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ETHANOL ABUSE, DEPENDENCE, AND WITHDRAWAL: NEUROBIOLOGY AND CLINICAL IMPLICATIONS

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Ethanol produces a striking array of behavioral effects in humans that are dependent on the dose of ethanol administered, whether ethanol levels are rising or falling, and the rate of change of ethanol levels (1). The euphoric, stimulant, and anxiolytic effects of ethanol contribute to its wide recreational use, whereas its sedative effects contribute to its consumption as a nonprescription hypnotic. Yet, at intoxicating doses, ethanol clouds memory and judgment (2), slows information processing and reaction time (3), impairs coordination (4), and disinhibits impulsive or aggressive behavior (5). Perhaps, then, it is not surprising that some of the most damaging consequences of ethanol abuse reflect the impact of ethanol intoxication on behaviors, such as driving, that place a high demand on these cognitive functions (6).

With chronic administration, ethanol produces both adaptation and neurotoxicity in the brain, accounting for tolerance and dependence. The ethanol withdrawal syndrome (7) includes anxiety, insomnia, and symptoms of sympathetic nervous system arousal. With more severe levels of dependence and repeated episodes of withdrawal, abstinence may be associated with substantial sympathetic arousal, agitation, perceptual changes, confusion, and seizures. These symptoms may emerge together in the context of delirium tremens, a potentially life-threatening complication of ethanol dependence that generally develops within the initial week of sobriety. Another syndrome, alcoholic hallucinosis, may develop during any phase of the cycle of intoxication and withdrawal. It is associated with persisting hallucinations that may or may not remit with extended sobriety.

Acute and protracted abstinence are important contexts for treatment to ensure the medical safety of recovering patients and to prevent their relapse to ethanol use. Although the most severe consequences of withdrawal appear during the initial week of sobriety, protracted components of withdrawal persist for many months (8). Protracted withdrawal symptoms include insomnia, anergia, and depressed mood. The effort to rid oneself of withdrawal symptoms may be an important motivator for relapse to ethanol use. As will be reviewed later, this phase of recovery is also associated with gains in cognitive function, cortical activity, and brain structure.

Nutritional deficits complicate the natural history of alcoholism (9). If thiamine-deficient individuals ingest glucose before thiamine repletion, the resulting demand on thiamine pyrophosphate-dependent metabolic processes compromises neuronal metabolic functions and may produce cell death associated with the Wernicke-Korsakoff syndrome (10). This eponym refers to a constellation of learning and memory impairment, psychosis, and motor findings.

This chapter provides a brief and selective overview of the basic and clinical neuroscience of alcoholism. Ethanol is now known to have multiple specific actions in the brain that contrast with the historical focus on its nonspecific perturbation of neuronal membrane bulk lipids (11,12). This chapter discusses the acute and chronic effects of ethanol at its protein targets in the brain, and the neural circuitry of human alcoholism that has become the focus of structural and functional neuroimaging studies.

MOLECULAR TARGETS OF THE ACTION OF ETHANOL: RELEVANCE TO INTOXICATION AND DEPENDENCE

Amino Acid Neurotransmission

Glutamate

Glutamate Receptors as an Ethanol Target in the Brain

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and glutamate utilizes both

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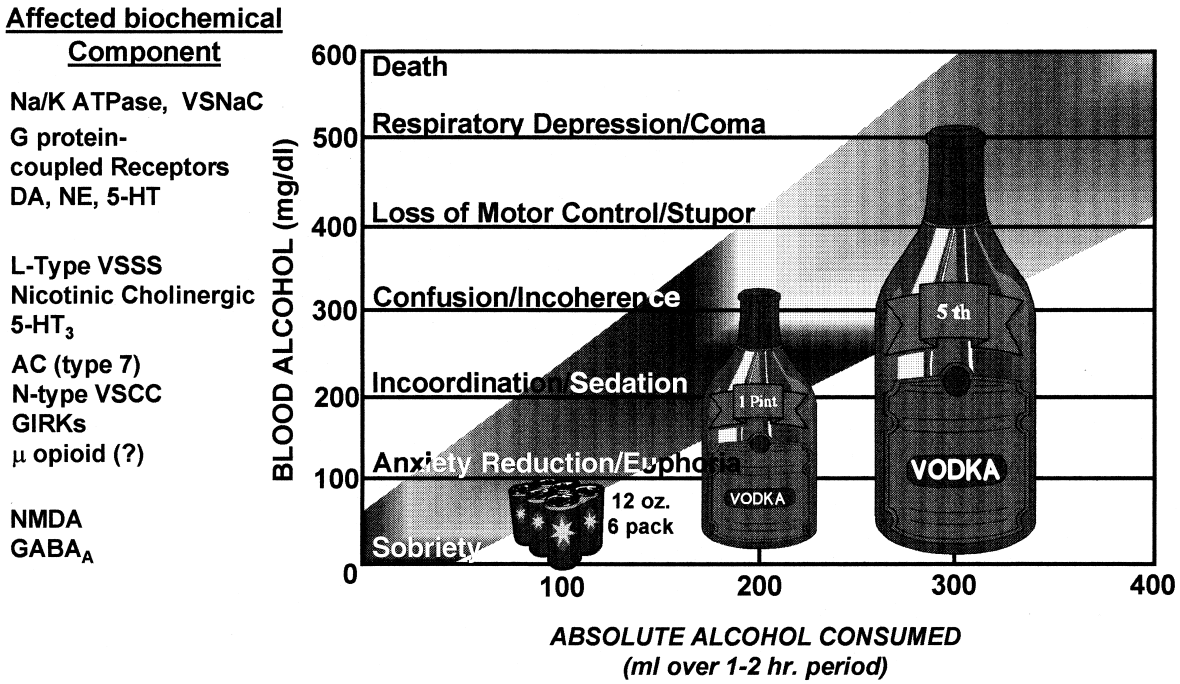

FIGURE 100.1. The relative potency of ethanol for its protein targets in the brain. Shown is the relationship between amounts of alcohol consumed and neurotransmission, neuroexcitatory components, and behavioral actions.

ionotropic and metabotropic receptors to transduce its signal. The ionotropic receptors, receptor-gated ion channels, include the *N*-methyl-D-aspartate (NMDA) α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA), and kainate receptors (13). NMDA receptors are gated by membrane potential and the simultaneous binding of both glycine and glutamate (14). Ethanol at concentrations as low as 5 mM (20 mg%) inhibits ion flux through the NMDA receptor-gated ion channels, making NMDA receptors one of the highest affinity ethanol targets in the brain (Fig. 100.1) (see ref. 15 for review). It shows lower affinity for AMPA and kainate glutamate receptors (15).

Ethanol effects on the NMDA receptor function are dependent on the concentration of glycine and the phosphorylation status of the receptor. In cultured cerebellar granule cells, ethanol lowered the NMDA receptor affinity for glycine, and ethanol effects were partially reversed by raising glycine levels (16). A protein kinase C (PKC)-mediated phosphorylation event may gate the effects of ethanol on glycine affinity at the NMDA receptor (16). Other protein kinases (e.g., tyrosine kinases such as Fyn and Src) may also play a role in ethanol's actions on the NMDA receptor (17).

