

Update on the Neurobiology of Alcohol Withdrawal Seizures

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Abrupt cessation of alcohol intake after prolonged heavy drinking may trigger alcohol withdrawal seizures. Generalized tonic-clonic seizures are the most characteristic and severe type of seizure that occur in this setting. Generalized seizures also occur in rodent models of alcohol withdrawal. In these models, the withdrawal seizures are triggered by neuronal networks in the brainstem, including the inferior colliculus; similar brainstem mechanisms may contribute to alcohol withdrawal seizures in humans. Alcohol causes intoxication through effects on diverse ion channels and neurotransmitter receptors, including GABA_A receptors—particularly those containing δ subunits that are localized extrasynaptically and mediate tonic inhibition—and N-methyl-D-aspartate (NMDA) receptors. Alcohol dependence results from compensatory changes during prolonged alcohol exposure, including internalization of GABA_A receptors, which allows adaptation to these effects. Withdrawal seizures are believed to reflect unmasking of these changes and may also involve specific withdrawal-induced cellular events, such as rapid increases in $\alpha 4$ subunit-containing GABA_A receptors that confer reduced inhibitory function. Optimizing approaches to the prevention of alcohol withdrawal seizures requires an understanding of the distinct neurobiologic mechanisms that underlie these seizures.

It is estimated that 2 million Americans experience the symptoms of alcohol withdrawal each year (1). Generalized tonic-clonic seizures (rum fits) are the most dramatic and dangerous component of the alcohol withdrawal syndrome. The brain substrates that trigger these seizures are largely in the brainstem and, therefore, are distinct from those believed to be

responsible for other clinically important seizure types. Moreover, because alcohol withdrawal seizures are pharmacologically induced, the pathophysiologic mechanisms almost certainly are different from those of the seizures that occur in genetic and acquired epilepsies. This review provides an overview of the current understanding of the cellular and molecular events that lead to alcohol withdrawal seizures.

Ethanol is a central nervous system depressant that produces euphoria and behavioral excitation at low blood concentrations and acute intoxication (drowsiness, ataxia, slurred speech, stupor, and coma) at higher concentrations. The short-term effects of alcohol result from its actions on ligand-gated and voltage-gated ion channels (2–4). Prolonged alcohol consumption leads to the development of tolerance and physical dependence, which may result from compensatory functional changes in the same ion channels. Abrupt cessation of prolonged alcohol consumption unmasks these changes, leading to the alcohol withdrawal syndrome, which includes blackouts, tremors, muscular rigidity, delirium tremens, and seizures (5,6). Alcohol withdrawal seizures typically occur 6 to 48 hours after discontinuation of alcohol consumption and are usually generalized tonic-clonic seizures, although partial seizures also occur (7,8).

Rodent models that mimic human alcohol withdrawal-related tonic-clonic seizures have been useful in defining the physiologic mechanisms underlying ethanol withdrawal seizures (9). In these models, animals are exposed to alcohol by intragastric intubation, inhalation, or feeding in a nutritionally complete liquid diet for periods of 2 to 21 days. The animals exhibit sound-evoked audiogenic seizures or handling-induced convulsions during the 1- to 3-day period after cessation of alcohol intake and may also experience spontaneous generalized seizures.

Brain Substrates for Alcohol Withdrawal Seizures

Audiogenic seizures are the best-studied type of alcohol withdrawal seizures. These seizures are mediated largely in the brainstem, although the hippocampus may be invaded after seizure initiation (10). In rodents, the cortical EEG shows no sign of paroxysmal activity (10,11). Similarly, in humans, epileptiform activity is rarely observed in the EEG between episodes of alcohol withdrawal-related tonic-clonic seizures (12,13). Thus, alcohol withdrawal seizures are unlikely to be triggered in the neocortex. Indeed, electrophysiological studies have demonstrated a critical role for the inferior colliculus (IC) in the initiation of audiogenic seizures in rodents. Acute alcohol intoxication

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suppresses spontaneously and acoustically evoked neuronal firing in the IC central nucleus (14), whereas at the transition to seizure, sustained increases in firing persist during wild running, the initial phase of the seizure (15). The IC external cortex is believed to amplify and propagate neuronal activity originating in the IC central nucleus. Neurons within the deep layers of the superior colliculus (16) and the periaqueductal gray (17) also may play a role in the initiation of audiogenic seizures. It is hypothesized that seizure activity propagates from the IC to deep layers of the superior colliculus (a major output of the IC) to trigger the wild running phase of the audiogenic seizure. The deep layers of the superior colliculus send projections directly to the spinal cord via the pontine reticular formation and the periaqueductal gray. The periaqueductal gray is thought to trigger clonic seizures, whereas the pontine reticular formation is implicated in the generation of the tonic phase of audiogenic seizures (18). Some evidence suggests that the IC plays a role in alcohol withdrawal seizures in humans, as it does in rodents. Thus, humans with alcohol withdrawal seizures exhibit abnormalities in auditory-evoked potentials that are not observed in other settings, including increased latency to wave V (19,20), whose major source is the IC (21).

