INVITED COMMENTARY

ALCOHOL DEPENDENCE: A COMMENTARY ON MECHANISMS

PAULA L. HOFFMAN and BORIS TABAKOFF*

Department of Pharmacology, University of Colorado Health Sciences Center, Box C236, 4200 East Ninth Avenue, Denver, Colorado 80262, USA

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Abstract — The alcohol dependence syndrome includes the presence of alcohol tolerance, physical dependence and an inability to control one's alcohol intake. Studies are reviewed that implicate the mesolimbic dopaminergic systems, and the γ-aminobutyric acid-A (GABA_A) and N-methyl-D-aspartate (NMDA) receptors as mediators of various aspects of the alcohol dependence syndrome. It is suggested that alcohol-induced changes in the GABA_A receptor may play a role in certain aspects of tolerance to alcohol and in altered abilities of an individual to terminate alcohol intake. Chronic alcohol-induced increases in the activity of NMDA receptors may contribute to the withdrawal signs that are the defining feature of physical dependence on alcohol. It is hypothesized that decreased mesolimbic dopaminergic function, which occurs during alcohol withdrawal, may be involved in the compulsion to initiate and maintain alcohol drinking, another aspect of the alcohol dependence syndrome. Furthermore, evidence is presented that this decreased dopaminergic function could occur secondarily to the increase in NMDA receptor function, such that the alcohol-induced increase in NMDA receptor function could underlie both the overt withdrawal signs and the compulsion to drink alcohol in the alcohol-dependent individual.

INTRODUCTION

Edwards (1986) has described an 'alcohol dependence syndrome', which consists of a number of elements that characterize the clinical picture of dependence on alcohol. Among the signs and symptoms of the alcohol dependence syndrome are tolerance and physical dependence, as well as alcohol-seeking behaviour and awareness of a compulsion to drink alcohol (Edwards, 1986). Similarly, the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, fourth edition (DSM-IV), and the International Classification of Mental and Behavioral Disorders of the World Health Organization, tenth edition (ICD-10), define diagnostic criteria for alcohol dependence that include the presence of alcohol tolerance, the presence of an alcohol withdrawal syndrome when drinking has ceased or been reduced (i.e. physical dependence on alcohol), the intake of alcohol to relieve signs of withdrawal, and the presence of difficulties in controlling drinking, with a strong desire or compulsion to drink. These definitions provide a framework within which to assess the biological/molecular mechanisms that underlie alcohol dependence, keeping in mind that not all of the elements of the dependence syndrome are always present, and that similar or different mechanisms may underlie each element.

Although situational/conditioning factors significantly influence the desire of an alcohol-dependent individual to ingest alcohol (Childers et al., 1992), alcohol tolerance, the alcohol withdrawal syndrome (physical dependence) and alterations in an individual's control over alcohol intake can all be considered to arise as a consequence of adaptive changes in the brain produced by the chronic presence of alcohol. Neuroadaptations that generate 'pressure' to drink alcohol may involve a change in the brain's reinforcement systems. The neuroadaptation(s) that leads to physical dependence involves a change in CNS excitability that is evidenced as the signs and symptoms of alcohol withdrawal. Neuroadaptation to alcohol's action in brain can also be used to explain the emergence of
functional (CNS) tolerance to alcohol. Current evidence is demonstrating that alcohol-induced adaptation in certain neuronal systems is preferentially responsible for defined components of the alcohol dependence syndrome, but there is little evidence that a singular neuroadaptive event underlies the full gamut of characteristics of alcohol dependence as defined by DSM-IV or ICD-10 criteria.

NEUROADAPTATION IN THE BRAIN
\textit{\gamma}-AMINOBUTYRIC ACID-A (GABA\textsubscript{A}) RECEPTOR SYSTEMS

