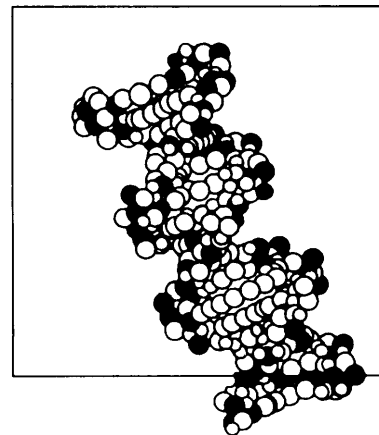


Genetics | 4

Why does one person become dependent on drugs while another, exposed to the same environment and experiences, does not? As progress in understanding the role of genetics in various conditions and diseases increases, there has been a realization that there is likely to be a genetic component to substance abuse and addiction. That is, inherited differences among individuals affect their response to drugs. To date, much of the work done in this field is related to alcoholism, less is known about the genetics of other drugs of abuse.

Studies in both humans and animals contribute to the understanding of genetic factors in substance abuse and dependence. Human studies shed light on the question of whether drug dependency is transmitted between generations. In addition, the study of individuals with substance abuse problems as well as animal studies provide information about what is actually inherited. For example, are there genetic differences in sensitivity and responsiveness to drugs? And, if yes, are the differences drug-specific, or are they related to general mechanisms associated with the actions of all abused drugs? Finally, the tools of modern molecular biology can be used to identify the specific genes that control various cellular and biochemical functions possibly involved in an inherited component of substance abuse and addiction.

While the existence of inherited differences seems likely, a genetic component alone probably is insufficient to precipitate substance abuse and addiction. Unlike disorders such as Huntington's disease and cystic fibrosis, which result from the presence of alterations in a single gene, substance abuse is likely



to involve multiple genes that control various aspects of the biological response to drugs. In addition, the complex nature of drug dependency, involving many behavioral and environmental factors, indicates that any genetic component acts in consort with other nongenetic risk factors to contribute to the development of substance abuse and addiction. Thus, neither the presence nor absence of a genetic factor ensures development of, or protection from, drug addiction.

DO INHERITED FACTORS EXIST?

A number of confounding factors complicates the study of genetic transmission of substance abuse liability in humans. One is the high incidence of psychiatric conditions among substance abusers (104), which raises questions about the role of psychiatric comorbidity in liability to illicit drug addiction. In particular, antisocial personality disorder (ASPD) is often associated with substance abuse. One study shows that 84 percent of individuals with ASPD also have some form of substance abuse during their lifetimes (104). Other psychiatric conditions that may be associated with substance abuse are depression, anxiety disorders, manic-depression, and schizophrenia.

Another issue related to studies of the genetics of liability to abuse of specific drugs is that many drug abusers engage in multiple drug use, so examining any familial trends in the use of a particular drug becomes difficult. Finally, rates of illicit drug use show strong secular trends. Even assuming a vulnerability to drug-specific addictions, there might be tremendous variations in expression of addiction, simply because of differences in drug availability over time: No matter how vulnerable an individual might be, addiction requires exposure. Such issues often hamper studies on the genetic transmission of drug liability.

I Family Studies

ALCOHOLISM

References to a familial tendency or hereditary “taint” of alcoholism date back to classical times (44); an observation repeatedly confirmed by family studies. While not all cases are familial, the risk of alcoholism consistently has been found to be higher among first-degree relatives (i.e., parents, siblings, children) of alcoholics as compared to the general population (79). Moreover, while family studies can establish that a disorder (or liability to a disorder) is transmitted; in general, they are unable to distinguish between biological and cultural transmission (though this issue can be evaluated in large family studies by analyzing multiple classes of relatives with differing degrees of genetic relatedness).

Results of numerous family studies indicate that alcoholism segregates within families, with male first-degree relatives of alcoholics having a higher incidence (ranging from 27 to 54 percent) than female first-degree relatives (6 to 17 percent) as compared to first-degree relatives of nonalcoholics (20 percent of males, 4 percent of females) (49,103,133). In fitting models of inheritance to family data, researchers concluded that observed patterns of inheritance were consistent with the hypothesis that familial factors predisposing to alcoholism were the same in men and women, but that nonfamilial environmental factors exerted more influence in the development of alcoholism in women (20). Familial alcoholics (those with at least one relative with alcoholism) appear to have earlier onset, more antisocial symptoms, more social complications of alcohol use, and worse treatment outcome than nonfamilial alcoholics (38,93,111).

Familial is not identical to genetic, and in the case of alcoholism, the familial patterns of inheritance are not consistent with those of a purely genetic condition (58,109). In addition, evidence suggests that the transmissibility of alcoholism has increased over time (102). Thus, any genetic factors promoting the development of

alcoholism are significantly moderated by non-genetic influences.