Regional variations in NMDA receptor subunit composition contribute to distinctions in ethanol effects on NMDA receptor function across brain regions (see ref. 14 for review). Functional NMDA receptors are composed of an NR1 subunit, with at least eight splice variants, and one NR2 subunit from among the four known subtypes (NR2 A–D). The relative affinity of ethanol for NMDA receptor subtypes may be important to its dose-related effects in the brain (18), but this issue remains under intensive investigation (19).

The inhibition of NMDA receptor function by ethanol has direct neuroprotective consequences (20). NMDA antagonist effects of ethanol may influence its modulation of the release of other neurotransmitters (21,22), perhaps reflecting the capacity of low-dose NMDA antagonism to preferentially attenuate the activation of local inhibitory circuits (23).

The subjective effects of ethanol are tested in animals by measuring their ability to discriminate the effects of ethanol and other drugs. NMDA antagonists substitute for ethanol in these experiments, where they resemble the effects of higher doses of ethanol than ethanol doses that are most similar to the effects of γ-aminobutyric acid (GABA) agonists (24). Supporting the importance of the NMDA site, WSP (withdrawal seizure prone) and WSR (withdrawal seizure resistant) mice differ in their NMDA receptor density in several brain regions (25) and in their capacity to discriminate ethanol from other substances (26).

NMDA Receptor Adaptations with Ethanol Tolerance and Dependence

Multiple lines of evidence implicate NMDA receptor up-regulation as a mechanism contributing to acute ethanol withdrawal. Chronic ethanol administration up-regulates

NMDA receptor number, particularly in the cerebral cortex and hippocampus (27). During acute ethanol withdrawal, NMDA receptor increases are associated with tremors, anxiety, ataxia, and convulsions (27). Similarly, the increased hippocampal NMDA receptor density in WSP mice is related to their increased expression of withdrawal seizures relative to WSR mice (25). Additionally, NMDA antagonists given during withdrawal suppress withdrawal seizures (28). Lastly coadministration of the ganglioside GM_1 and ethanol prevents NMDA receptor up-regulation and the display of withdrawal seizures (29).

NMDA receptor up-regulation is subunit specific. In cultured cells and whole animals, chronic ethanol administration increases the levels of the NR2A and NR2B protein subunits and their subunit messenger RNA (mRNA) levels (30). Some, but not all, studies also suggest that NR1 subunit protein level increases may be accompanied by increases in NR1 mRNA levels (31). In cultured cells, the increases in NMDA receptor subunit proteins are associated with increased NMDA receptor function (32).

The consequences of NMDA receptor up-regulation during dependence are compounded by increases in glutamate release associated with the initiation of abstinence (33). Perhaps as a result, ethanol withdrawal is associated with seizures and neurotoxicity (see ref. 34 for review).

Glutamate: Clinical Correlates

Glutamate and the Complex Discriminative Stimulus Effects of Ethanol. As is seen in Fig. 100.2, the NMDA antagonist, ketamine, produced dose-related ethanol-like effects in recently detoxified alcoholic patients (35). As with the preclinical studies (24), both the intensity and the degree of similarity of the ethanol-like effects of ketamine were greater at a higher subanesthetic dose (0.5 mg/kg) than at 0.1 mg/kg. Ketamine did not stimulate ethanol craving in patients, although craving was associated with the ethanol-like effects of another NMDA antagonist dextromethorphan (36).

Clinical studies examining the interactive effects of ketamine and other drugs may provide insights into the NMDA antagonist component of ethanol effects in the brain. The NMDA antagonist-induced euphoria does not yet appear dopamine dependent. For example, the euphoric properties of ketamine are not blocked by haloperidol pretreatment (37) or markedly potentiated by amphetamine pretreatment (38). These findings parallel clinical findings describing the lack of interaction of ethanol and amphetamine (39). In contrast, the euphoric effects of ketamine (40), like ethanol (41), are attenuated by pretreatment with the μ opiate receptor antagonist naltrexone. Ethanol may possess actions at other brain targets that attenuate the dysphoric properties arising from its blockade of NMDA receptors including the facilitation of $GABA_A$ receptor function (42) or blockade of voltage-gated cation channels (43,44).

Glutamatergic Dysregulation in Ethanol Dependent Patients: Relationship to the Familial Risk to Develop Alcoholism. Postmortem studies of brain tissue from ethanol-dependent individuals suggest that the B_{max} or K_d of NMDA receptors are increased in cortical structures alcoholics (45,46). *In vivo*, ethanol withdrawal increases cerebrospinal fluid (CSF) glutamate levels. The combination of increased glutamate release during withdrawal and NMDA receptor up-regulation promotes withdrawal-related neural plasticity and neurotoxicity (47). With repeated episodes of withdrawal, patients show increased seizure risk (48) and hyperreflexia (49).

NMDA receptor function in recovering ethanol-depen-

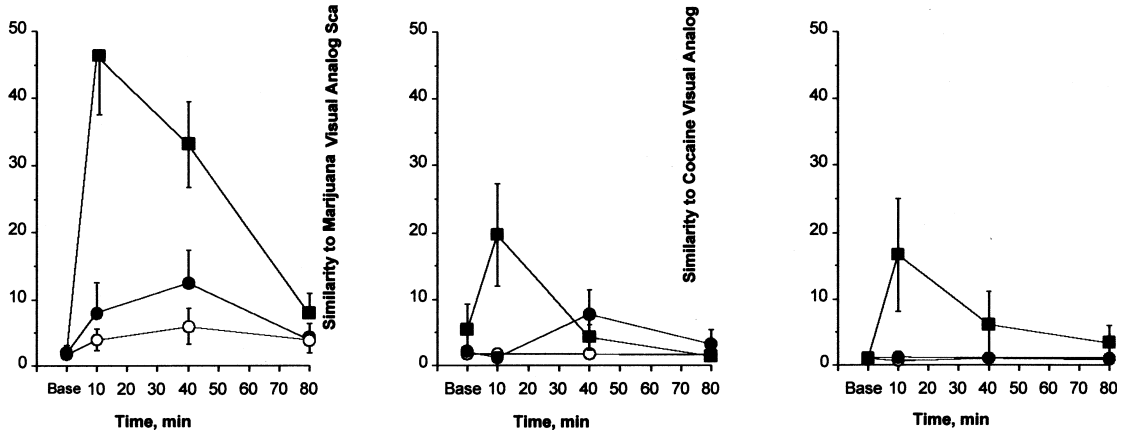

FIGURE 100.2. Similarity of the effects of placebo (*open circles*), ketamine 0.1 mg/kg (*solid circles*), and ketamine 0.5 mg/kg (*solid squares*) to ethanol (**left**), marijuana (**middle**), and cocaine (**right**) in alcoholic patients ($n = 20$). Values are expressed as mean ± standard error of the mean (SEM). Ketamine effects were significantly more similar to ethanol than both marijuana and cocaine by post-hoc contrast ($F1 = 6.7$, $p = .02$). (Data are from ref. 70.)

dent patients also may shift the reward valence of the NMDA antagonist component of ethanol response from dysphoria to euphoria, promoting further alcohol use. Recently detoxified ethanol-dependent patients show reductions in their sensitivity to the perceptual, mood, and cognitive effects of ketamine (50) and the glycine-B partial agonist D-cycloserine (51). In contrast, preliminary data suggest that these patients exhibited preserved euphoric responses to ketamine relative to a healthy comparison group (Krystal, unpublished data). Thus, NMDA receptor alterations associated with ethanol dependence might contribute to relapse to ethanol use in two ways: (a) by contributing to the signs and symptoms of ethanol withdrawal, and (b) by enhancing the rewarding properties or reducing the dysphoric properties of ethanol during the early phases of relapse to ethanol use.

