; or (2) subcutaneous injection of the vehicle alone once daily for 21 days. The remaining rats did not receive any treatments for the duration of the experiment. The dose of corticosterone used in this study had previously been shown to result in serum corticosterone levels which are initially above the physiological range and then decline to basal levels within 24 h.

At the end of the treatment period, these rats were deeply anesthetized with Ketamine HCl and transcardially perfused with 150 ml 4.0% paraformaldehyde in 0.1 M phosphate buffer with 1.5% (v/v) picric acid. Brains were postfixed in the perfusate for 5 days. Sections, 100 μm thick, were cut with a Vibratome into a bath of 3.0% potassium dichromate in distilled water. Some sections were rinsed in 0.1 M phosphate buffer, mounted onto gelatinized slides and stained for Nissl with Cresyl violet. The remaining sections were then processed according to a modified version of the single-section Golgi impregnation procedure. Briefly, the brain sections were incubated in 3.0% gelatinized slides and coverslipped under Permount.

Data analysis

Slides containing brain sections were coded prior to quantitative analysis; the code was not broken until the analysis was complete. In order to be selected for analysis, Golgi-impregnated neurons had to possess the following characteristics: (1) location in the appropriate subregion of the rostral hippocampus; (2) dark and consistent impregnation throughout the extent of all of the dendrites; (3) relative isolation from neighboring impregnated cells which could interfere with analysis; and (4) a cell body in the middle third of the tissue section in order to avoid analysis of impregnated neurons which extended largely into other sections. For each brain, 5 CA3 pyramidal cells (3 from the CA3c region and 2 from the CA3b region), 5 CA1 pyramidal cells and 5 dentate gyrus granule cells from the suprapyramidal blade (3 with a single primary dendrite and 2 with multiple primary dendrites) were selected. Each selected neuron was drawn at 500× using a camera lucida drawing tube. From these drawings, the number of dendritic branch points was determined for each selected neuron. In addition, the length of the dendrites present in a 100-μm-thick section was determined for each dendritic tree using the SMI (Southern Micro Instruments) image analysis morphometry program. Cross-sectional cell body area measurements were also made for each of the 3 cell types. Ten cell bodies per cell type per brain were traced at 1250× using a camera lucida drawing tube and cross-sectional area was determined using the SMI morphometry program. Means were determined for each variable for each brain and the resulting values were subjected to a one-way ANOVA with Tukey HSD posthoc comparisons.

RESULTS

At the end of the treatment period, all animals in each treatment group appeared to be healthy. Qualitative analysis of Golgi-impregnated tissue revealed sufficient numbers of CA3 pyramidal cells, CA1 pyramidal cells and dentate gyrus granule cells which met our selection criteria in brains from each treatment group (see Tables I, II and III). These brains were subjected to quantitative analysis.

Quantitative analysis of Golgi-impregnated CA3 pyramidal cells revealed significant differences in the number of apical dendritic branch points present in a 100-μm-thick section with corticosterone (CORT) treatment ($F_{2,12} = 10.9, P < 0.003$). CA3 pyramidal cells of CORT-treated animals had significantly fewer apical dendritic branch points than CA3 pyramidal cells of either sham-injected ($P < 0.007$) or non-injected ($P < 0.004$) control animals (Figs. 1 and 2; Table I). In contrast, no differences in the number of CA3 pyramidal cell basal dendritic branch points were detected with CORT treatment (Figs. 1 and 2; Table I). Quantitative analysis of CA1 pyramidal cells revealed no significant differences between treatment groups in the number of dendritic branch points present in a 100-μm-thick section in either the apical or basal dendritic tree (Table I).