OTHER DRUGS

Fewer family studies have been conducted on the genetic transmission of liability to other drugs of abuse. Nonetheless, the evidence available suggests that, as in the case of alcohol, addiction to other psychoactive substances appears to run in families.

One study found evidence for familial aggregation of drug use, based on family history obtained from individuals admitted for substance abuse treatment (78). However, this study also combined use of all illicit drugs into one category and relied on self-reports by the subject on his or her drug use as well as that of family members. In a large family interview study comparing 201 opiate addicts and 82 normal controls, as well as interviews of 1,398 first-degree relatives of these subjects, the relatives of opiate users had elevated rates of drug addiction as compared with the controls (105). In addition there was an association between opiate use and the presence of ASPD. Further analysis of these data revealed that the incidence of both drug abuse and ASPD was higher among the siblings of the opiate subjects than among their parents (69,70).

Some studies note a familial association between opiate addiction and alcoholism (65). However, another family history study (51), comparing families of 32 alcoholics, 72 opiate addicts, and 42 individuals addicted to both substances, found that while both opiate addiction and alcoholism clustered within families, co-occurrence of the disorders within families occurred no more frequently than expected by chance, thus supporting the hypothesis of independent transmission. However, a later study of 201 opioid addicts and 877 of their first-degree relatives also showed familial aggregation of both alcoholism and depressive illness suggesting a possible co-occurrence of the disorders (64).

Little research has been done to test hypotheses regarding familial transmission of liability to addiction to specific substances other than opiates or alcohol. One study involving 350 treated drug abusers and 1,478 relatives, found that alcoholism was equally common among relatives of individuals who preferentially abused opiates, cocaine, or sedative-hypnotics (27 percent, 31 percent, and 24 percent of male relatives, respectively), whereas relatives of sedative-hypnotic users were subject to diagnoses of other substance abuses (2 percent of male relatives, versus 11 percent of male relatives of opiate abusers and 16 percent of male relatives of cocaine abusers) (80).

I Twin and Adoption Studies

While family studies can establish that a disorder (or liability to a disorder) runs in a family, they generally are unable to distinguish between biological and cultural transmission. However, two other methods are used to help disentangle the effects of genetic and nongenetic factors. Adoption studies compare the presence of a trait among biological versus adoptive family members or other control groups. In this way individuals that share the same environment but different genetic heritages, or vice versa, can be compared. Twin studies, by contrast, involve siblings raised in the same environment, but compare how often identical twins, who are genetically identical, and fraternal twins,¹ who are not, are similar, or concordant, for a trait. A high concordance rate for a trait among identical twins versus fraternal twins usually indicates a genetic component for the trait.

TWIN STUDIES

Evidence from twin studies suggests genetic influences on drinking patterns as well as alcohol-related problems. Results from twin studies demonstrate genetic influences on measures of alcohol consumption such as abstinence, average

¹Fraternal twins share the same in **utero** environment but are genetically no more similar than any two siblings,

alcohol intake, and heavy alcohol use (50,60,92). Twin studies also indicate an inherited risk for smoking (24).

When evaluating how alcoholism develops, twin studies generally support the existence of genetic influences on the development of the disorder. One study found a higher concordance rate for alcohol abuse between identical twins (54 percent) versus fraternal twins (28 percent) (57), while two subsequent studies found no such relationship (48,92.). A 1991 study (94) examined 50 male and 31 female identical twin pairs and 64 male and 24 female fraternal twin pairs, with 1 member of the pair meeting alcohol abuse or dependence criteria. The study found that identical male twins differed from fraternal male twins in the frequencies of both alcohol abuse and dependence as well as other substance abuse and/or dependence. On the other hand, female identical and fraternal twins were equally likely to abuse alcohol and/or become dependent on other substances, but identical female twins were more likely to become alcohol dependent. Another study of 356 twin pairs also found higher identical than fraternal rates of concordance for problems related to alcohol and drug use as well as conduct disorder (77). The same study also noted that among men, heritability was greater for early rather than late onset of alcohol problems, whereas no such effect was seen for women. Finally, a study of 1,030 female twin pairs found evidence for substantial heritability of liability to alcoholism, ranging from 50 to 60 percent (61).

Thus, twin studies provide general agreement that genetic factors influence certain aspects of drinking. Most twin studies also show genetic influence over pathological drinking, including the diagnosis of alcoholism, which appears (like many psychiatric disorders) to be moderately heritable. Whether genetic factors operate comparably in men and women, and whether severity of alcoholism influences twin concordance is less clear. How psychiatric comorbidity may affect heritability of alcoholism also remains to be studied.