A number of studies (although not all) have demonstrated that alcohol at concentrations of 10–30 mM potentiates the actions of GABA at the GABA\textsubscript{A} receptor (reviewed by Tabakoff and Hoffman, 1996). Since GABA\textsubscript{A} receptors gate chloride channels that mediate neuronal hyperpolarization (inhibition of firing), and have been implicated in the sedative, anxiolytic and anticonvulsant actions of a number of drugs (e.g. benzodiazepines, barbiturates), alcohol’s CNS depressant properties have been proposed to be mediated, in part, by actions at the GABA\textsubscript{A} receptor. Adaptation to the chronic presence of alcohol in brain could be postulated to result either in changes in the GABA\textsubscript{A} receptor, which alter the receptor’s response to the neurotransmitter GABA, or to result in changes in the sensitivity of the receptor to alcohol’s actions, or both. A change in the response of the GABA\textsubscript{A} receptor to GABA (e.g. down-regulation of the receptor as an adaptive response to the acute potentiating effects of alcohol) would be expected to result in CNS hyperexcitability when alcohol was withdrawn from an animal. On the other hand, if only the response to alcohol is altered during chronic alcohol intake, one may see only manifestations of alcohol tolerance.

In one biochemical study, in which muscimol (a GABA\textsubscript{A} receptor agonist)-stimulated chloride flux was measured in cerebral cortical tissue of rats exposed chronically to alcohol, a reduced response of the GABA\textsubscript{A} receptor to the agonist was reported (Morrow \textit{et al.}, 1988). There have also been reports of decreased behavioural responses to GABA or GABA\textsubscript{A} receptor agonists in animals exposed chronically to alcohol (Taberner and Unwin, 1981; Martz \textit{et al.}, 1983; Gonzalez and Czachura, 1989). However, other studies have not found decreases in muscimol-stimulated chloride flux in brain tissue from animals treated chronically with alcohol (Allan and Harris, 1987), and have found little or no change in the number of receptors, or binding characteristics of GABA\textsubscript{A} receptors, in brains of chronically alcohol-treated animals (reviewed in Tabakoff and Hoffman, 1996). There does appear to be an increase in binding of the benzodiazepine partial inverse agonist, Ro15-4513, in the cerebellum of alcohol-treated animals, as well as an enhanced ability of Ro15-4513 to inhibit the actions of muscimol (Mhatre \textit{et al.}, 1988; Buck and Harris, 1990). The relationship between the increase in Ro15-4513 binding and manifestations of alcohol withdrawal hyperexcitability and/or alcohol tolerance is difficult to contemplate, since it is unclear what physiologic function is subserved by the GABA\textsubscript{A} receptor subtypes in the cerebellum that show a preferential affinity for Ro15-4513. A recent electrophysiological study also found no evidence that alcohol withdrawal hyperexcitability in isolated hippocampal slices is caused by decreases in the function of GABA\textsubscript{A} receptors (Whittington \textit{et al.}, 1992). This latter study, in conjunction with the inconsistent findings regarding changes in response of the GABA\textsubscript{A} receptor to GABA or other GABA agonists, and lack of change in receptor number in brains of alcohol-treated animals, argues against a major role for GABA\textsubscript{A} receptor down-regulation in generation of signs of CNS hyperexcitability during alcohol withdrawal. The fact that benzodiazepines can attenuate alcohol withdrawal signs may simply reflect the strong anticonvulsant and anxiolytic properties of these drugs, rather than indicating that the changes in GABA\textsubscript{A} receptors are directly responsible for alcohol withdrawal hyperexcitability of the CNS. In humans, while benzodiazepine treatment (in high doses) can clearly prevent the development of delirium tremens, the selective efficacy of benzodiazepines in preventing alcohol withdrawal seizures during the early stages of withdrawal has been questioned (Earnest, 1993).

Given the evidence that alcohol tolerance and alcohol physical dependence are dissociable phenomena (Tabakoff and Ritzmann, 1977), one can consider the role of the GABA\textsubscript{A} receptor in alcohol tolerance independently of GABA\textsubscript{A} receptor involvement in withdrawal hyperexcitability.
In two investigations of brain preparations obtained from animals that were chronically exposed to alcohol, the potentiation by alcohol of GABA-stimulated chloride flux was greatly reduced, i.e. the system became tolerant to the effect of alcohol (Allan and Harris, 1987; Morrow et al., 1988). The proposal that GABA receptors with a particular subunit composition (e.g. those containing the α₁ subunit and having a high affinity for the drug zolpidem) are selectively sensitive to alcohol (Criswell et al., 1995) would lead one to investigate changes in α₁-containing GABA receptors after chronic alcohol ingestion. Interestingly, one of the most consistently observed changes in such studies has been a decreased expression (mRNA and protein) of the α₁ subunit of the GABA_A receptor (reviewed in Tabakoff and Hoffman, 1996). However, expression of GABA_A receptor β subunits was increased after chronic alcohol exposure, and changes in the expression of a number of other GABA_A receptor subunits have also been reported in various brain regions after chronic alcohol exposure (e.g. decrease in α₂, increase in γ₃, increase in α₆) (reviewed in Hoffman and Tabakoff, 1996). These changes could also have an effect on the ability of alcohol to potentiate GABA responses. Although the chronic alcohol-induced changes in the GABA_A receptor may predispose to the development of tolerance to certain actions of alcohol, recent evidence has also provided a role for the GABA_A receptor, and for adaptations in this receptor, in the control (or loss thereof) of alcohol intake (see Hodge et al., 1995 and further discussion below).