<table>
<thead>
<tr>
<th>Neural region</th>
<th>Non-injected</th>
<th>Sham</th>
<th>CORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA3 pyramidal</td>
<td>12.6±1.1</td>
<td>12.4±0.8</td>
<td>7.3±0.5*</td>
</tr>
<tr>
<td>apical dendrites</td>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>CA3 pyramidal</td>
<td>9.8±0.9</td>
<td>11.0±1.5</td>
<td>10.8±0.6</td>
</tr>
<tr>
<td>cell basal dendrites</td>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>CA1 pyramidal</td>
<td>23.4±1.5</td>
<td>27.5±2.0</td>
<td>24.8±1.2</td>
</tr>
<tr>
<td>cell apical dendrites</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>CA1 pyramidal</td>
<td>11.8±0.8</td>
<td>13.9±1.0</td>
<td>13.7±0.8</td>
</tr>
<tr>
<td>cell basal dendrites</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Dentate gyrus</td>
<td>6.8±0.6</td>
<td>7.2±0.2</td>
<td>7.5±0.3</td>
</tr>
<tr>
<td>granule cell dendrites</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 5)</td>
</tr>
</tbody>
</table>

* Significant difference from non-injected and sham ($P < 0.007$).
Fig. 1. Golgi-impregnated CA3c pyramidal cells from brains of sham-injected (A) and CORT-injected (B) animals. These neurons were selected to approximate mean values for both numbers of dendritic branch points and dendritic length. Camera lucida drawings of these cells are shown in Fig. 2. Scale bar = 50 μm and applies to both frames.

TABLE II

Total dendritic length present in a 100-μm-thick section

Values represent mean ± S.E.M. n refers to the number of animals in each treatment group. Data were analyzed with one-way analysis of variance followed by Tukey HSD post hoc comparisons.

<table>
<thead>
<tr>
<th>Neural region</th>
<th>Non-injected (μm)</th>
<th>Sham (μm)</th>
<th>CORT (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA3 pyramidal cell apical dendrites</td>
<td>1435.6 ± 92.8</td>
<td>1607.4 ± 228.0</td>
<td>908.8 ± 77.7*</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td>CA3 pyramidal cell basal dendrites</td>
<td>1069.2 ± 67.7</td>
<td>1265.6 ± 226.6</td>
<td>1062.6 ± 29.9</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 5)</td>
<td></td>
</tr>
<tr>
<td>CA1 pyramidal cell apical dendrites</td>
<td>2038.3 ± 162.9</td>
<td>2784.2 ± 289.5</td>
<td>2311.9 ± 108.3</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td></td>
</tr>
<tr>
<td>CA1 pyramidal cell basal dendrites</td>
<td>1380.0 ± 154.6</td>
<td>1667.6 ± 64.1</td>
<td>1647.4 ± 67.0</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td></td>
</tr>
<tr>
<td>Dentate gyrus granule cell dendrites</td>
<td>1043.5 ± 76.4</td>
<td>1276.7 ± 81.4</td>
<td>1279.8 ± 96.8</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 5)</td>
<td></td>
</tr>
</tbody>
</table>

* Significant difference from non-injected and sham (P < 0.05).

Similarly, no significant differences with CORT treatment were detected in the number of dendritic branch points present in a 100-μm-thick section in dentate gyrus granule cells (Table I).

In addition to the observed changes in the number of apical dendritic branch points in CA3 pyramidal cells,

TABLE III

Cross-sectional cell body area

Values represent mean ± S.E.M. n refers to the number of animals in each treatment group. Data were analyzed with one-way analysis of variance followed by Tukey HSD post hoc comparisons. No significant differences were detected.

<table>
<thead>
<tr>
<th>Neural region</th>
<th>Non-injected (μm²)</th>
<th>Sham (μm²)</th>
<th>CORT (μm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA3 pyramidal cell</td>
<td>410.0 ± 12.4</td>
<td>410.9 ± 8.2</td>
<td>380.2 ± 11.1</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 6)</td>
<td></td>
</tr>
<tr>
<td>CA1 pyramidal cell</td>
<td>225.0 ± 4.7</td>
<td>238.0 ± 6.3</td>
<td>228.6 ± 5.9</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 6)</td>
<td></td>
</tr>
<tr>
<td>Dentate gyrus granule cell</td>
<td>176.6 ± 3.8</td>
<td>182.8 ± 3.1</td>
<td>171.1 ± 3.6</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(n = 4)</td>
<td>(n = 6)</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 2. Camera lucida drawings of the same CA3c pyramidal cells from the brains of sham-injected (A) and CORT-injected (B) animals depicted in Fig. 1. For these cells, numbers of dendritic branch points are: (A) apical, 15 and basal, 10; (B) apical, 9 and basal, 9. Dendritic length values for these cells are: (A) apical, 1636.9 μm and basal, 1164.7 μm; (B) apical, 1136.3 μm and basal, 1285.0 μm. Note the decrease in both number of dendritic branch points and dendritic length in the apical tree of (B) compared to (A) whereas there is no change in these parameters in the basal tree. Scale bar = 50 μm and applies to both frames.