ADOPTION STUDIES

Adoption studies have supported the role of heritable factors in risk for alcoholism (11,18,17). The results from a series of studies conducted in Denmark during the 1970s are typical. Of 5,483 nonfamily adoption cases from the Copenhagen area between 1924 and 1947, the researchers studied 55 male adoptees, and later compared 20 adoptees with 30 nonadopted brothers. They also studied 49 female adoptees, comparing them with 81 nonadopted daughters of alcoholics. Comparisons also were made with matched control adoptees. The Copenhagen study revealed that adopted-away sons of alcoholic parents were four times as likely as adopted-away sons of nonalcoholics to have developed alcoholism; evidence also suggested that the alcoholism in these cases was more severe. The groups differed little on other variables, including prevalence of other psychiatric illness or “heavy drinking.” Being raised by an alcoholic biological parent did not further increase the likelihood of developing alcoholism. That is, rates of alcoholism did not differ between the adopted-away children and their nonadopted brothers. In contrast, daughters of alcoholics were not at elevated risk of alcoholism. Among adoptees, 2 percent had alcoholism (and another 2 percent serious drinking problems), compared with 4 percent of alcoholism among the adopted controls and 3 percent among nonadopted daughters (44).

Another analysis examined factors promoting drug abuse as well as alcoholism (17). In this study, all classes of illicit drug use were collapsed into a single category of “drug abuse.” Most of the 40 adopted drug abusers examined had coexisting ASPD and alcoholism; the presence of ASPD correlated highly with drug abuse. Among those without ASPD, a biological background of alcoholism (i.e., alcoholism in a biological parent) was associated with drug abuse. Also, turmoil in the adoptive family (divorce or psychiatric disturbance) was also associated with increased odds for drug abuse in the adoptee.

Finally, results from other adoption studies suggest two possible forms of alcohol abuse (12,19). The two forms have been classified as “milieu-limited” or type 1 alcohol abuse and “male-limited” or type 2 alcohol abuse (21). Type 1 alcohol abuse characterized by mild alcohol problems and minimal criminal behavior in the parents, is generally mild, but occasionally severe, depending on presence of a provocative environment. Type 2 is associated with severe alcohol abuse and criminality in the biological fathers. In the adoptees, it was associated with recurrent problems and appeared to be unaffected by postnatal environment.

In summary, adoption studies of alcoholism clearly indicate the role of biological, presumably genetic, factors in the genesis of alcoholism. They do not exclude, however, a possible role for nongenetic, environmental factors as well. Moreover, evidence suggests more than one kind of biological background conducive to alcoholism. In particular, one pattern of inheritance suggests a relationship between parental antisocial behavior and alcoholism in the next generation. Thus, adoption studies, like other designs, suggest that even at the genetic level, alcoholism is not a homogeneous construct.

WHAT IS INHERITED?

Although studies indicate that genetics contributes to alcoholism and probably other drug abuse, they lack information about what exactly is inherited. For example, do individuals with a family history of drug abuse have an increased susceptibility or sensitivity to the effects of drugs with reinforcing properties? If a susceptibility exists, what are the biological mechanisms that underlie it? To understand what might be inherited, both individuals who have a substance abuse problem and animals models of substance abuse are studied. Various types of information can be derived from these studies. As with family, twin, and adoption studies, much more information is

available about alcoholism as compared with other drugs of abuse.

First, specific inherited risk markers for alcoholism and other substance abuse can be identified. A risk marker is a biological trait or characteristic that is associated with a given condition. Thus, if an individual is found to have an identified marker for substance abuse, he or she is at risk for developing a drug dependency. To date, no biological characteristic has been clearly identified as being a risk marker for either alcoholism or substance abuse, although evidence suggests some possible candidates. The identification of a valid and reliable risk marker could provide important information about the fundamental mechanisms underlying substance abuse and addiction and would be an invaluable aid in diagnosis and treatment.

Second, inherited differences in biochemical, physiological, and anatomical processes related to differences in drug responses might be identified and studied. Thorough biological assays can be performed using animal models of substance abuse. Animal models of substance abuse consist of strains of animals (usually rodents) that have been selectively bred to either exhibit a preference for taking a drug, exhibit a preference for not taking a drug, or differ in some way in their behavioral or physiological response to a drug. Thus, such differences represent inherited traits related to drug-taking behavior, and these animals can be studied to determine what biological mechanisms are involved in the expression of such traits.