Healthy individuals at increased familial risk for developing alcoholism, relative to a ''family history negative'' group, show reductions in the dysphoric effects of NMDA receptor antagonists resembling the changes seen in ethanol dependent patients (52). Thus, inherited differences in NMDA receptor function may contribute to alterations in the set point for sensitivity to ethanol effects that promote the development of the abuse of ethanol. Further research is needed to clarify the impact of ethanol dependence and alcoholism vulnerability on glutamatergic function.

The mechanism through which ketamine sensitivity is altered in individuals at increased familial risk for alcoholism is not yet clear. In individuals without a family history of alcoholism, antagonism of voltage-gated cation channels clearly reduces the dysphoric effects of ketamine and may enhance its euphoric effects (43,44); i.e., these pretreatments may produce changes in the reward valence of ketamine effects that are similar to the alterations associated with a family history of ethanol dependence. The genes underlying altered ketamine response in individuals at risk for alcoholism are not yet known.

Acamprosate: A Putative Glutamatergic Pharmacotherapy for Alcoholism. Acamprosate is a homotaurine derivative without ethanol-like behavioral effects that reduces alcohol consumption in animals (53). This drug is a promising agent for treating alcoholism (54,55). It reduces NMDA receptor function, contributing to its capacity to suppress ethanol withdrawal (56). However, it also has promotes some NMDA receptor-mediated effects (57). The site of action of acamprosate is not known and the mechanisms related to its efficacy are not fully understood.

GABA

GABA Receptors as Targets for Ethanol Action

Ethanol produces sedative-hypnotic effects that resemble other drugs that facilitate $GABA_A$ receptor function, particularly muscimol, benzodiazepines, and barbiturates (15). The similarity between the behavioral effects of GABA agonists and ethanol is dose-dependent, with the greatest similarity between these drug classes observed with relatively low training doses of ethanol (15).

Ethanol has effects at the $GABA_A$ receptor at concentrations of 10 to 100 mM. In one study, ethanol acted similarly to benzodiazepines by potentiating the effects of GABA (58), whereas in another study ethanol resembled barbiturates by increasing the entry of chloride without the addition of GABA (59). The microsac preparation employed in these studies, however, would be expected to contain certain sufficient amounts of endogenous GABA to influence their interpretation.

Ethanol actions at $GABA_A$ receptors vary across brain regions and may be related to the differential expression of $GABA_A$ receptor subunits (60). This receptor is composed of five subunits that associate to form a Cl^- channel. Subunit families (e.g., α, β, γ, δ) and isoforms within each family (e.g., α_1–α_6) have been identified (61). Variation in subunit composition imparts functional distinctions in $GABA_A$ receptor subtypes relevant to ethanol action (61). For example, isoforms of the γ subunit [i.e., α_{2S} or α_{2L} (62)] that differ in their sensitivity to PKC isoforms differ in their sensitivity to ethanol (63). However, studies now question the importance of these particular $GABA_A$ receptor subunits (64). Some of these differences between studies may reflect the importance of a particular PKC isoform, PKC-ϵ.

The adenylyl cyclase signaling system and protein kinase A (PKA) also modulate ethanol's actions at $GABA_A$ receptors. Ethanol potentiates GABA inhibition of cerebellar Purkinje cell firing, but only when there is concomitant stimulation of β-adrenergic receptors (65) and activation of PKA (66).

Chronic Actions of Ethanol on $GABA_A$ Receptor Function

Changes in the levels of $GABA_A$ receptor subunits occur in animals treated chronically with ethanol (67). It consistently decreases the mRNA and protein for the α_1 subunit of the $GABA_A$ receptor, whereas other subunits may show no change or even increases (67). *In vitro* studies form ethanol-treated animals demonstrated a reduced ability of ethanol to potentiate GABA-mediated chloride flux, suggestive of the development of ethanol tolerance (58). *In vivo*, hyperexcitability, fear behaviors, and convulsions during acute ethanol withdrawal may reflect decreases in GABAergic neurotransmission (68). WSP and WSR mice, noted earlier to differ in NMDA receptor regulation, also differ in predicted directions with respect to their $GABA_A$ receptor characteristics and their vulnerability to withdrawal seizures (69).

GABA: Clinical Correlates

GABA Systems and Alcoholism Vulnerability. To date, the genes underlying the GABA-related vulnerability for

alcoholism are unknown. A haplotype relative-risk study did not find evidence associating either the α_1- or α_3-subunit genes with alcoholism, although suggestive data supporting further study was obtained for the latter gene in an association study (70). The strongest tie between $GABA_A$ receptor involvement and the vulnerability to alcoholism has come from studies evaluating ethanol and benzodiazepine effects in populations at high-risk for developing alcoholism. Most (71,72), but not all (73), studies found that male offspring of alcoholics have reduced sensitivity to the cognitive, behavioral, and motor effects of both benzodiazepines and ethanol. Similarly, individuals at risk for alcoholism exhibited blunted cerebellar metabolic inhibition, but not cortical metabolic inhibition, following a dose of lorazepam (74). However, there may be greater sensitivity to or preference for the euphoric effects of benzodiazepines in this population (71), although these effects are not uniformly replicated (75). The rewarding effects of alcohol and benzodiazepines in humans may be increased in anxious individuals, who tend to experience more pronounced anxiolytic effects of these drugs (76).

Clinical Evidence of GABA Dysregulation in Alcoholism. GABAergic regulation differs in alcoholic and nonalcoholic populations. GABA levels are reduced in plasma, CSF, and brain in recently detoxified alcoholics during the first month of detoxification (77,78). In patients, low plasma GABA levels predicted relapse (79), perhaps because low GABA levels were associated with protracted abstinence symptoms. These changes may in part reflect ethanol dependence and withdrawal-related effects on the levels or function of enzymes regulating GABA synthesis and degradation (80).