CORT treatment resulted in significant differences in the total apical dendritic length present in a 100-μm-thick section in CA3 pyramidal cells ($F_{2,12} = 7.5; P < 0.009$). Total dendritic length present in a 100-μm-thick section of the apical dendritic tree in CA3 pyramidal cells of CORT-treated animals was significantly reduced compared to either sham injected ($P < 0.008$) or non-injected ($P < 0.05$) control animals (Figs. 1 and 2; Table II). In contrast, no significant differences in total basal dendritic length in a 100-μm-thick section in CA3 pyramidal cells were observed with CORT treatment (Figs. 1 and 2; Table II). Additionally, no significant differences in either total apical or basal dendritic length present in a 100-μm-thick section of CA1 pyramidal cells were observed with CORT treatment (Table II). Likewise, in dentate gyrus granule cells, no significant differences in total dendritic length present in a 100-μm-thick section were detected between treatment groups (Table II).

No changes in CA3 pyramidal cell cross-sectional cell body area were observed with corticosterone treatment (Table III). Similarly, no differences in CA1 pyramidal cell or dentate gyrus granule cell cross-sectional cell body area were observed between treatment groups (Table III).

Fig. 3. Nissl-stained CA3c pyramidal cells in the brain of a CORT-treated animal. Note the presence of several small, darkly staining cells (arrowheads) adjacent to apparently healthy pyramidal neurons (long arrows). Scale bar = 25 μm.

No changes in CA3 pyramidal cell cross-sectional cell body area were observed with corticosterone treatment (Table III). Similarly, no differences in CA1 pyramidal cell or dentate gyrus granule cell cross-sectional cell body area were observed between treatment groups (Table III).

Qualitative examination of Nissl-stained tissue revealed no obvious signs of degeneration in the CA3 pyramidal cell, CA1 pyramidal cell or dentate gyrus granule cell layers in any of the treatment groups in this study. Very few pyknotic cells (0–1/100-μm-thick section) were observed in the CA3 pyramidal cell layer of brains from any treatment group; they were observed in brains from both control and CORT-treated animals. However, the presence of a small number of darkly staining, apparently shrunken cells in the CA3 pyramidal cell layer (Fig. 3) was noted in some brains from both CORT-treated and control animals. Such apparently unhealthy pyramidal cells were observed in more CORT-treated than control brains and within each brain in which they were noted, they were seen more frequently in CORT-treated than control brains. In some cases, these cells appeared elongated, staining well into the apical dendritic shaft. In other cases, while still possessing visible dendrites, shrunken cells appeared small and irregularly shaped. Such cells did not seem to be associated with areas of degeneration as they were usually observed adjacent to apparently healthy CA3 pyramidal cells (Fig. 3). In some, but not all, CORT-treated brains, an increase was noted in the number of very small, darkly staining cells which appeared to be glia.

DISCUSSION

These results demonstrate that chronic administration of high levels of corticosterone to the adult rat results in alterations in dendritic morphology of Golgi-impregnated
hippocampal CA3 pyramidal cells. Specifically, we have observed decreases in the number of apical dendritic branch points and total apical dendritic length in a 100-μm-thick section with CORT treatment. The fact that we observed no differences in cross-sectional cell body area supports the notion that the cells selected for quantitative analysis in this study were representative of the same neuronal population between treatment groups.

The changes in dendritic morphology, i.e. the apparent atrophy of the apical dendritic tree, we have observed are consistent with the previously reported finding that prolonged exposure to excess CORT is damaging to hippocampal pyramidal cells in the CA3 region. However, qualitative analysis of Nissl-stained tissue provided no conclusive evidence for CORT-induced death of CA3 pyramidal neurons; in the CA3 region, no increase in the number of pyknotic cells was observed in the hippocampi of CORT-treated compared to control animals and the small numbers of apparently unhealthy pyramidal cells observed were detected in brains from each treatment group, albeit substantially more frequently in CORT-treated than in control animals. However, an apparent increase in the number of glial cells in the CA3 region of CORT-treated brains could indicate neuronal degeneration as astrocytes are known to migrate toward and proliferate within an area of neuronal damage.

