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Review Article

Overexcitement and Disinhibition

Dynamic Neurotransmitter Interactions in Alcohol Withdrawal

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In alcohol withdrawal, abnormalities occur in a number of neurotransmitter systems: there is reduced inhibitory function, and increased activity of excitatory systems. The former, indicated by reduced GABA and alpha-2-adrenoceptor activity, acts in conjunction with, and is exacerbated by, the latter, which itself may be due to the potentiation of NMDA activity by depletion of magnesium, and overactivity of catecholaminergic and CRF neurones. These dysfunctions produce immediate effects and may also contribute to the long-term changes in brain excitability by a kindling-like process. It is possible that early and active treatment may oppose this process. Present strategies for treatment of alcohol withdrawal enhance GABA and alpha-2 inhibitory, or reduce excitatory, mechanisms. Future possibilities include the use of CRF and/or NMDA antagonists.

The pathophysiology of alcohol withdrawal is incompletely understood. Disturbances have been reported in a number of measures, including electrolyte imbalances, altered neurotransmitter levels and receptor sensitivity, although these reports have tended to focus on only one or two areas of disturbance. In this article we attempt to integrate several of the different receptor and neurotransmitter abnormalities seen in alcohol withdrawal with the clinical symptoms and signs. These changes can be divided into those involving reduced inhibitory function and those related to increased excitation. They are represented diagrammatically in Fig. 1. From this information, more rational treatment strategies for alcohol withdrawal are proposed.

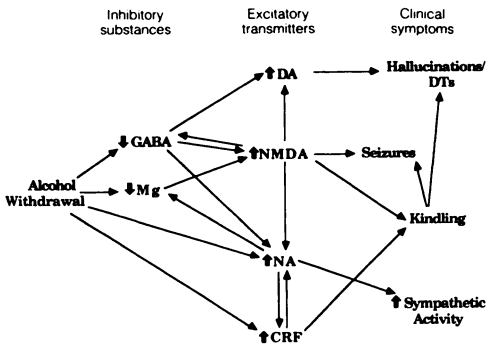

FIG. 1 Summary of receptor dysfunction in alcohol withdrawal: thin arrows (→) indicate the direction of relationships between alcohol withdrawal, inhibitory substances, excitatory transmitters and clinical symptoms; thick arrows indicate inhibition (↓) or excitation (↑) of receptor. (e.g. alcohol withdrawal results in a low concentration of Mg. Overactivity of NMDA receptors, due to this low Mg, can induce seizures and accentuate NA or DA release.)

Reduced inhibitory input

Magnesium

Recent pharmacological investigators unrelated to alcohol research have thrown light on the association between low plasma magnesium (Mg) concentrations and propensity for seizures in alcohol withdrawal. The new understanding of the complexity of the excitatory amino acid/N-methyl-D-aspartate (EAA/NMDA) complex has revealed that activation of glutamate/NMDA receptors in brain areas associated with seizures (e.g. hippocampus) is accompanied by an increased cation flux into cells. This leads to increased cell firing, increased calcium entry, and possibly, if uncontrolled, intracellular damage or cell death (Garthwaite & Garthwaite, 1986). The cation channel gated by the NMDA receptor is partly controlled by the presence of Mg ions, which appear to occupy part of the ionophore (Nowak *et al*, 1984). Thus, Mg ions block the cation channel and oppose the effects of NMDA stimulation, and so are important endogenous inhibitory modulators. The Mg blockade of this channel is concentration-dependent and, in model systems, low Mg levels lead to paroxysmal firing of certain hippocampal cells (Herron *et al*, 1985*a*). We propose that the hypomagnesaemia of chronic alcoholism would lead to chronic excitatory activation (see Fig. 1), and so predispose to many of the symptoms of withdrawal, especially seizures and delirium tremens (DTs).