Finally, the genetic technique of linkage analysis can narrow the area on a chromosome where a gene may be located. It can lead to the identification of the gene itself, which, in turn, can improve the understanding of the molecular events that underlie the expression of the gene. There have been few genetic linkage studies related to substance abuse since few specific biological traits associated with drug dependency have been identified. Some studies in humans have been carried out related to alcoholism but the

44 | Biological Components of Substance Abuse and Addiction

findings of these studies are contradictory and inconclusive (see later discussion).

Specific Risk Markers

ELECTROPHYSIOLOGICAL ACTIVITY

Attempts to correlate distinctive patterns of spontaneous electrical activity of the brain with alcoholism and substance abuse have been equivocal. A few studies have found distinctive electroencephalograph (EEG) patterns in individuals at risk for alcoholism (32,39), but others have not (31,59,101). Similarly, the use of alcohol challenge (i.e., giving the subject alcohol and then recording EEG) on subjects at high risk for alcoholism has likewise yielded inconclusive results. The rationale for challenge studies rests on the observation that alcohol has been shown to affect resting EEG, and thus might have a differential effect on those at low and high risk for alcoholism (100). Again, some studies have seen distinctive responses (100,101), while other have not (39,59).

A logical extension of studying resting EEG activity is examining event-related potentials (ERPs). ERPs are patterns of brain electrical activity produced in response to a particular stimulus (e.g., auditory, visual); they can reflect a variety of sensory and cognitive processes. Since ERPs may reflect heritable differences in cognitive function or capability that may in turn contribute to liability to alcoholism, some have suggested that ERP changes may allow discrimination between those at low and high genetic risk for alcoholism. The results of these studies have also been equivocal. Some have found characteristic responses among individuals at risk for alcoholism (3,4,33,52,53,89,90,125) while others have not (95,96,97,98). In addition to being equivocal, the specificity for alcoholism of such findings is unclear. In particular, it is not yet known whether similar findings might be identified in subjects with (or at risk for) illicit drug abuse.

Currently, both EEG and ERP findings seem best viewed as possible markers. Further studies **are** needed to confirm or refute the positive results that have been observed. In addition, while ERP findings in particular might relate to aspects of sensory, perceptual, or cognitive functioning that may differ among those at risk for alcoholism, how such differences contribute to risk for alcoholism and perhaps substance abuse is not well understood.

BIOCHEMICAL ASSAYS

Serotonin—Results over the last two decades from both human and animal studies have supported a relationship between low levels of central nervous system (CNS) (i.e., brain and spinal cord) serotonin and impulsive and violent behavior (130,131). Since problematic use of alcohol (as well as other drugs) has long been associated with a wide range of violent behavior, scientists have examined the relationship between alcoholism and serotonergic abnormalities. While a consistent relationship between alcoholism and low CNS levels of serotonin and its metabolites is lacking, mounting evidence supports the presence of such abnormalities in a subgroup of alcoholics with early-onset problems and a history of violence (16,67,68,107,130).

Because measures of serotonin activity are difficult to obtain, researchers have used pharmacologic probes of serotonin function, such as hormonal response to drugs that affect serotonin. These indirect measures have also indicated a relationship between impulsivity, substance abuse, and abnormal serotonin function (37,42,71,83).

For alcoholism, given that early-onset alcoholism and ASPD overlap substantially (16), the specificity of the serotonin findings is unclear, especially as similar results have been found in substance abusers with ASPD (71). However, at least one report has indicated that, even after controlling for the presence or absence of ASPD and illicit drug abuse, other neurochemical findings remained significantly associated with alcoholism (106). While further work might delineate

the relationship between decreased CNS serotonin levels and Specific psychiatric syndromes, current evidence suggests relatively specific biological differences may exist between early- and late-onset alcoholics; raising the possibility of defining biologically homogeneous subgroups.

Aldehyde and alcohol dehydrogenase enzymes-Many Asians rapidly develop a prominent facial flush following ingestion of a small amount of alcohol. Continued drinking leads to nausea, dizziness, palpitations, and faintness. This reaction is due to inactivity in individuals' aldehyde dehydrogenase, an enzyme that helps metabolize (i.e., break down) alcohol in the body. Ineffective enzyme activity results in a buildup of the chemical acetaldehyde in the blood following alcohol consumption. Clinicians have taken advantage of the aversive properties of acetaldehyde buildup by using the drug Antabuse to inhibit aldehyde dehydrogenase, thus inducing a severe form of the adverse reaction in abstinent alcoholics who begin to drink (30,135).

Alcohol dehydrogenase is another enzyme involved in the metabolism of alcohol. A mutant form of alcohol dehydrogenase also produces a transient increase in the acetaldehyde concentration after alcohol ingestion. This form of the enzyme also has been reported in Asian populations.