Reductions in $GABA_A$ receptor binding in postmortem and antemortem neuroimaging studies may reflect the combined effects of vulnerability, ethanol dependence, and alcoholism-related neurotoxicity. Some postmortem studies found reductions in $GABA_A$/benzodiazepine (BZ) binding, but other studies had conflicting results (81–83). Variability between studies may reflect a compensatory up-regulation in BZ/$GABA_A$ binding that follows alcoholism-related neurotoxicity (84) or the failure to employ ligands that differentiate between subtypes of $GABA_A$ receptors. *In vivo*, positron emission tomography (PET) and single photon emission computed tomography (SPECT) neuroreceptor imaging has provided evidence of reductions in BZ binding (Fig. 100.3) (85,86). Neurotoxicity contributed to, but did not account for, reductions in BZ receptor binding in patients (87). Reductions in BZ binding may be consistent with evidence of reduced regional brain metabolic sensitivity to lorazepam in ethanol-dependent individuals (88). However, metabolic blunting did not rapidly recover with sobriety (89), raising the possibility that this deficit reflected genetic vulnerability or irreversible toxicity.

Psychopharmacologic studies also implicate GABA systems in withdrawal and relapse. Clearly, drugs facilitating $GABA_A$ receptor function including BZs, barbiturates, and anticonvulsants suppress acute ethanol withdrawal (90).

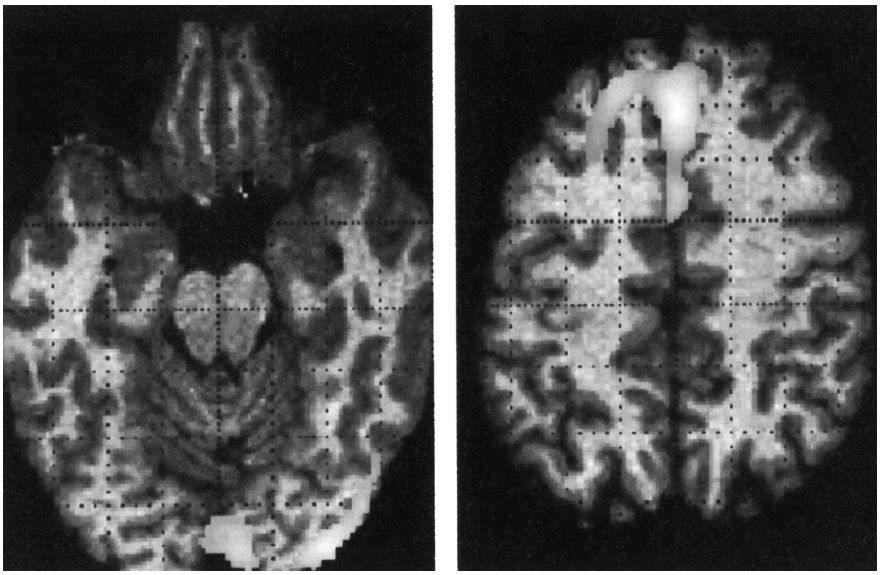

FIGURE 100.3. Transaxial slice of regions where benzodiazepine receptor distribution volume in alcoholic patients was significantly lower than in comparison subjects based on a statistical parametric mapping analysis (*yellow*). Single photon emission computed tomography (SPECT) data were superimposed on an MRI template. (From Abi-Dargham A, Krystal JH, Anjivel S, et al. Alterations of benzodiazepine receptors in type II alcoholics measured with SPECT and [123I]iomazenil. *Am J Psychiatry* 1998;155:1550–1555, with permission.) See color version of figure.

The BZ antagonist flumazenil may reduce ethanol intoxication in humans at doses greater than required to antagonize BZ effects (91). However, this drug does not produce ethanol withdrawal symptoms in ethanol-dependent individuals (92). It is not yet clear whether flumazenil exposure during ethanol withdrawal alters the course of recovery from ethanol dependence.

Neurosteroids

There is growing interest in the role of neuroactive intermediates in sex steroid synthesis and metabolism in alcoholism (93). Allopregnanolone, a coagonist of the steroid anesthetic site of the $GABA_A$ receptor, shares discriminative stimulus properties with ethanol and suppresses the ethanol abstinence syndrome in animals (94,95). Allopregnanolone also may potentiate the effects of ethanol (96). Allopregnanolone levels, like those of its precursor progesterone, vary markedly during the menstrual cycle. In the late luteal phase, drops in allopregnanolone levels may contribute to premenstrual mood disturbances (97) and increase the intensity of the discriminative stimulus properties of ethanol (98). These factors may increase ethanol consumption during this phase of the menstrual cycle (99). Supporting this view, higher allopregnanolone levels in the late luteal phase are associated with reduced triazolam self-administration in women (100). Thus, cyclical variation in neurosteroid levels may be a focus for future pharmacotherapies for female alcoholics.

Voltage-Sensitive Calcium Channels (VSCCs)

Preclinical Studies

In the brain, VSCCs play a major role in gating synaptic calcium influx and thereby modulating a range of calcium-dependent intracellular processes, membrane potential, and neurotransmitter release (101,102). There are six known VSCC classes: L-type (dihydropyridine-sensitive), N-type ("neuronal"), P-type ("Purkinje"), Q-type, R-type, and T-type ("transient") channels (103,104).

Ethanol blocks L-type channels. Supporting this hypothesis, L-type VSCC antagonists show some ethanol-like effects in rats (105). Ethanol, at concentrations over 50 mM, inhibited [$^{45}Ca^{2+}$] influx in *in vitro* preparations (106). These studies suggested a wide range of L-type channel sensitivity to inhibition by ethanol, ranging from 10 to >200 mM, perhaps reflecting differences in channel subunit composition. The variability in L-type channel sensitivity to ethanol may depend on the characteristics of its subunits, post-translational modifications, and other regulatory mechanisms (107,108).

Chronic exposure to ethanol *in vivo* or cultured cells up-regulates L-type channels via a PKC-dependent mechanism (108). The up-regulation of L-type channels may contribute to signs of ethanol withdrawal (109,110), perhaps in part, by partially depolarizing cell membranes and recruiting NMDA receptors.

Electrophysiologic studies with transformed cells or pituitary neuron terminals also indicated that both N and T channels could be inhibited by an ethanol concentration of 50 mM (111,112). Recent evidence (113) also indicates that chronic administration of ethanol to mice up-regulates the number and function of N-type calcium channels.

VSCCs: Clinical Correlates

Ethanol actions at VSCCs may modulate its behavioral effects in humans. Despite the apparent similarities between the effects of ketamine and ethanol, ketamine produces more profound perceptual effects than ethanol at doses studied to date (114). However, the perceptual effects of ketamine are attenuated in humans by both the L-type VSCC antagonist nimodipine (44) and by lamotrigine, a drug with multiple effects on cation channels, including an antagonist action at P- and N-VSCCs (43). These studies suggest that the combination of NMDA and VSCC antagonist properties of ethanol enhance its tolerability.

The relevance of adaptations in VSCCs for the clinical phenomenology of ethanol withdrawal is not yet clear. L-channel antagonists may reduce the severity of some withdrawal symptoms, but they do not clearly suppress withdrawal seizures (115). However, the existing studies are limited by shortcomings in their study design and the selection of agents with limited CNS penetration.