Cellular Mechanisms of Alcohol Dependence

Until the 1980s, it was generally believed that the actions of ethanol on biologic systems largely result from alterations in the fluidity of cell membranes, perhaps, with secondary effects on integral membrane proteins. This idea arose from the recognition that ethanol is a member of a group of anesthetic substances whose potency is related to their lipid solubility in accordance with the Meyer–Overton rule (22). More recently, it has been appreciated that some anesthetic actions are stereospecific and that direct protein interactions are likely (23). Indeed, ethanol modifies the functional activity of many receptors and ion channels, including NMDA (24,25), kainate (26), serotonin 5-HT₃ (27), GABA_A (28), and glycine (29) receptors as well as G protein–coupled inwardly rectifying potassium channels (30) and calcium channels (31). In most cases, alcohol affects these targets only at high, suprapharmacologic concentrations. However, certain GABA_A-receptor isoforms are exquisitely sensitive to alcohol so that functionally relevant effects can occur at concentrations within the intoxicating range (32,33).

Since 1980, it has been known that alcohol can positively modulate the activity of some GABA_A receptors (34,35), but the importance of this finding was questioned because of inconsistency in the results from different laboratories and variability among brain regions. In addition, in experiments with recombinant GABA_A receptors, low concentrations of GABA were not found to affect the most abundant GABA_A-receptor isoforms, which contain the $\gamma 2$ subunit. Recently, however, it has been

discovered that GABA_A receptors containing the δ subunit, in particular $\alpha 4\beta 2\delta$ (36) and $\alpha 6\beta 2\delta$ (37) receptors, are exceptionally sensitive to ethanol. Because δ subunit–containing GABA_A receptors have a highly specific regional distribution, the lack of uniformity in the experimental results is now understandable. Indeed, brain regions that express δ subunits, including the cerebellum, cortical areas, thalamic relay nuclei, and brainstem (38), are among those that are recognized to mediate the intoxicating effects of alcohol. Mody (39) has proposed that such δ subunit–containing GABA_A receptors are located largely perisynaptically or extrasynaptically, where they mediate tonic inhibition of neurons by ambient GABA. The functional role of tonic GABA current is still obscure (40), but the current could act to reduce network oscillations (41). It is interesting to speculate that extrasynaptic GABA_A receptors may be activated by spillover of GABA when GABAergic interneurons are intensely activated, such as during a seizure discharge, thus producing negative feedback. Potentiation of extrasynaptic GABA receptors likely contributes to the anticonvulsant activity of ethanol, including its protective activity against alcohol withdrawal seizures.

Alcohol dependence—the existence of spontaneous behavioral disturbances that are produced by alcohol removal and suppressed by alcohol replacement—underlies the alcohol withdrawal syndrome. The mechanisms of alcohol dependence are less well understood than are those responsible for acute intoxication. However, it now appears that compensatory adaptation of GABA_A receptors to prolonged ethanol exposure plays a critical role in alcohol dependence (42–44). Among the possible adaptive mechanisms, downregulation of GABA_A receptors, as a result of decreases in the surface expression of $\alpha 1$ (45,46) or $\gamma 2$ (47) subunits, is emerging as an important candidate. Indeed, prolonged ethanol exposure has been shown to increase the endocytic internalization of $\alpha 1$ subunit–containing receptors in clathrin-coated vesicles (48). The number of GABA_A receptors in the postsynaptic density correlates directly with inhibitory synaptic strength. Thus, when alcohol is withdrawn and its potentiating effects are no longer present, the reduction in synaptic GABA_A receptors is associated with impaired inhibitory tone, predisposing to withdrawal seizures. The mechanisms responsible for altered GABA_A-receptor trafficking in response to prolonged alcohol exposure are not known. However, it has been proposed that enhancement of tonic GABA current could play a role (40).

In addition to decreases in $\alpha 1$ - or $\gamma 2$ -subunit expression that occur with prolonged ethanol exposure, abrupt discontinuation of alcohol leads to a rapid increase in the abundance of $\alpha 4$ subunits (47,49). Inhibitory synaptic currents mediated by GABA_A receptors containing the $\alpha 4$ subunit exhibit markedly faster decay, leading to reduced charge transfer and decreased inhibitory function. Enhanced seizure susceptibility is observed

in animals with increased $\alpha 4$ -subunit expression (50,51). Thus, alcohol withdrawal is associated with reduced density of synaptic GABA_A receptors as well as alterations in GABA_A-receptor subunit composition that lead to reduced inhibitory efficacy; both effects would be expected to predispose to seizures. Indeed, susceptibility to alcohol withdrawal seizures has been associated with a loss of GABA-mediated inhibition (52,53).