The two enzymes, aldehyde and alcohol dehydrogenase, probably interact in some individuals to amplify the adverse reaction to alcohol consumption (129). Since this reaction discourages heavy drinking, the observation that it commonly occurs in some populations where alcoholism is relatively rare suggests that alcohol and aldehyde dehydrogenase mutations might be a major determinant of alcohol consumption, abuse, and dependence. This would seem to hold true for Taiwan and Japan where the reaction occurs in 30 to 50 percent of individuals.

The genetics of the aldehyde and alcohol dehydrogenases are well described. The production of the different forms of these enzymes is caused by variations of their normal genes. The

presence of these gene variations in an individual accounts for variations in the metabolism of alcohol (54). Thus, the presence of these genes can also effect alcohol consumption. For example, the gene variations that code for the ineffective form of aldehyde dehydrogenase is not only less common in alcoholics, but also is rare in Japanese patients with alcoholic liver disease (27, 121,135). Despite identification of such genes, the relationship between their inheritance and the familial transmission of alcoholism remains unstudied.

Alcohol challenge-A number of studies have been conducted investigating the effect of administering alcohol to young adult sons of alcoholics (99). These studies indicate that, despite similarity of blood alcohol levels, sons of alcoholics demonstrate less intense subjective responses to alcohol, as well as less intense upper body sway (110,111,113,114). Thus, one mechanism by which alcoholism might develop is that since these individuals have less of a reaction to alcohol, they would find it more difficult to self-regulate alcohol consumption, thus increasing the risk of developing dependence. In conjunction with these findings, other studies have found that sons of alcoholics demonstrate slightly lower levels of certain hormones (i.e., prolactin, cortisol, adrenocorticotropin hormone (ACTH)) after ingesting alcohol as compared to controls (82,114,115,116,118). The relationship, if any, of these decreased hormonal levels to alcohol consumption is unclear.

COGNITIVE DIFFERENCES

Study of high-risk populations (e.g., sons of alcoholics) has revealed temperamental, as well as biological, differences between high-risk and control subjects, leading to the suggestion that vulnerability to alcoholism can be conceptualized from a behavior-genetic perspective (127). Heritable, constitutional differences, in other words, might affect temperament and, hence, risk for alcoholism and addiction to other drugs. In particular, these differences might influence cog-

native styles, learning ability, and capability to control one's own behavior.

In general, it appears that sons of alcoholics demonstrate group differences from low-risk populations in that the former tend to have impairment on tests of cognitive development, academic achievement, and neuropsychological function (34,12,8). However, the magnitude of these differences may depend greatly on how the population is ascertained. To date, little is known of what specific psychological, temperamental, or cognitive factors might distinguish between high-risk subjects who actually go on to develop alcoholism from those who do not (128).

I Biological Mechanisms

Animals that have been bred for specific characteristics are a valuable tool in drug use and abuse research. For example, certain strains of rodents differ in their response to the analgesic and body temperature regulating effects of morphine, the motor activating effects of stimulant drugs, and the convulsant producing properties of benzodiazepines (28,122). Since the essential characteristic of human drug abuse and addiction is persistent drug-seeking behavior, the most salient models are those of genetic differences in drug self-administration and the factors associated with it (e.g., tolerance). While there are some genetic models of self-administration or preference for different drugs (i.e., alcohol, opiates, cocaine) (28,41), more information is available about the hereditary biological mechanisms that underlie the self-administration of alcohol than other drugs.

ALCOHOL

A general working hypothesis is that alcoholics are sensitive to the low-dose rewarding properties of alcohol, are less sensitive to the high-dose actions of ethanol (i.e., have a higher aversive threshold) and develop tolerance to the aversive effects of alcohol. The fact that rats can be selectively bred to have such alcohol drinking

characteristics supports a genetic link to these traits.

Dopamine and alcohol intake—Studies of dopamine content in the brains of two different strains of rats bred for either preference or nonpreference for alcohol have found 25 to 30 percent lower levels of dopamine in the nucleus accumbens and the olfactory tubercle of the alcohol-preferring rats (45,74,86). No other differences in dopamine content have been observed in other brain areas. These data suggest an abnormality in the dopamine system projecting from the ventral tegmental area to limbic regions (nucleus accumbens and/or olfactory tubercle) of the alcohol-preferring rats. Since this system is thought to be involved in mediating the actions of various drugs of abuse (see ch. 2) and alcohol is thought to increase dopamine levels in the system (see ch. 3), it may indicate that an abnormal functioning of the mesocorticolimbic dopamine system might be involved in promoting high alcohol drinking behavior. That is, the alcohol preference may be related to the ability of alcohol to compensate for the abnormality. The nature of this abnormality is unknown but may be due to one or more of the following factors: decreased dopamine synthesis, a lower number of dopamine neurofibers, and/or reduced functional activity of dopamine neurons.