NEUROADAPTATION IN BRAIN N-METHYL-D-ASPARTATE (NMDA) RECEPTOR SYSTEMS

There is substantial evidence for up-regulation of the NMDA subtype of glutamate receptor after chronic alcohol exposure of mice and rats and of cells in culture. When mice were fed alcohol in a liquid diet to produce physical dependence, there was an increase in the number of NMDA receptors in the brain, as measured by binding of the NMDA receptor antagonist, dizocilpine (Grant et al., 1990b). A similar change was found in rats (Sanna et al., 1993). This change in NMDA receptor properties has been suggested to result from increased levels of NMDA receptor subunit proteins in various brain areas of chronically alcohol-treated animals (Trevisan et al., 1994; Snell et al., 1996). The time course for the dissipation of the change in NMDA receptor properties paralleled the time course for disappearance of alcohol withdrawal seizures (Gulya et al., 1991), and administration of NMDA receptor antagonists has been shown to effectively attenuate alcohol withdrawal seizure activity (Grant et al., 1990b; Morrisett et al., 1990) (although, again, this effect could result from the general anticonvulsant properties of these drugs). In cerebellar granule cells maintained in primary culture, chronic alcohol exposure also resulted in an increased number of NMDA receptors (Hoffman et al., 1995) and in increased function of these receptors, measured as an increase in intracellular Ca²⁺ (Iorio et al., 1992). This increased receptor function has been suggested to lead not only to increased neuronal excitability, but also to enhanced susceptibility to glutamate-induced neurotoxicity, both in the cerebellar granule cells and in cultured cerebral cortical cells (Iorio et al., 1993; Ahern et al., 1994). Electrophysiological studies of hippocampal slices obtained from mice treated chronically with alcohol further indicated an enhanced NMDA receptor-mediated component of synaptic excitation during alcohol withdrawal (Whittington et al., 1995). In this study, it was suggested that a synergistic effect of increased NMDA receptor function and voltage-sensitive calcium channel (VSCC) function might contribute to alcohol withdrawal hyperexcitability. The findings of differences both in NMDA receptors and in VSCC in lines of mice bred selectively for high and low susceptibility to alcohol withdrawal seizures (Valverius et al., 1990; Brennan et al., 1990) further support a role for both of these systems in alcohol physical dependence and the overt manifestations of CNS hyperexcitability during alcohol withdrawal. Interestingly, there is little evidence suggesting that the chronic alcohol-induced changes in the NMDA receptor systems generate tolerance to ethanol’s actions. Studies by Iorio et al. (1992) and White et al. (1990) demonstrated that the magnitude of inhibition of NMDA receptor function by ethanol was equivalent in neurons chronically exposed to alcohol, compared to control neurons. On the other hand, the adaptations of the NMDA receptor system may
have implications in initiation and maintenance of alcohol intake in physically dependent animals (see below), as well as having a role in generating alcohol withdrawal seizures.