Sapolsky et al. have reported that chronic CORT administration results in a shift toward decreasing values in the distribution of cross-sectional cell body areas and in a concomitant decrease in the absolute number of pyramidal cells in the CA3 region. Although we do not have evidence for such dramatic effects of CORT treatment, there are differences between our study and that of Sapolsky et al. in both the age and strain of animals used as well as the dose of CORT used and duration of treatment. Thus it is quite possible that had we extended the duration of our CORT treatment, we might have obtained more convincing evidence for neuronal loss. In addition, as our quantitative analysis was based upon Golgi-impregnated tissue, it is possible that our criteria for selection of neurons for analysis excluded some degenerating neurons, i.e. perhaps degenerating neurons are less likely to be well impregnated. Thus, the changes in dendritic morphology reported here may be indicative of neurons in the very early stages of degeneration. It should be noted that more subtle effects of CORT can be detected relatively rapidly as increases in the surface densities of rough endoplasmic reticulum and Golgi apparatus in pyramidal cells of the CA3 and CA1 regions as well as dentate gyrus granule cells have been observed with as few as 3 days of CORT treatment.

Sapolsky has suggested that CORT acts directly on hippocampal pyramidal neurons to effect a state of increased metabolic vulnerability thereby compromising their ability to survive subsequent metabolic challenges. This hypothesis is supported by the observation that CORT treatment potentiates the damaging effects of kainic acid, an excitotoxin, on hippocampal CA3 pyramidal neurons in vivo and cultured hippocampal neurons in vitro. In vivo, the damaging effects of CORT in combination with kainic acid can be prevented by administration of mannose. Presumably the presence of an excess of this ‘brain fuel’ attenuates the synergy between CORT and the neurotoxin. Both in vivo and in vitro studies have indicated that glucocorticoids decrease glucose uptake in hippocampal neurons and glia providing a possible mechanism for CORT-induced disruption of energy metabolism in the brain.

Direct effects of elevated levels of CORT could be mediated by either one or both of the corticosteroid receptor systems in the rat brain. In the hippocampus, CORT binds the type 1 receptor with high affinity and the type 2 receptor with lower affinity; type 1 receptors are largely occupied by basal levels of endogenous hormones whereas higher glucocorticoid levels are required to occupy the type 2 receptor. As such, the CORT-induced changes in dendritic morphology measured in this study are likely to be mediated by the type 2 receptor. It is, however, possible that the morphologic effects we have observed are the result of changes in receptor number which could involve either the type 1 or the type 2 receptor system. Further study utilizing selective receptor antagonists in vivo will be required to distinguish between these possibilities.

Interestingly, we have observed CORT-induced changes in dendritic morphology only in hippocampal CA3 pyramidal cells. No differences in morphological parameters were detected in CA1 pyramidal cells or granule cells of the dentate gyrus. Thus, within the hippocampus, the effects of chronic CORT treatment on dendritic morphology appear to be specific to neurons of the CA3 region. Although this is consistent with previous findings that CA3 neurons are particularly sensitive to high levels of glucocorticoids, it is a puzzling result as the CA3 region has been shown to contain lower levels of CORT receptors than other subregions in the hippocampus. Immunocytochemical localization as well as in situ hybridization have been used to demonstrate fewer type 2 (glucocorticoid) receptors and less receptor mRNA in the CA3 region compared to the CA1 region or the dentate gyrus. In addition, binding studies have shown that the CA3 region contains fewer type 2 receptors than the dentate gyrus and fewer type 1 receptors than either the dentate gyrus or CA1 region. In situ hybridization studies have shown that the CA3
region contains approximately the same amount of type 1 (mineralocorticoid) receptor mRNA as other subfields in the hippocampus.