Levels of Mg in the plasma and cerebrospinal fluid (CSF) tend to be lower in chronic alcoholics than in normal controls (Flink, 1986). Alcohol ingestion causes increased Mg excretion in both alcoholics (Krystal, 1959) and normal subjects (Heaton *et al*,

1962). It is likely there is substantial depletion of whole-body Mg in alcoholics, because, after Mg administration, alcoholics have a net retention of Mg in contrast to normal subjects who have no retention (Flink *et al*, 1957). Acute cessation of drinking in chronic alcoholics causes a simultaneous fall in plasma Mg (Wolfe & Victor, 1969). This may be partly a response to the increase in plasma catecholamine concentrations (Whyte *et al*, 1987) seen in alcohol withdrawal (Potter *et al*, 1984).

Low levels of Mg have been associated with increased convulsive sensitivity to photic stimulation in alcoholics, which can be reversed by infusion of magnesium sulphate (Wolfe & Victor, 1969). The most severe withdrawal symptoms are seen in patients with the lowest Mg levels (Flink, 1986). Withdrawal seizures also occur more frequently in alcoholics with hypomagnesaemia (Wolfe & Victor, 1969), and can be reduced by Mg treatment (Daus *et al*, 1985).

Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS). Furthermore, the benzodiazepines also work through a receptor which facilitates GABA function. Although not seen in all studies, there is an extensive literature on the potentiation of GABA function by alcohol (Ticku *et al*, 1983). This can be seen in neuronal responses (Banna, 1969; Davidoff, 1973; Nesteros, 1980), receptor binding and chloride flux studies (Seilicovich *et al*, 1985; Suzdak *et al*, 1986*a*,*b*; Ticku & Rastogi, 1986; Ticku *et al*, 1986) as well as in behavioural models (Cott *et al*, 1976; Frye & Breese, 1982; Liljeqvist & Engel, 1982; Martz *et al*, 1983). Furthermore, alcohol may potentiate benzodiazepine receptor binding and function (Ticku & Davis, 1981; Ticku *et al*, 1983; Rottenburg, 1985). Recent studies have shown that a new class of benzodiazepine receptor ligand, the inverse agonists, will oppose many of the pharmacological effects of alcohol (Suzdak *et al*, 1986*a*; Lister & Nutt, 1987). Finally, a genetic component to GABA/alcohol interactions has been reported in certain mouse strains (Marley & Wehner, 1987). Clearly, this has marked implications for understanding the inheritance of alcoholism, and warrants evaluation in humans.

There is evidence that GABA/benzodiazepine receptor function is down-regulated after chronic alcohol administration, presumably in compensation for the enhancing effect of alcohol (Freund, 1980; Rottenberg, 1985; Rastogi *et al*, Allan & Harris, 1987). Such a down-regulation of GABA function could cause or contribute to the symptoms of alcohol withdrawal (Littleton, 1989). Consistent with this hypothesis, benzodiazepines (Cowen & Nutt, 1982), and more recently, selective GABA-agonist drugs such as progabide (Fadda *et al*, 1985) and gamma-hydroxybutyrate (Gallimberti *et al*, 1989), have been shown to reduce withdrawal symptoms. Furthermore, Lister & Karanian (1987) demonstrated that benzodiazepine inverse agonists exacerbate alcohol-withdrawal symptoms.

There are fewer clinical studies looking at GABA function in withdrawal. Cerebrospinal-fluid GABA levels during alcohol withdrawal and early abstinence are similar, although in the absence of a control group it is not possible to determine if they differ from normal (Hawley *et al*, 1981). In addition, chronic alcoholics have reduced plasma GABA levels (Coffman & Petty, 1985). Post-mortem study of alcoholics' brains has shown increased GABA receptor numbers (Tran *et al*, 1981). This could be an adaptive response to the potentiation of GABA inhibition by alcohol by altering receptor affinity states (see above).

GABA neurones have major inhibitory influences on monoamine and NMDA neurones. Activity of noradrenergic and dopaminergic neurones is reduced by GABA or by benzodiazepine agonists (Taylor & Laverty, 1969). Epileptiform activity in hippocampal cells caused by the GABA-A antagonist bicuculline is reduced by NMDA antagonists (Herron *et al*, 1985*b*), and after electrical kindling, reduced sensitivity to GABA and increased sensitivity to NMDA are seen (Stelzer *et al*, 1987). This would suggest that reduced GABA activity in alcohol withdrawal would lead to reduced inhibition of monoamine and NMDA neuronal activity; the increased NMDA activity may in turn further reduce GABA activity, leading to a vicious circle of progressively increasing excitation (see Fig. 1).