**ALCOHOL-INDUCED REINFORCEMENT AND CHANGES IN CONTROL OF ALCOHOL INTAKE: ROLE OF DOPAMINERGIC NEURONS AND THE NMDA AND GABA<sub>A</sub> RECEPTOR SYSTEMS**

Alcohol has not been found to be an efficacious positive reinforcer, either in animals or in humans, when a heterogeneous population* is investigated, and often experimental animals must be induced to drink alcohol by procedures such as food deprivation, alteration of the taste of the alcohol, acclimatization to increasing concentrations of alcohol, or association of alcohol with the presence of other reinforcers (see Grant et al., 1990a; Samson and Harris, 1992). However, although alcohol reinforcement has been more difficult to measure than positive reinforcement produced by other abused drugs, it has been hypothesized that the same neuronal systems mediate reinforcement for alcohol and for other addictive drugs (Koob, 1992; Nestler et al., 1993). These systems are believed to include the mesolimbic dopaminergic pathways in the brain (Koob, 1992; Wise and Hoffman, 1992; Pennartz et al., 1994), consisting of dopamine neurons with cell bodies in the ventral tegmental area and projections to the nucleus accumbens, frontal cortex and other limbic areas. For example, dopamine release has been shown to be increased in the nucleus accumbens during self-administration of cocaine (see, e.g., Hurd et al., 1989). Although demonstration of dopaminergic involvement in the reinforcing effects of opiates has been more controversial, opiates have also been reported to increase dopamine release in the rat nucleus accumbens, and some studies of place preference have also suggested a dopaminergic component to opiate reinforcement (Di Chiara and Imperato, 1988; Di Chiara and North, 1992). Alcohol has similarly been reported to stimulate dopamine release in the rat nucleus accumbens (Imperato and Di Chiara, 1986), and electrophysiological studies have also demonstrated a concomitant alcohol-induced increase in the activity of ventral tegmental dopamine neurons (Gessa et al., 1985; Brodie et al., 1990). The mechanisms by which alcohol increases the activity of dopaminergic neurons and promotes the release of dopamine in the nucleus accumbens or other brain areas is not well-defined, but this action of alcohol may be mediated by alcohol's actions at receptors known to be sensitive to alcohol (e.g. NMDA receptors). Imperato et al. (1990) have suggested that glutamatergic neuronal systems exert a tonic inhibitory control on mesolimbic dopaminergic neurons. It has been shown that administration of NMDA receptor antagonists results in increased dopamine release in the nucleus accumbens (Imperato et al., 1990; Löscher et al., 1991). Since a significant amount of evidence has accumulated that alcohol, acutely, at concentrations of 5–10 mM (25–50 mg/dl), can inhibit the function of the NMDA receptor (for review, see Hoffman, 1995), one can conjecture that alcohol would, like other NMDA antagonists, increase dopamine release. The location of the NMDA receptors which mediate alcohol's actions on the mesolimbic dopaminergic neurons would be expected to be on cell bodies or dendrites of the dopaminergic neurons or on interneurons providing input to the dopaminergic cells. Presynaptic NMDA receptors do exist, but since these receptors, when activated, promote release of neurotransmitters, including dopamine, alcohol's inhibition of the function of presynaptic NMDA receptors would be difficult to reconcile with an increase in dopamine release produced by alcohol. There may, however, be other receptors that synergize with alcohol's actions on NMDA receptors in promoting dopamine release. Low to moderate concentrations of alcohol (≤50 mM) have been shown to promote the binding of opioid agonists to μ opioid receptors (Tabakoff and Hoffman, 1983), and μ opioid receptors are present on the cell bodies of dopaminergic neurons in the ventral tegmental area (VTA). As noted above, activation of these receptors promotes the firing of dopaminergic neurons and release of dopamine in the nucleus accumbens (Matthews and German, 1984; Di Chiara and Imperato, 1988). It is thus of some interest that the opiate receptor antagonist, naltrexone, was found to

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*Animals can, however, be selectively bred for alcohol preference (cf: Li et al., 1993).
reverse the dopamine-releasing effect of alcohol (Benjamin et al., 1993). Naltrexone has also been shown to reduce relapse in a significant proportion of alcoholics (Volpicelli et al., 1992). The limited effectiveness of naltrexone in human alcoholics (see Volpicelli et al., 1995) may, however, indicate that actions of ethanol at receptors other than the opioid receptors (e.g. NMDA receptors) contribute to the positive reinforcing effects of ethanol.