Serotonin (5-HT)

5-HT systems contribute to the discriminative properties of ethanol in animals and humans. Ethanol facilitates that activity of $5\text{-}HT_{1B}$, $5\text{-}HT_{2C}$, and $5\text{-}HT_3$ receptors, and it shares discriminative stimulus properties with drugs acting at these sites (15,116).

The administration of the 5-HT partial agonist, *m*-chlorophenylpiperazine (mCPP), produces a euphoric effect that is perceived as ethanol-like in early-onset alcoholic patients (117–119). However, mCPP effects were not specifically similar to ethanol, i.e., the effects were similar to several substances of abuse (117). The two mCPP studies that administered mCPP intravenously also reported the induction of craving (117,119), whereas the study administering this drug orally found the opposite (120). mCPP also produced anxiety and irritability (117). The induction of dysphoria by this drug may have contributed to the elicitation of craving. Several studies report that the cortisol or prolactin response to mCPP is reduced in early onset patients (118,119,121). Further, the cerebral metabolic response to mCPP was reduced in early-onset alcoholics (122). In contrast, the euphoric responses to mCPP were enhanced in early-onset

patients relative to patients with a later onset of alcoholism (119).

The site of action of the ethanol-like effects of mCPP is not clear. Its partial 5-HT_{2C} agonist action appears to figure most prominently in its general discriminative stimulus effects (123). mCPP also has activity at 5-HT_3 (124) and 5-HT_7 receptors (125). Preliminary data suggested that ritanserin, a drug that blocks 5-HT (5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7, 5-HT_{1D}) and dopamine (D2) receptors, reduced mCPP effects in healthy humans (125–129). The lack of specificity regarding the site of action of both mCPP and ritanserin limits the interpretation of the mechanisms underlying the ethanol-like and craving effects of mCPP. Also, the failure of ritanserin as an alcoholism pharmacotherapy (130) further raises concerns about the therapeutic applicability of the mCPP studies.

Molecular genetic studies further increased interest in genetic variation associated with the function of the 5-HT transporter and the regulation of central 5-HT turnover. Although the findings have not been replicated (131,132), two groups have associated 5-HT transporter alleles with reduced central 5-HT function or poor impulse control in alcoholic individuals (133,134). However, one study failed to find that alleles of the 5-HT transporter were associated with alcoholism (131). One hypothesis guiding these studies was that reduction in the efficacy or availability of synaptic 5-HT resulting from enhanced density or function of the 5-HT transporter would contribute to the constellation of behaviors associated with early-onset alcoholism (135,136). Alternatively, reduced density of 5-HT transporter binding in the brain might reflect reductions in the density of 5-HT terminals that might contribute to reduced central 5-HT function (137,138). Studies suggest that 5-HT transporter antagonists have limited efficacy for alcoholism and may make some early-onset patients worse (139,140). However, 5-HT–related vulnerability may be reflected in comorbid conditions. Ethanol-dependent patients with depression may benefit from treatment with 5-HT transporter antagonists (141), and patients with comorbid anxiety may benefit from the addition of the 5-HT_{1A} agonist buspirone (142).

Preclinical research suggests that ethanol stimulates 5-HT_3 receptors and that 5-HT_3 antagonists may attenuate the discriminative stimulus properties of ethanol and ethanol self-administration in animals (143). In humans, the 5-HT_3 antagonist odansetron did not robustly attenuate the discriminative stimulus effects of ethanol (144). However, a clinical trial employing odansetron found evidence of efficacy in early-onset ethanol-dependent patients (145).

Catecholamines

Dopamine

Dopamine-mediated neurotransmission has received much attention due to the involvement of dopamine in rewarding properties of ethanol and other drugs (146). Doses of ethanol that produce motor stimulation or ataxia increase the firing rate of midbrain dopamine neurons of unanesthetized rats (147). *In vitro*, ethanol added to brain slices in concentrations of 20 to 320 mM also stimulated the activity of ventral tegmental dopamine neurons (148).

Ethanol increases dopamine release in brain regions involved in the reinforcing effect of ethanol, such as the ventral tegmental area and nucleus accumbens (21). Further, rats bred to drink ethanol, compared to ethanol nonpreferring animals, show increased dopamine release associated with ethanol consumption (149). In addition, dopaminergic drugs alter ethanol self-administration in animals (150). Ethanol also has effects on dopamine release that may be mediated by opioid and nicotinic cholinergic systems (151,152). During ethanol withdrawal, there are reductions in dopamine release in the ventral striatum and in the nucleus accumbens (153). These decreases may contribute to withdrawal-related dysphoria. Ethanol, NMDA receptor antagonists, and L-type VSCC antagonists attenuated these dopamine deficits (153–155).

Norepinephrine

The locus coeruleus (LC) contains the cell bodies for the brain dorsal noradrenergic system (156). LC basal activity and activation are reduced by ethanol, an action that may contribute to sedative effects of ethanol (157,158). Ethanol also produced biphasic effects on norepinephrine turnover in the brain, with low doses increasing turnover and higher doses depressing turnover. The sensitivity of noradrenergic systems to ethanol effects varies among brain regions (159).

Catecholamines: Clinical Correlates

Modulation of catecholamine function modulates the stimulant and intoxicating effects of ethanol. Catecholamine synthesis inhibition, produced by α-methyl-para-tyrosine, modestly reduced ethanol intoxication in healthy humans (160). Similarly, dexamphetamine and methamphetamine pretreatment either had no effect or modestly potentiated ethanol intoxication in humans (39). In contrast, the α_2-adrenergic antagonist yohimbine potentiated the intoxicating effects of ethanol, but did not substantially alter the subjective sense of euphoria associated with intoxication (161). These data may conflict with other studies suggesting that β-adrenergic stimulation attenuates ethanol intoxication, whereas β-adrenergic blockade enhances intoxication (162,163). In recently detoxified early-onset alcohol-dependent patients, yohimbine effects have a low degree of similarity to ethanol effects and it reduced ethanol craving levels below baseline (117).

Several studies document reduced sensitivity of both dopamine and noradrenergic receptors in recently detoxified patients. Reduced sensitivity of dopamine receptors is sug-

gested by blunted growth hormone responses to dopamine agonists (164). These data are consistent with neuroimaging data, suggesting that the density of dopamine transporter binding is preserved but striatal D2 receptor density is decreased in ethanol-dependent patients (137,165). Downregulation of postsynaptic α_2-adrenergic receptors is suggested by blunted growth hormone responses to clonidine and increased cortisol responses to yohimbine (121,166). In contrast, presynaptic noradrenergic activity appears to normalize rapidly following withdrawal, as measured by the CSF levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) (167). Similarly, the presynaptic component of the noradrenergic response to yohimbine, reflected by plasma MHPG levels, is normal in patients sober for approximately 1 month (121).