Some evidence exists that the mesocorticolimbic dopamine system may respond to systemic ethanol administration to a greater degree in the alcohol-preferring strains than in the nonpreferring strains. Studies have found that levels of dopamine metabolites were higher in areas of this system (i.e., caudate nucleus, medial prefrontal cortex, and olfactory tubercle) after ingestion of alcohol in alcohol-preferring rats as compared to nonpreferring rats (35,36). Also, one study has reported that the oral self-administration of alcohol, under experimental conditions where the animal was allowed to receive alcohol as a reward for performing a task, increased the synaptic levels of dopamine significantly more in the nucleus accumbens of these alcohol-preferring

rats than in nonpreferring rats (132). It was also established that the alcohol-preferring strain of rats will self-administer alcohol directly into the ventral tegmental area (73,74). These studies suggest that the mesocorticolimbic dopamine system is involved in regulating alcohol drinking behavior and that alcohol may be a stronger positive reinforcer in alcohol-preferring rats than in the nonpreferring rats.

Differences in dopamine receptor populations have also been reported. Two genetically determined high-alcohol seeking lines of rats have been reported to have fewer of one type of dopamine receptor (i.e., the D_2 receptor) in their limbic system compared with the nonalcoholic rats (74,124). Twenty percent fewer D_2 receptors were observed in the olfactory tubercle and nucleus accumbens of these rats. These studies, along with genetic linkage studies (see later discussion), provide support for the involvement of the D_2 receptor in alcohol-preference.

Serotonin and alcohol intake--Examination of alcohol-preferring and nonpreferring rats has indicated a relationship between high alcohol preference and a deficiency in the CNS serotonin system. A number of studies have reported 10 to 30 percent lower levels of serotonin and its metabolites in the brains of alcohol-preferring rats as compared with alcohol nonpreferring rats (45,66,74,84,85,86). Only one study, using a strain of rats not used in any of the others, did not find lower brain serotonin levels (63). Areas of the brain found to have low serotonin levels include the cerebral cortex, frontal cortex, nucleus accumbens, anterior and corpus striatum, septal nuclei, hippocampus, olfactory tubercle, thalamus, and hypothalamus.

Since several of these CNS regions may be involved in mediating the rewarding properties of drugs of abuse, including alcohol, these findings suggest a relationship between lower contents of serotonin in the brain and high alcohol preference. Evidence suggests that the serotonin system is involved in regulating the activity of the dopamine mesocorticolimbic system (136). Also, some

of the areas found to have low serotonin levels (i.e., hypothalamus, hippocampus) may be involved in mediating the aversive effects of alcohol. Since the development of tolerance to the aversive actions of alcohol is one possible characteristic of alcoholic abuse, a deficiency in serotonin in these areas may be an innate factor promoting tolerance to the aversive effects of ethanol in alcohol-preferring lines of rodents.

Further study of one of the rat strains used in these studies showed that low serotonin in the alcohol-preferring line compared with the nonpreferring line was due to fewer serotonin-containing axons (137). This study found fewer serotonin presynaptic fibers forming synapses in the nucleus accumbens, frontal cortex, cingulate cortex, and hippocampus of alcohol-preferring rats. These results suggest that the low serotonin is the result of structural differences in the CNS serotonin system rather than lower production of serotonin. Examination of this same strain of rats found that there were increased numbers of one type of post-synaptic serotonin receptor in areas of the frontal cortex and hippocampus (73,76,134). This increase in the number of serotonin postsynaptic receptors may represent a compensation for the lower number of presynaptic serotonin fibers. No such increase in receptors was found in the strain of rats with normal levels of brain serotonin activity discussed earlier (62).

Overall, the animal data favors an inverse relationship between the functioning of the CNS serotonin system and alcohol drinking behavior. Thus, innate low functioning of the serotonin system may be associated with high alcohol preference. In support of this concept, some studies have found lower cerebrospinal fluid serotonin metabolite concentrations in alcoholics than in various control populations (2,14).

GABA and the actions of alcohol—Evidence indicates that alcohol can exert some of its antianxiety and intoxicating effects by potentiating the actions of the neurotransmitter gamma amino butyric acid (GABA) at the $GABA_A$ receptor (see ch. 3) and that this receptor might be

48 | Biological Components of Substance Abuse and Addiction

involved in mediating alcohol drinking behavior of alcohol-preferring rats (75). However, little has been published that indicates an innate abnormality may exist in the GABA system that could be associated with alcohol preference. A recent study examined the densities of GABA containing fibers in the nucleus accumbens and other brain areas of two different strains of alcohol-preferring and nonpreferring rats (55). The results of this study indicated a higher density of GABA fibers in the nucleus accumbens of the alcohol-preferring rats compared with the nonpreferring rats. There were no differences between the respective lines in the other regions. These results suggest alcohol preference may involve an innate, abnormal GABA system within the nucleus accumbens.