The postulated role of mesolimbic dopaminergic neuronal systems in drug and alcohol reinforcement also provides a basis for hypotheses regarding the neuroadaptive changes in NMDA and GABA_A receptors, and the control of alcohol intake in the dependent animal. In general, it has been hypothesized that adaptations in the systems that mediate reinforcement, which occur following chronic drug administration, result in an enhanced desire for the drug. Withdrawal from chronic administration of alcohol, opiates and cocaine have all been found to be associated with decreased dopamine release in the limbic forebrain areas (Rossetti et al., 1992). Withdrawal from alcohol is also associated with a decreased firing rate of spontaneously active dopaminergic neurons in the VTA (Shen and Chiodo, 1993; Diana et al., 1993). This decreased dopaminergic activity is the opposite to the potentiated dopaminergic activity caused by the acute administration of alcohol, and is therefore expected to be associated with anhedonia and to generate internal cues that lead to a desire to ingest alcohol.

As described above, glutamate, acting through NMDA receptors, has been proposed to exert a tonic inhibitory action on dopamine release in the nucleus accumbens. Although the interactions of the NMDA receptor and dopamine systems need further study (Pap and Bradberry, 1995), it may be proposed that an adaptive up-regulation of NMDA receptors during chronic alcohol ingestion could increase the tonic inhibitory control over dopamine release, resulting in the decreased dopaminergic activity and dopamine release observed after alcohol withdrawal (Rossetti et al., 1992; Shen and Chiodo, 1993; Diana et al., 1993). It is noteworthy that an NMDA receptor antagonist has been reported to reverse the decreased dopamine release in the ventral striatum associated with alcohol withdrawal (Rossetti et al., 1991). Systemic administration of alcohol also reversed the decreased release of dopamine observed in the nucleus accumbens of alcohol-withdrawing animals (Diana et al., 1993).

A recent study by Koob and his colleagues showed that the threshold for intracranial self-stimulation (ICSS) reward was increased with the same time course, after alcohol withdrawal, as the overt signs of alcohol withdrawal (Schulteis et al., 1995). It is believed that decreased dopaminergic transmission is one contributor to ICSS threshold enhancement (Markou and Koob, 1991; Weiss et al., 1992), which results in the negative affective symptoms associated with alcohol and drug withdrawal. This decreased dopaminergic activity and the associated affective symptoms may then play a role in the initiation and maintenance of alcohol drinking. Interestingly, both the decrease in limbic area dopamine release, and the increase in brain NMDA receptors, display a time course that parallels the occurrence of alcohol withdrawal signs (Gulya et al., 1991; Rossetti et al., 1991). These findings suggest the possibility that the same neurochemical change, i.e. increased NMDA receptor function, could underlie both the overt signs of alcohol withdrawal, such as seizures, and the decreased dopaminergic function resulting in the affective or emotional disturbances that are a concomitant of the increased reward threshold. Thus, in the parlance of Edwards (1986), 'the compulsion to drink alcohol' and the withdrawal hyperexcitability elements of the dependence syndrome may be produced by a single neuroadaptive change.

However, it must be kept in mind that systems other than the mesolimbic dopaminergic neuronal pathway can be involved in the control of alcohol intake by animals. In a review of the effects of dopaminergic agonists and antagonists on alcohol reinforcement, Samson and Harris (1992) concluded that only a portion of the control of alcohol intake by animals is mediated by the mesolimbic dopaminergic pathways. In this context, it has been suggested that the GABA_A receptor system of the nucleus accumbens may provide additional control of alcohol intake (Hodge et al., 1995). Experiments in which muscimol was administered into the nucleus accumbens of rats demonstrated that the GABA_A receptor may be involved in the early termination of alcohol self-administration, but not in the initiation or maintenance of alcohol-reinforced responding (which, as described above,
may involve dopaminergic systems). Adaptive changes in the GABA_A receptor in animals chronically treated with alcohol, which render the receptor 'tolerant' to alcohol potentiation of GABA effects, could also alter the ability of the GABA_A receptor to terminate alcohol intake (i.e. interfere with 'feedback control' for termination of alcohol intake by alcohol itself).

CONCLUSION

It is attractive to postulate that neuroadaptations in NMDA and GABA_A receptor systems not only play important roles in the development of alcohol tolerance and physical dependence, but may also be pivotal in the loss of control over alcohol intake, and/or the increased compulsion to drink which is evident in the alcohol-dependent individual.

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REFERENCES


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