Genetic studies relating catecholamine receptor alleles to the vulnerability to alcoholism have been a promising but controversial research strategy that has not yet born fruit. Initial studies suggested that D2 receptor alleles were associated with alcoholism (168,169). However, more definitive subsequent studies were negative (170). Reanalysis of published studies suggested that the positive findings reflected ethnic differences between the patient and control population (171). A subsequent study also suggested that D2 receptor alleles predicted an anticraving response to bromocriptine (172). However, studies using dopamine agonists to treat alcoholism have so far had limited promise (173, 174). A tentative association between versions of the D4 receptor and novelty-seeking (175) was reported. However, this finding was not replicated, and studies of other dopamine receptor genes to alcoholism have been negative (133, 176–182).

Opiates

Preclinical Studies

Ethanol modulates opioid neuropeptides in regionally specific ways. Acute ethanol administration to animals or ethanol perfusion of cultured pituitary or hypothalamic tissue increased (183) or had no effect on (184) tissue content or release of β-endorphin. Ethanol also raised enkephalin and dynorphin levels in some brain regions in some studies (183,185). Chronic ethanol administration to rodents decreased pituitary β-endorphin processing and reduced hypothalamic mRNA levels of the peptide precursors proopiomelanocortin (POMC) and prodynorphin (186,187).

In vitro, ethanol has a biphasic effect on μ opioid receptor binding. Ethanol concentrations, in the range of 10 to 25 mM, produce a small, but significant, increases in the binding of μ receptor ligands, whereas higher concentrations of ethanol inhibit ligand binding to the μ receptor (188). Under physiologic conditions, the μ receptor may be more sensitive to ethanol-induced inhibition than the δ receptor (189). Chronic ethanol administration reduces the density and function of striatal and accumbens μ opioid receptors (190). In contrast, chronic ethanol administration also modulates the binding and function of δ opioid receptors (191,192).

Opiates: Clinical Correlates

Naltrexone appears to reduce the rewarding effects of ethanol and ethanol consumption in social drinkers (41, 193). Also, naltrexone maintenance appears to reduce the pleasurable aspects of ethanol consumed during treatment for alcoholism (194,195). This property appears to contribute to the capacity of opiate antagonists to reduce ethanol consumption in alcoholic patients (196,197).

The contributions of endogenous opiate systems to the rewarding effects of ethanol are further supported by evidence of abnormalities in these systems in alcoholic patients. However, the current data do not yield a clear picture of these abnormalities. Postmortem studies have described both increased μ-receptor density (198) and decreased μ-receptor affinity (199). CSF and plasma studies have also suggested the existence of reductions in β-endorphin levels and ethanol-stimulated increases in plasma β-endorphin levels (200,201). Naltrexone reductions in ethanol effects appear to be particularly evident in individuals at high risk for developing alcoholism (202). These data suggest a genetic component underlying the efficacy of naltrexone treatment for alcoholism. To date, there have been negative studies evaluating the association of the proenkephalin A gene and μ opiate receptor gene with alcoholism (203,204).

THE NEURAL CIRCUITRY OF ALCOHOL ABUSE AND DEPENDENCE: INSIGHTS FROM NEUROIMAGING AND NEUROPSYCHOLOGY

Structure (Computed Tomography, Magnetic Resonance Imaging, Postmortem)

Preclinical studies describe alcoholism-related neurotoxicity. These toxic effects appear to reflect a combination of the neurotoxic effects of ethanol, the interaction of ethanol with nutritional deficiencies, and the neurotoxic consequences of ethanol withdrawal (205). In rats, extended consumption of an ethanol diet did not produce anatomic deficits. However, ethanol withdrawal was associated with reductions in dendritic arborization and neuronal loss (206).

Brain shrinkage and neuronal loss has been documented in the brain tissue from individuals with alcoholism in both cortical and limbic regions (207). With respect to brain volume, postmortem research suggests that white matter loss appears to be more prominent than gray matter loss

(208). Neuronal loss appears to be primarily loss of pyramidal neurons, with relative sparing of interneurons (208). Another study was unable to replicate neuronal loss using uniform sampling and unbiased neuron counting methods (209). However, even when neurons are extant, they may exhibit structural deficits consistent with neurotoxicity (210). Generally, cortical and limbic brain shrinkage and neuronal loss may be more prominent in individuals whose alcohol dependence is complicated by Wernicke's encephalopathy and Korsakoff's psychosis (211). The Wernicke-Korsakoff syndrome has been associated with abnormalities in frontal cortex, as well as in several subcortical structures including the thalamus, hippocampus, mamillary bodies, and amygdala (10).

Structural neuroimaging studies are consistent with the findings in postmortem research. Cortical and limbic volumetric losses in ethanol-dependent patients have been described using computed axial tomography (CAT) and magnetic resonance imaging (MRI) (212,213). Gray and white matter volumetric losses are progressive with heavy drinking and are most prominent in frontal and temporal cortex (213–215). Ethanol-dependent individuals also show sulcal and ventricular enlargement (215), as well as hippocampal volume reduction (216). Reductions in the volume of the corpus callosum has also been described (217). Brain atrophy documented in structural neuroimaging studies is most more prominent with advancing age in adults (Fig. 100.4) (218). This age-related effect may reflect an age-related vul-