These observations suggest that CA3 pyramidal cells are specialized in some way other than increased corticosteroid receptor number to be particularly sensitive to high levels of CORT. There are at least two, not mutually exclusive, possibilities which could explain the heightened vulnerability of these neurons. First, as several studies have linked at least one form of depolarization-induced cell death with increased Ca$^{2+}$ influx, Sloviter has suggested that CA3 pyramidal neurons could be relatively poorly protected from the damaging effects of high levels of intracellular Ca$^{2+}$ because they contain low levels of Ca$^{2+}$ binding proteins. In support of this hypothesis, Sloviter has recently demonstrated a positive correlation between the seizure-resistance of neurons within the hippocampus and the presence of the Ca$^{2+}$ binding proteins calbindin-D-28k or parvalbumin. As CORT has been shown to positively regulate Ca$^{2+}$ conductance in hippocampal pyramidal neurons, it seems quite possible that the effects of prolonged corticosterone exposure on neurons of the CA3 region could be exacerbated by an inability to sequester potentially damaging Ca$^{2+}$.

Second, the effects of CORT on CA3 pyramidal cells could be mediated at least in part, indirectly by a CORT-sensitive afferent population. In that light, it is interesting to note that the granule cells of the dentate gyrus contain high levels of both type 1 and type 2 CORT receptors and project heavily to CA3 pyramidal cells via the mossy fibers. Studies have demonstrated that selective damage to CA3 pyramidal cells as a result of intraventricular injections of kainic acid requires intact mossy fiber input. In addition, stimulation of the perforant path selectively damages pyramidal cells of the CA3 region apparently due to part to mossy fiber activation. Thus, in two cases where CA3 pyramidal cell damage is presumed to be due to hyperexcitation, it appears that the damaging effects are mediated, at least in part, through excitatory innervation from the dentate gyrus. The granule cells of the dentate gyrus have been shown to be highly dependent on CORT as short-term adrenalectomy without hormone replacement (3 and 7 days) results in massive cell death in this hippocampal subfield. Thus, it seems possible that excess CORT could exert a stimulatory effect on these neurons which could, in turn, hyperactivate and promote damage to the pyramidal cells of the CA3 region. Further experimentation will be necessary in order to determine the effects of elevated CORT levels on granule cell activity.

As the intracellular events ultimately resulting in CA3 pyramidal cell damage are not yet understood, it is unclear to what extent the damaging effects of increased activity of excitatory afferents could be local, i.e. restricted to the region of the dendritic tree receiving input, or generalized throughout the neuron. Interestingly, the mossy fibers of the dentate gyrus granule cells make synaptic contact with CA3 pyramidal cells primarily on specialized spines located on the apical dendritic shaft. We have observed the effects of excess CORT only in the apical dendritic tree; the basal dendritic tree, which is far less densely innervated by the dentate gyrus, is apparently not morphologically sensitive to our CORT treatment. It is also interesting to note that we observed no morphological effects of CORT treatment on CA1 pyramidal cells, a region to which the dentate gyrus has no known projection in the rostral hippocampus of the rat.

The changes in dendritic morphology we have observed are likely to have profound consequences for hippocampal neuronal function. Differences in dendritic branching patterns and in amount of dendritic material have been suggested to modulate the spatial/temporal integration of synaptic input to an individual neuron. Decreases in these parameters could result in a smaller total dendritic surface area available for synaptic contact and/or could alter the pathway for the flow of current in the dendrites. Thus, quantitatively less dramatic but qualitatively similar changes in hippocampal dendritic morphology may be involved in the alterations in hippocampal function which have been demonstrated under physiological conditions in which CORT levels are chronically elevated such as in aged or chronically stressed animals.

In addition, if the apparent atrophy of the apical dendritic tree in CA3 pyramidal cells does, in fact, reflect neuronal degeneration in this region, then our study may shed some light on morphological transitional phases undergone by neurons in the process of degeneration. In other words, the fact that we have observed decreases in parameters of apical dendritic arborization with elevated levels of glucocorticoids, i.e. under conditions which have been suggested to result in prolonged catabolism, might indicate that this region of the neuron is energetically costly to maintain and that it may be compromised in an unhealthy cell.

While the ultimate functional consequences of hippocampal exposure to elevated glucocorticoid levels are not yet understood, it is clear that, in addition to the neuron loss that has been reported by others, there are dramatic differences in the dendritic architecture of the remaining CA3 pyramidal cells. Future studies will be required in order to determine the extent to which Ca$^{2+}$ binding proteins and/or excitatory afferents play a role in mediating the neuronal specificity of glucocorticoid effects on neuronal morphology.
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