Increased excitatory input

Catecholamines: noradrenaline and dopamine

Alcohol has a complex effect on noradrenergic neurones (Nutt & Glue, 1986). However, noradrenaline (NA) overactivity is almost certainly present in alcohol withdrawal. Plasma and CSF NA and its major metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) are increased by alcohol intoxication and withdrawal from single doses of alcohol (Borg *et al*, 1981). Much higher levels are seen during withdrawal from chronic intoxication (Potter *et al*, 1984; Hawley *et al*, 1985). The increase in NA activity may result from reduced alpha-2-adrenoceptor autoreceptor inhibition (Nutt

et al, 1988*b*), which may persist into abstinence (Glue *et al*, 1989). Increased NA levels may aggravate hypomagnesaemia (see above), thus producing another positive feedback loop (see Fig. 1).

It is possible that dopamine (DA) dysfunction may be a contributing factor in the hallucinations of alcohol withdrawal, especially DTs (see Fig. 1). There is evidence of enhanced DA receptor sensitivity in the nucleus accumbens of rats following very long-term alcohol administration (Engel & Liljeqvist, 1976; Liljeqvist, 1978). Annunziato *et al* (1983) found endocrine evidence of DA receptor super-sensitivity four to seven days after withdrawal. Whether these changes would lead to increased DA function in withdrawal, or merely reflect reduced DA activity, is a matter for further research.

Corticotrophin-releasing factor

This is a hypothalamic peptide that controls the release of adrenocorticotrophic hormone (ACTH) from the pituitary (Vale *et al*, 1981), but also is found in many other brain regions. Koob & Bloom (1985) suggested that the role of corticotrophin-releasing factor (CRF) is to co-ordinate stress responses at endocrine and behavioural levels. For instance, intra-cerebroventricular (i.c.v.) administration of CRF in rats causes changes suggestive of increased fear or anxiety (Koob & Bloom, 1985). However, CRF can also produce long-term behavioural changes, in particular seizures. Administration of CRF into the cerebral ventricles in rats induces seizures (Weiss *et al*, 1986) which resemble those caused by electrical kindling of the amygdala (Ehlers *et al*, 1983). Furthermore, pre-treatment with CRF sensitises to electrical kindling (Weiss *et al*, 1986).

Alcohol has several effects on CRF in animals. Acute exposure to alcohol appears to increase CRF production, whereas chronic alcohol reduces hypothalamic CRF content (Rivier *et al*, 1984), either by depletion or inhibition of synthesis (Dave *et al*, 1986). Despite this, behavioural responses to i.c.v. CRF, which are enhanced in rats given chronic alcohol, are further increased during alcohol withdrawal, and it has been suggested that this may reflect CRF-induced kindling (Ehlers & Chaplin, 1987).

Evidence for CRF dysfunction in alcoholics comes from the disruption of the hypothalamic–pituitary–adrenal axis in alcohol withdrawal. Excessive cortisol secretion has been reported (Valimaki *et al*, 1984). A detailed longitudinal study demonstrated that as well as marked hypocortisolaemia, the normal diurnal rhythm of cortisol is lost during this time (Risher-Flowers *et al*, 1988). These findings are consistent with CRF overactivity in withdrawal, a supposition which is supported by the blunted ACTH response to CRF in early abstinence (Adinoff, 1987; Holsboer *et al*, 1987; Heuser *et al*, 1988). Excessive CRF release would be expected to produce receptor subsensitivity, and the elevated cortisol levels should produce further inhibition (Adinoff, 1987).

Plasma concentrations of CRF in alcoholics have not been studied as the concentrations of this hormone in peripheral blood are below the sensitivity of present assay methods. CRF concentrations have been measured in the CSF of recently detoxified alcoholics, and were similar to those of normal controls (Nutt *et al*, 1988*a*). However, this has not been studied in acute withdrawal, which would be more relevant.