The experimental drug RO 15-4513 binds to the GABA_A-BDZ-Chloride channel receptor complex (see ch. 3) and is known to block the actions of alcohol at this receptor (126). The administration of RO 15-4513 reduced alcohol but not water intake in a study using one of the alcohol-preferring line of rats (75). The blocking effect of RO 15-4513 on alcohol intake could itself be blocked by administration of a drug that blocks the benzodiazepine receptor. These results indicate that the GABA_A-BDZ-chloride channel receptor complex may be involved in mediating the reinforcing actions of ethanol that promote alcohol drinking behavior in these rats. The observation that RO 15-4513 blocks oral self-administration of alcohol supports this idea (56,108). Furthermore, treatment with a drug that activates the GABA_A receptor was shown to markedly increase the acquisition of voluntary ethanol consumption in laboratory rats (123). Also, GABA_A receptor function is enhanced by alcohol in animals selected for sensitivity to alcohol intoxication, but alcohol has little effect on GABA_A receptors of animals selected for resistance to alcohol intoxication (28). Overall, these results are consistent with the involvement of the GABA_A receptor in regulating alcohol consumption. (See also ch. 3).

Alcohol withdrawal severity—Animal models have been developed for differential genetic susceptibility to alcohol withdrawal. For example, withdrawal seizure-prone mice display a higher incidence of convulsions than do seizure-resistant mice when exposed to identical alcohol concentrations (29). Other studies suggest that this alcohol withdrawal reaction is mediated by an increased sensitivity of channels for calcium ions, coupled to receptors for excitatory amino acids (46,47). Several results have emerged in studies of these mouse lines that are potentially important for understanding drug abuse. For example, studies indicate that independent genetic factors control alcohol sensitivity, tolerance, and dependence, suggesting that these features of drug abuse are maintained by different neurobiological mechanisms (28). In addition, the alcohol withdrawal seizure-prone mice have more severe withdrawal to other depressant drugs (i.e., diazepam, phenobarbital, nitrous oxide) (6,7,8) suggesting that a group of genes acts to influence drug withdrawal severity not only to alcohol, but also to a number of other depressant drugs.

OTHER DRUGS

A variety of strains of rats and mice has been developed that exhibit genetic variations in their sensitivity to the reinforcing effects of drugs of abuse and in their drug-seeking behavior (28). In addition, genetic differences in various biological and neurochemical mechanisms have been observed in these animals.

For example, strains of rats and mice that differ in their sensitivity to the reinforcing properties of cocaine and in their cocaine-seeking behavior have also been observed to have differences in the number of dopamine containing neurons and receptors in certain brain areas (120). While the role of these biological findings in the expression of the behavioral traits is unclear, given that dopamine is the key neurotransmitter in cocaine's action, it is likely that a link may exist. Other studies have shown that the development of nicotine tolerance is genetically related. Strains of

mice that differ in the rate at which they develop tolerance to nicotine have also been found to differ in nicotine receptor changes following chronic administration of the drug (72). Thus, inherited differences in nicotine receptor mechanisms may underlie inherited differences in the development of nicotine tolerance.

A recent study indicates that inherited differences in the intracellular mechanisms of the neurons in the mesocorticolimbic pathway could contribute to a genetic predilection to drug addiction (87). In a comparison of rats with either high or low rates of self-administering drugs of abuse, the higher self-administering strain exhibited differences in the intracellular mechanisms that control activity in the neurons of the ventral tegmental area and nucleus accumbens (5).

The further examination of causative relationships between inherited neurochemical alterations and inherited behavioral traits would produce valuable information about the biological mechanism that underlies genetic factors related to substance abuse and addiction. The recent development of new and more sensitive techniques to analyze brain activity and processes will facilitate such studies.

I Linkage Studies

Genetic linkage studies establish an association between an area of a specific chromosome and the expression of a trait. Linkage analysis uses specific markers that identify the area on a chromosome that might contain the gene of interest. If the marker consistently occurs in association with the expressed trait, then it is likely that the gene interest is in chromosomal region.