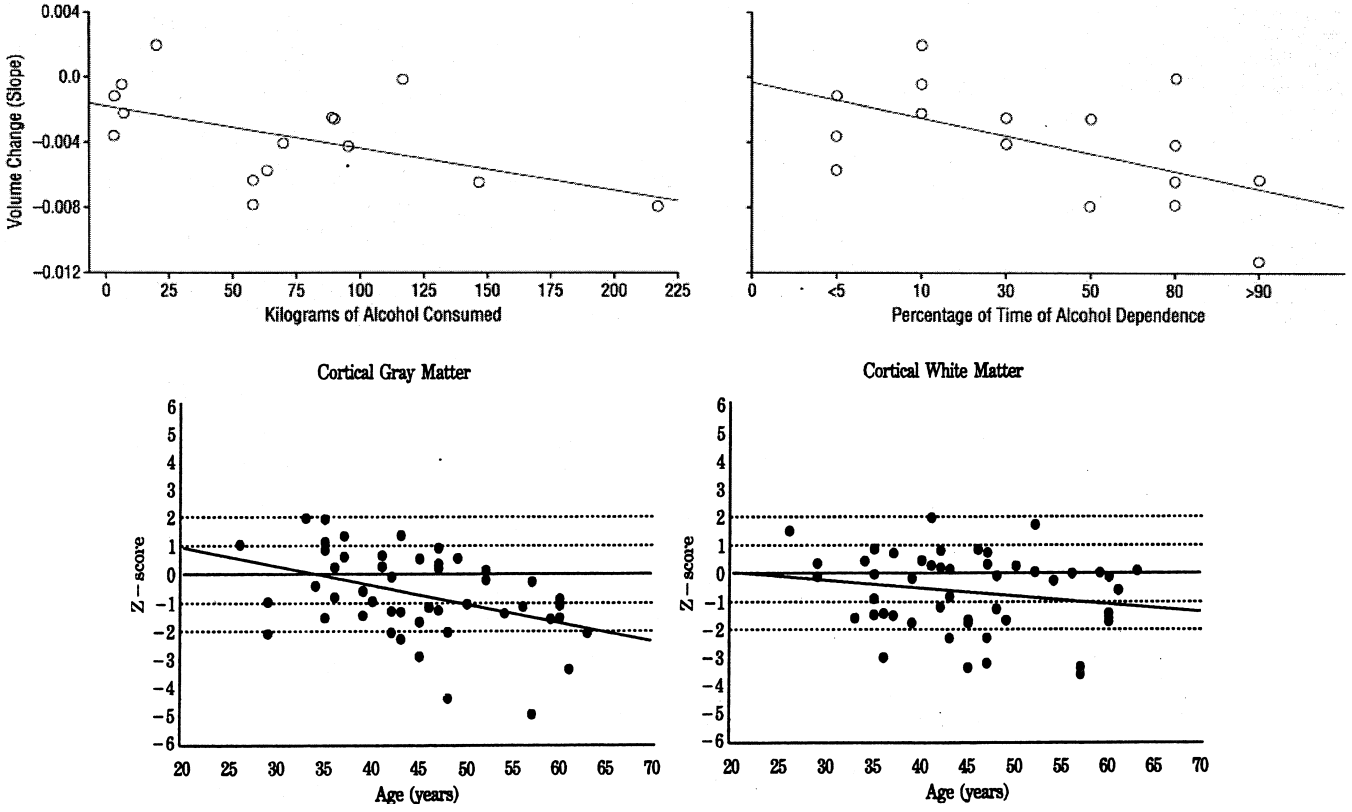

FIGURE 100.4. The **top two panels** illustrate the relationship between drinking severity and duration with gray and white matter volume loss in ethanol-dependent patients. The **bottom two panels** illustrate the interaction between alcoholism and volume loss with age. **Top figures**: The relationship between cortical gray matter rate of change and the amount of alcohol consumed during the follow-up period (*left*) (Spearman rho = −0.52, p = .04) and between the cortical gray matter rate of change and the estimated amount of time during past 5 years that alcoholic patients (group 1) met *Diagnostic and Statistical Manual of Mental Disorders*, third edition revised (DSM-III-R) criteria for alcohol dependence during the follow-up period (*right*) (Spearman rho = −0.53, p = .04). One alcoholic patient who reported 950 kg of alcohol consumption is omitted from the **left panel** so as not to distort scaling. The *darker circle* represents two patients with overlapping values. (From Pfefferbaum A, Sullivan EV, Rosenbloom MJ, et al. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. *Arch Gen Psychiatry* 1998;55:905–912.) **Bottom figures**: Cortical gray (*left*) and white matter (*right*) volume changes with age in ethanol-dependent patients. Data from individual ethanol-dependent patients are expressed as age-corrected Z-scores plotted as a function of age. (From Pfefferbaum A, Lim KO, Zipursky RB, et al. Brain gray and white matter volume loss accelerates with aging in chronic alcoholics: a quantitative MRI study. *Alcohol Clin Exp Res* 1992;16:1078–1089, with permission.)

nerability to ethanol in older populations, the interaction of aging processes, and the neurotoxicity of alcoholism, i.e., the ''premature aging of the brain'' (219), as well as the accumulated impact of long-standing alcoholism on older populations. Thus, atrophy may not be detectable in young healthy ethanol-dependent populations (220). In contrast, ethanol-dependent adolescents show hippocampal volumetric changes not seen in the studies of healthy young adults (221). The study in adolescents raises the possibility that adolescents show disruptive effects on brain development or an increased sensitivity to the neurotoxic effects of ethanol.

Over the initial years of sobriety, there is recovery in the volumes of gray and white matter and reductions in sulcal and ventricular volume (222). There are differences in the rate of particular brain regions and particular tissue types with regard to the rate of recovery (222,223). The relatively rapid recovery of white matter volume with sobriety does not appear to reflect the return of tissue water displaced by ethanol, i.e., tissue rehydration (224).

Nutritional status, neurologic complications of ethanol withdrawal, and hepatic function appear to be related to findings in structural neuroimaging studies. Ethanol withdrawal seizures have been linked to neurotoxicity in these patients (225). Supporting this association, temporal cortex white matter loss was particularly associated with ethanol withdrawal seizures (226). Although cortical atrophy has been described in ethanol-dependent patients with good nutritional status (227), the Wernicke-Korsakoff syndrome and hepatic cirrhosis are generally associated with more prominent MRI volumetric deficits in cortical and limbic structures than ethanol-dependent patients who are otherwise healthy (228).

To date, there has been very little study of structural factors that might predispose individuals to develop alcoholism. One risk factor, antisocial personality disorder, appears to be independently associated with reductions in frontal cortex gray matter volume (229). Thus, the observation that frontal gray matter volume loss is present in young ethanol-dependent patients could reflect a combination of the vulnerability to alcoholism and atrophic effects of ethanol dependence (214).

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) has been applied to the evaluation of structural deficits in alcoholic patients in a limited fashion. Proton-MRS ([^{1}H]MRS) enables the measurement of N-acetyl-aspartate (NAA), a constituent of viable neurons. One study found reductions in the NAA/creatine ratio in the frontal cortex and cerebellum of ethanol-dependent patients (230,231). A phosphorus-MRS ([^{31}P]MRS) study found reductions in phosphodiester and phosphocreatine levels in cortical white matter in ethanol-dependent patients (232).

Findings From Functional Neuroimaging

Functional neuroimaging studies described reductions in cortical blood flow and metabolism associated with ethanol withdrawal. There is a limited understanding of the extent to which these studies also reflect genetic or alcohol-related structural abnormalities. Studies of ethanol intoxication suggest that it reduces cortical metabolism in humans (233). Clinical studies of withdrawal, mostly conducted during or following medications for detoxification, predominately describe reductions in regional cerebral perfusion or glucose metabolism in frontal and temporal cortex (234,235). More pronounced deficits were observed in patients with evidence of cortical atrophy based on structural neuroimaging (236), years of ethanol use, age (237), and multiple ethanol detoxifications (238). Cerebral perfusion and metabolic deficits may attenuate over the initial months of sobriety (237), and improvement may continue over several years (239). Antisocial personality (240), a risk factor for developing alcoholism, but not family history of alcoholism (241), was associated with more pronounced volumetric deficits.

Across several studies, reductions in resting frontal cortical perfusion and metabolic rate is associated with reduced performance on cognitive tests that engage the frontal cortex (242). Similarly, cerebellar metabolic deficits are associated with behavioral evidence of cerebellar dysfunction (236).

Behavioral Studies

The most profound cognitive deficits associated with alcoholism are the memory impairments arising from nutritional deficiency, as in Korsakoff syndrome (10), or hepatoxicity, as in hepatic encephalopathy (243). Although the most severe consequences of alcoholism for cognition may not reflect the direct toxic effects of ethanol on the brain, many patients exhibit cognitive deficits independent of these factors that reflect the combined impact of age, familial vulnerability for alcoholism, adaptations to ethanol effects on the brain, perhaps degree of liver injury (244), presence of comorbid depression, and ethanol-related neurotoxicity (245). Cognitive function is further compromised in those patients who continue to drink, due to the direct effects of ethanol on cognition (246).