N-methyl-D-aspartate

N-methyl-D-aspartate (NMDA) receptors are increasingly recognised as having a major influence in synaptic transmission in the brain (Watkins & Evans, 1981). They have been implicated in long-term potentiation (LTP) of hippocampal neurones (Collingridge & Bliss, 1987), a process whereby repetitive stimulation produces long-lasting increases in synaptic efficacy. LTP is probably also important in the generation of seizures since it is critical to the development of kindling (Racine *et al*, 1983; Vezzani *et al*, 1988). Selective NMDA antagonists such as MK-801 and D-2-amino-5-phosphonovalerate (AVP) have provided tools with which to explore the functions of this system. Blockade of NMDA receptors prevents kindling-like phenomena *in vitro* (Slater *et al*, 1985; Anderson *et al*, 1987) and *in vivo* (McNamara *et al*, 1988; Vezzani *et al*, 1988). To date there have been few studies looking at the effects of alcohol on NMDA function, although potentially such defects could explain the cognitive and neuropathological defects seen in chronic alcoholics (see Lishman, 1987). Acute doses of alcohol reduce NMDA function in that there is a reduction in NMDA-stimulated calcium (Ca) uptake and Ca-dependent production of cyclic guanosine monophosphate (Hoffman *et al*, 1989*b*). Sensitivity of hippocampal neurons to NMDA (Lovinger *et al*, 1989) and of Purkinje neurones to glutamate (Franklin & Gruol, 1987) is reduced. Although chronic alcohol reduces LTP in rat hippocampal neurones (Durand & Carlen, 1984), MK-801 binding is increased by approximately 25% in this area, perhaps in compensation. It appears that NMDA function is increased in alcohol withdrawal, as an increase in hippocampal MK-801 binding of up to 80% has been recently described (Hoffman *et al*, 1989*a*).

Calcium channels

Experiments have demonstrated an important role for Ca channels in the chronic effects of alcohol. Lynch & Littleton (1983) showed neurones were sensitised to Ca by chronic alcohol exposure. Later studies revealed an increase in the subtype of Ca channel labelled by the dihydropyridines (Dolin *et al*, 1987). Central effects of increased numbers of Ca channels would produce increased neuronal excitability, while peripheral changes may include increased adrenal catecholamine release (see Littleton, 1989). Blockade of these channels during alcohol withdrawal has been demonstrated to attenuate some symptoms, especially the seizures (Little *et al*, 1986; Littleton & Little, 1988). Administration of Ca antagonists before withdrawal, reduced tolerance development and withdrawal symptoms, and prevented the increase in dihydropyridine binding (Whittington & Little, 1989; Dolin & Little, 1990). Trials of Ca antagonists in alcohol withdrawal in animals (Little *et al*, 1986) have shown improvement in physical symptoms, especially seizures, although Bone *et al* (1989) suggested that benzodiazepines are more effective against other symptoms such as tremor. Preliminary work in humans suggests that Ca antagonists may be of some use clinically (Koppi *et al*, 1987). More comprehensive studies are clearly required in this area.

Excitatory interactions

Clearly, there are many interactive factors that may contribute to alcohol withdrawal. It would appear that a series of positive-feedback loops are generated, and these lead to massive central hyperexcitability (see Fig. 1). For instance, there are mutual interactions between adrenergic and CRF systems. CRF stimulates NA neurones of the locus coeruleus (Al-Damluji *et al*, 1987), the major source of ascending NA neurones in the CNS (Swanson, 1976). Direct injections of CRF into this area disrupts NA neuronal responses to sensory stimulation with the production of excessive and irregular firing patterns (Valentino *et al*, 1983). Additionally, administration (i.c.v.) of CRF stimulates sympathetic nervous system activity (Brown *et al*, 1982). Finally, CRF-conditioned fear responses are antagonised by the beta-blocker propranolol (Cole & Koob, 1988).

Corticotrophin-releasing factor neurones are themselves innervated by catecholaminergic neurones (Kitazawa *et al*, 1987), and NA can stimulate CRF release (Alonso *et al*, 1986). In this way, CRF stimulation of NA pathways could lead to a positive-feedback loop that results in greater CRF secretion (Fig. 1). Processes like this may underlie CRF kindling (Weiss *et al*, 1986). A further factor provoking CRF release may be the reduction of alpha-2-adrenoceptor inhibition of NA release. This has been demonstrated in alcohol withdrawal for other alpha-2-adrenoceptor-mediated responses (Nutt *et al*, 1988*b*).