In the area of substance abuse and addiction, genetic linkage studies have purported to show a linkage between the gene for the dopamine D₂ receptor and alcoholism. The gene for the D₂ receptor has two forms associated with two markers, the A1 and A2 alleles. The A1 allele occurs in about 20 percent of the population,

while the A2 allele is found in the remaining 80 percent (1). Two separate studies (9,10) reported that the frequency of the A1 allele for the D₂ dopamine receptor was significantly greater in severe alcoholics compared with nonalcoholics. Furthermore, another study (88) found that individuals with the A1 allele had fewer D₂ receptors than those with the A2 allele. In agreement with these findings, another study (91) observed a significant association between the A1 allele of the D₂ receptor and alcoholism. An association of the A1 allele with alcoholism and decreased numbers of D₂ dopamine receptors implies a role for an inherited deficit in the dopamine system in alcoholism. However, in contrast to these results, other studies have not found an association between the frequency of the A1 allele of the D₂ receptor and alcoholism (13,26,40,1 **19**). The discrepancies between these studies has called into question the validity of the association of the A1 allele with alcoholism.

Moreover, the report of a higher prevalence of the A1 allele not only in alcoholics, but also in other disorders such as autism, attention deficit hyperactivity disorder, and Tourette's syndrome (25), suggests that the presence of the A1 allele is not specific for alcoholism, but that it has a more diffuse effect that can contribute to the occurrence of other conditions. Also, recent findings indicate that the frequency of the A1 allele varies markedly among different populations (e.g., it is high in some Native Americans) but there does not appear to be an association with its increased frequency and the occurrence of alcoholism (43). This complexity, coupled with the heterogeneous and complex nature of alcoholism, could account for the disagreements among these studies. Such complexity makes construction of appropriate control groups difficult, which in turn can affect study results. Additional research is needed to unravel the disagreement and establish the importance of these findings. It might be that the presence of the A1 allele is not unique to alcoholism, but rather, causes a general alteration

in the brain dopamine system that then exacerbates or contributes to alcohol abuse.

SUMMARY

The existence of heritable influences on normal and pathological consumption of alcohol is supported by results from family studies, twin studies, and adoption studies as well as research on animal models. Animal studies have established that alcohol preference and the reinforcing actions of alcohol are influenced by genetic factors. While there have been fewer studies examining the genetic component of vulnerability to the addictive properties of other drugs of abuse, evidence from animal studies supports a genetic influence on the use and abuse of drugs other than alcohol. The study of nonalcohol drug abuse in humans is more difficult because of substantially smaller populations that use or abuse these drugs and marked changes in availability and, hence, exposure to these agents. Investigation in this area is further hampered by the complexity of subjects' drug use: Most drug abusers have used multiple agents. This has led researchers either to concentrate on one class of drug or to treat all illicit drug use as equivalent. The tendency to lump all illicit drugs into one category makes results difficult to interpret or compare.

In the case of alcohol, studies indicate that low doses of alcohol are stimulating and produce a strong positive reward in animals susceptible to the addictive properties of alcohol. Another component of excessive alcohol consumption might be that alcoholics have a high threshold to the aversive effects of ethanol. This could be a result of an innate low sensitivity to medium and high doses of alcohol and/or acute tolerance to its aversive effects. Results from animal studies suggest an association between high alcohol preference and acute tolerance to the medium- and high-dose effects of ethanol. These animal experiments need to be extended and consideration should be given to related studies in humans.

Findings with animals selectively bred for alcohol preference need to be extended to studies of sensitivity, tolerance, and preference for other drugs of abuse.

Neurobiological evidence points to common pathways mediating the positive reinforcing actions of alcohol and other drugs of abuse. Most evidence is consistent with the involvement of the mesocorticolimbic dopamine system in drug reinforcement mechanisms. Other neuronal pathways that regulate the activity of the mesocorticolimbic dopamine system may also be involved in mediating the rewarding properties of ethanol and other drugs of abuse. In the case of serotonin, innate, genetically determined factors appear to reduce CNS activity of serotonin, which is associated with heavy alcohol drinking. In addition, animal and human studies suggest an inherited difference in dopamine response to alcohol consumption and possibly an anomaly in the D₂ receptor for Dopamine associated with alcohol abuse. Additional studies with animals and humans are needed to clarify these differences and to explore the relationship of other neurobiological mechanisms related to the inherited components of other drugs of abuse.

Alcoholism and drug abuse are complex conditions that are the result of multiple causal factors. Alcoholism and other forms of addiction represent entities that have a genetic component but require specific (but as yet poorly understood) environmental influences to manifest. Thus, consideration of the impact of genetic factors must also take into account general social conditions such as availability and cost of substances, acceptability of use, and specific environmental influences on initiation of use, maintenance or cessation of use, and development of use-related problems. A major goal of addiction research in clinical populations is to determine who is vulnerable under what conditions. Understanding this interaction might lead to better prediction of relapse as well as improved matching of patients and treatments.

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