The familial vulnerability to alcoholism and traits associated with that vulnerability are associated cognitive deficits and educational achievement (247). Although reductions in attention, planning, visual-spatial learning, and impulse control have been described in children of alcoholics (248), these findings are not universal (249). These findings may be largely accounted for by comorbid traits such as antisocial personality, similar to both MRI and event-related potential (ERP) findings in alcohol dependent patients (250,251). Consistent with this view, the familial risk for cognitive deficits associated with alcoholism is particularly associated with poor prognosis of the parent in alcoholism treatment,

a characteristic of antisocial alcoholism (252). Familial history of alcoholism appears to compound the negative consequences of social drinking on cognitive function (253). However, children of alcoholics exhibit attenuated impairment in attention and memory relative to individuals with a familial alcoholism history (254). Thus it is possible that cognitive responses to ethanol may also contribute to the risk for making the transition from social drinking to alcoholism.

Although traits associated with the vulnerability to alcoholism contribute to cognitive deficits seen in ethanol-dependent patients, they do not account for the deficits in patients (255). Ethanol-dependent patients show many impairments in cognitive function. Deficits in the level of performance and efficiency of verbal skills, learning and memory, problem-solving and abstracting, and perceptual-motor skills have been described (256). Cognitive deficits may reflect in part the degree of neurotoxicity related to alcoholism. For example, young ethanol-dependent patients may show normal brain volumes on MRI and normal cognitive function (257,258). With repeated episodes of ethanol withdrawal and advancing age, cognitive deficits become more pronounced (259).

Cognitive function improves over the initial year of sobriety; however, the domains of cognitive function do not recover at the same rate and recovery may be partial (260, 261). Poor cognitive function at the time that treatment is initiated appears to predict improved alcohol-related treatment outcomes (262). However, progress in treatment may be reflected in improved cognitive function (263). Consistent with the view that treatment may modulate cognitive recovery, some cognitive deficits in recovering patients appear to respond to cognitive rehabilitation (264).

In summary, the behavioral studies describe the display of deficits in cognitive functions that may have implications for circuitry dysfunction in alcoholism: executive function deficits associated with the prefrontal cortex, visual-spatial deficits associated with the parietal cortex, and learning/memory deficits that may involve the hippocampus and related temporal cortical structures. Overall, these studies are consistent with the findings related to reduced tissue volume on MRI, reductions in cortical metabolism with fluorodeoxyglucose (FDG)-PET (242), and information processing deficits in ERP studies (265). This overlap implies a connection between alterations in brain structure, function, and behavior related to alcoholism.

THE INTERPLAY OF THE NEURAL CIRCUITRY AND NEUROCHEMISTRY OF ALCOHOLISM: IMPLICATIONS FOR TREATMENT

Ethanol has multiple specific effects on amino acid, monoamine, and neuropeptide neurotransmitter systems, and these effects contribute to its complex array of behavioral effects in animals and humans. Direct effects of ethanol on excitatory and inhibitory neurotransmission also are modulated by direct and indirect effects of ethanol on ion channels. Further, the cellular consequences of exposure to ethanol are modulated by ethanol-sensitive regulatory enzymes, such as PKA and PKC.

The diversity of ethanol targets in the brain and frequent co-localization of the neural circuitry bearing the sites of ethanol action raise the possibility of convergent mechanisms underlying the rewarding effects of ethanol in the brain. In this regard, there is growing evidence that the interplay of the prefrontal cortex (PFC) and limbic structures including the nucleus accumbens (NAc) and amygdala generally plays an important role in reward (266,267). Ethanol has many component actions that directly inhibit the output of the NAc including NMDA receptor antagonism, GABA facilitation, and enhancement in 5-HT and dopamine release (267). Drugs that antagonize the inhibitory effects of ethanol in the NAc, such as naltrexone (268), may play an important role in the treatment of alcoholism even if μ opiate receptors are not a major site of action for many of the behavioral effects of ethanol.

Abnormalities in PFC development may be an important factor influencing the vulnerability to alcoholism, in part by altering the interplay of PFC and NAc that underlies reward. As noted above, the vulnerability to alcoholism, particularly in the case of individuals with antisocial personality disorder or impulsive traits, appears to be associated with behavioral, physiologic, and structural evidence of PFC dysfunction. An important and unanswered question is, How does PFC dysfunction contribute to the vulnerability to alcoholism? Hypotheses have been presented that suggest that alcoholism is just one of several forms of impulsive behavior that these individuals fail to inhibit due to a general deficiency in behavioral inhibition or as a consequence of the failure to anticipate the negative consequences of alcoholism (269,270).

These cognitive hypotheses may be complemented by a reward dysfunction hypothesis resting on a consideration of the impact of PFC dysfunction on mechanisms underlying reward. The PFC input into limbic structures responsible for reward is critical to the experience, anticipation, and seeking of reward (271,272). The activation of PFC outputs to limbic structure causes a release of glutamate that may serve to activate, for example, the GABAergic output neurons of the NAc, and this action opposes direct effects of ethanol (268). From this perspective, PFC activation serves as a ''brake'' on reward mechanisms. In fact, it is tempting to think of this PFC-NAc interplay as a pathway contributing to the capacity of human judgment to restrain impulsive reward-related behavior. Yet abnormal PFC input would also be expected to disturb NAc function with respect to both the processing of rewarding stimuli generally and drugs of abuse in particular. Thus, it may not be surprising that

the familial vulnerability to alcoholism is associated with both PFC functional deficits and alterations in the capacity of drugs representing multiple component actions of ethanol (GABA, NMDA, opiate) to generate rewarding or aversive experiences in humans. If so, then genes controlling corticolimbic neurodevelopment and genes encoding the individual targets or intracellular mediators of ethanol action may provide a diversity of potential foci for the study of the genetics of alcoholism.

The cellular adaptations to chronic ethanol underlie tolerance to ethanol effects and withdrawal symptoms that develop upon the initiation of abstinence. As reviewed in this chapter, acute withdrawal symptoms reflect an enhancement of glutamatergic function and a deficit in GABAergic function. When examined beyond these generalizations, the neurobiology of ethanol dependence appears to be complex. For example, dependence-related adaptations may be reflected in absolute numbers of receptors in binding studies or perhaps changes in receptor subunit composition. Also, protracted withdrawal may produce functional changes in the opposite direction of acute withdrawal. Withdrawal is a critical juncture in the treatment of alcoholism because withdrawal symptoms may present an immediate medical risk, motivate relapse to ethanol use, induce withdrawal-related neuroplasticity that can increase risk for subsequent withdrawal-related medical complications, and may promote neurotoxicity. In light of these issues, novel treatments for withdrawal aim to achieve multiple therapeutic objectives (273).

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