Stimulation of NMDA receptors releases NA from hippocampal slices (Jones *et al*, 1987; Lalies *et al*, 1988). Overactivity of NMDA receptors due to low Mg would accentuate NA release, which may in turn further reduce Mg levels, leading to further increases in NMDA (see Fig. 1). Since DA release from nigral slices is also potentiated by excitatory amino acids via an NMDA receptor and can be inhibited by Mg (Araneda & Bustos, 1989), NMDA receptor overactivity may produce excessive DA release.

Receptor dysfunction and clinical symptoms

There are many symptoms and signs in alcohol withdrawal but these fall into a few clusters. Three areas can be determined in relation to the receptor disturbances described above (Table I). These are: increased sympathetic activity, kindling and seizures, and hallucinations and DTs. The increase in sympathetic activity produces symptoms such as tremor, sweating and anxiety, the severity of which have been found to be correlated with indices of central noradrenergic overactivity (Hawley *et al*, 1985). These symptoms respond to administration of the alpha-2-adrenoceptor agonists clonidine (Wilkins *et al*, 1983; Glue & Nutt, 1987) and lofexidine (Brunning *et al*, 1986), which act to reduce sympathetic outflow (Kobinger, 1984). However, it should be noted that clonidine appears to be ineffective in stopping more severe withdrawal symptoms and seizures (Robinson *et al*, 1989), and benzodiazepines are still the best treatment for the global management of alcohol withdrawal.

TABLE I

Summary of possible relationships of neurotransmitter disturbances to symptoms of alcohol withdrawal (arrows indicate inhibition (↓) or excitation (↑) of neurotransmitter)

Symptoms	*Neurotransmitter disturbances*
Increased sympathetic activity	↑NA; ↑CRF; ↓GABA
Hallucinations/DTs	↑DA
Seizures kindling	↓GABA; ↑NMDA (↓Mg)[1]; ↑CRF

1. ↑NMDA related to ↓Mg.

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Kindling has been used to explain a number of clinical features of alcoholism and alcohol withdrawal, especially the progressive worsening of symptoms and signs with prolonged drinking, and increased risk of seizures (Ballenger & Post, 1978; Brown *et al*, 1988). Despite this being a compelling hypothesis there is little evidence to support it (Ballenger & Post, 1978). The only pharmacological evidence from humans is that indices of NA activity are correlated with duration of drinking (Nutt *et al*, 1988*b*). Further support for this hypothesis comes from the probable stimulatory effects of alcohol administration and withdrawal upon CRF and NMDA activity, and their roles in producing kindling.

During alcohol withdrawal, symptoms occur at particular times after stopping alcohol rather than all at once or randomly (Victor & Adams, 1953; Kanzow, 1986). For instance, symptoms associated with increased sympathetic drive (such as anxiety, tremor and sweating) tend to be maximal 24 hours after stopping drinking, whereas seizures occur 24–48 hours after the last drink. The severe agitation and delirium, vivid hallucinations and autonomic overactivity of DTs occur between 48–72 hours after the cessation of drinking (Victor & Adams, 1953; Victor, 1966). The role of NA overactivity in early withdrawal symptoms of tremor and sweating has been clearly demonstrated (Hawley *et al*, 1985). We hypothesise that there is overactivity of NMDA and CRF systems which may contribute to these early signs and also lead to the occurrence of seizures.

The receptor disturbances underlying DTs are more speculative, but may well involve DA overactivity as well as kindling. Alcohol withdrawal possibly has an initiating effect, with the DTs then occurring as a result of short-term kindling (as described above with CRF). The DTs differ from other withdrawal phenomena in that they are difficult to bring under control using presently available treatment regimes (Thompson *et al*, 1975; Kramp *et al*, 1979). Hypnosedative drugs are more effective in reducing the incidence of DTs than DA-antagonists such as haloperidol (Palsson, 1986). However, once DTs have developed, these drugs influence different groups of symptoms. For instance, the delirium of DTs has been shown to respond to haloperidol, which has little effect on autonomic symptoms (Holzbach & Buhler, 1978). It would be interesting to know if NMDA antagonists are of use in treating this state. One approach to this might be to use Mg supplements, since other NMDA antagonists are not yet available for clinical use.

Therapeutic possibilities

Present pharmacological practice for alcohol withdrawal is to use one of the hypnosedative drugs, chlormethiazole or benzodiazepines. The use of loading-dose benzodiazepines has been demonstrated to be clinically efficacious, very cost- and time-effective, and probably the preferred treatment for withdrawal at present (Sellers *et al*, 1983). The shorter half-life and lower therapeutic ratio of chlormethiazole makes it a less attractive treatment. Supplementation of Mg, although it may be included in concomitant vitamin and nutritional supplementation, is less frequently used, and may have a considerably greater role due to its action on NMDA receptors. Clonidine, an alpha-2-adrenoceptor agonist, which reduces NA release, has been used as a treatment for alcohol withdrawal (Bjorkqvist, 1975; Walinder *et al*, 1981), although it is only of limited benefit in severe withdrawal (Robinson *et al*, 1989), and should not be used as sole treatment in patients with a history of seizures. In combination with hypnosedatives, neuroleptics have a place in the management of DTs, with drugs such as haloperidol being preferred to the less dopamine-selective compounds (e.g. phenothiazines) as the latter are associated with increased incidence of seizures and DTs (Thomas & Freedman, 1965; Golbert *et al*, 1967; Kaim *et al*, 1969; Feuerlein & Reiser, 1986). Potentially, newer DA antagonists of markedly greater receptor selectivity (e.g. pimozide) may prove to be more efficacious, since there is some evidence to suggest a reduced tendency to potentiate seizures in animals (Meldrum *et al*, 1975). Finally, Ca antagonists given either before or during alcohol withdrawal are promising therapeutic agents, although further clinical trials are required in this area.

One aspect of withdrawal treatment that is little recognised is kindling. This is suggested by the tendency for withdrawal symptoms to recur more rapidly and to increase in severity with repeated episodes of drinking (Ballenger & Post, 1978). Given the considerable evidence from animal models of the role of NMDA and CRF in kindling, and their increased activity during chronic alcohol intake and withdrawal, specific treatments to slow down or stop kindling processes may be of great importance. In view of the dangers of kindling, Linnoila (1987) suggested that withdrawal symptoms should receive aggressive medical treatment, to prevent the progression of kindling phenomena. This challenges the notion that withdrawal is a relatively self-limiting and harmless event that may be managed without medical intervention. It suggests that such a policy might increase the risk of kindling, and lead to long-term

problems of exacerbated withdrawals and their many sequelae. In other words, there is now good evidence that the state of increased excitability of the brain accompanying withdrawal may cause long-lasting changes. These are manifest as worsening (kindling) of withdrawal symptoms in subsequent drinking bouts. Active management of the earlier withdrawals could be expected to prevent this.

One important consequence not yet discussed is alcoholic dementia. There is good evidence that NMDA receptor overactivity (Olney, 1984) and hypercortisolaemia (Sapolsky & Pulsinelli, 1985) lead to hippocampal cell death. The long-term cognitive dysfunction of alcoholic dementia could be produced by loss of these neurones (Walker *et al*, 1980). The potential of selective NMDA and CRF antagonists to prevent this process could be of great clinical benefit. As mentioned above, they might also be of value in treating DTs.

The NMDA antagonists that are presently available are anticonvulsant and neuroprotective in animal models (Croucher *et al*, 1982; Schwarcz *et al*, 1982; Schwarcz & Meldrum, 1985). However, as related compounds such as phencyclidine cause hallucinations in humans (Snyder *et al*, 1980), this may limit the usefulness of NMDA antagonists. It would seem that Mg supplementation is the only viable way at present of reducing NMDA receptor activity in humans. CRF antagonists are only just becoming available, and being large peptides, would be unlikely to be peripherally active. The discovery of a stable non-peptide analogue is awaited with interest.

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