Compensatory upregulation of NMDA and kainate receptors (54) as well as calcium channels (55,56) also have been implicated in alcohol dependence and withdrawal seizures. For example, the inhibitory effects of ethanol on NMDA receptors (24,25) leads to upregulation in the number of NMDA receptors in many brain regions, which may be an additional factor in the susceptibility to alcohol withdrawal seizures (57,58). The relevance of this mechanism is highlighted by the fact that NMDA-receptor antagonists are highly effective anticonvulsants in animal models of alcohol withdrawal seizures (59).

Anticonvulsant Drug Pharmacology of Alcohol Withdrawal Seizures

Up to one third of patients with significant alcohol withdrawal may experience alcohol withdrawal seizures. Although seizures in this setting are usually self-limited, they can be associated with status epilepticus and, therefore, are potentially serious (60). In the United States, benzodiazepines are considered the drugs of choice to treat alcohol withdrawal and to prevent the occurrence of seizures (61,62). In Europe, carbamazepine, chlormethiazole, and valproate are often used (63,64). Although benzodiazepines are protective in some animal models of alcohol withdrawal seizures (65,66), they do not exhibit high potency (Table 1). The relatively modest activity of benzodiazepines is not surprising because alcohol withdrawal is associated with increases in $\alpha 4$ subunit-containing GABA_A receptors, which are benzodiazepine insensitive (67,68). Nevertheless, clinical experience demonstrates that benzodiazepines do reduce the risk of recurrent seizures in patients with an alcohol withdrawal seizure (62), so that in practice, no complete benzodiazepine resistance occurs. However, GABA_A-receptor modulators, other than benzodiazepines, might be superior therapeutic agents. Chlormethiazole is a positive modulator of GABA_A receptors, which has high efficacy in enhancing GABA_A receptors containing $\alpha 4$ subunits (69) and has been shown to protect transiently against alcohol withdrawal seizures in mice withdrawn from exposure to inhaled ethanol (70). Although chlormethiazole may be a preferred agent from a theoretical point of view, it is not currently registered for sale in the United States.

As shown in Table 1, the sodium channel-blocking antiepileptic drugs carbamazepine and phenytoin are weak or ineffective in rodent models of alcohol withdrawal seizures, which corresponds with their lack of effectiveness in many other

TABLE 1. Potencies of Anticonvulsant Substances for Protection in Rodent Alcohol Withdrawal Seizure Models

Substance	ED ₅₀ (mg/kg)	
	Audiogenic seizures (rat)	Handling-induced convulsions (mouse)
GABA _A -receptor Modulators		
Diazepam	NE*	20 [†]
Lorazepam		~1 [‡]
Chlormethiazole		~100 [§]
Sodium-channel Modulators		
Phenytoin	50	NE [¶]
Carbamazepine	150 ^{**}	NE ^{††}
Antiepileptic Drugs: Other Antiepileptic Drugs		
Gabapentin	~50 (mouse) ^{‡‡}	
Valproic acid		300 ^{§§}
NMDA-receptor Antagonist		
Dizocilpine (MK-801)	0.33	0.1 ^{††}

Adapted from N'Gouemo and Rogawski (9), with permission.

ED₅₀, median effective dose; NE, not effective.

*Little et al. (91); [†]Crabbe (92); [‡]Becker and Veach (66); [§]Green et al. (70); ^{||}Chu (93); [¶]Gessner (94); ^{**}Chu (95); ^{††}Grant et al. (59); ^{‡‡}Watson et al. (80); ^{§§}Goldstein (73); ^{|||}Morrissett et al. (96).

types of generalized seizures. In line with results from animal studies, there is little evidence that carbamazepine prevents alcohol withdrawal seizures and delirium in humans, although it may be useful to treat alcohol craving (1). Similarly, phenytoin is not effective in protecting against the occurrence of seizures in withdrawing alcoholics (71,72). Valproate is protective against alcohol withdrawal convulsions in mice (73). The intravenous formulation is gaining acceptance in the clinical management of status epilepticus so that it could potentially be used in prophylaxis against alcohol withdrawal seizures. Increasing interest is expressed in the potential of gabapentin as a treatment for alcohol withdrawal (74–78) and of topiramate in alcohol dependence (79). Animal studies confirm that both drugs have protective activity against ethanol withdrawal seizures (80,81), and evidence from a preliminary clinical trial suggests that topiramate is effective in preventing seizures in human subjects undergoing withdrawal (82).

Multiple Detoxifications Kindle Susceptibility to Alcohol Withdrawal Seizures

The severity of alcohol withdrawal symptoms progressively increases over years of alcohol abuse, and repeated detoxifications augment the likelihood of alcohol withdrawal seizures (83,84). Similarly, studies in rodents have shown that repeated alcohol withdrawal experiences increase the severity and duration of subsequent withdrawal seizures (85,86). These observations have led to the view that alcohol withdrawal causes

permanent epileptogenic changes in brain systems relevant to ethanol withdrawal seizures—a type of kindling phenomenon. Indeed, in accordance with the central role of the IC in triggering alcohol withdrawal seizures, multiple alcohol withdrawal episodes in rats facilitate the development of IC kindling (87,88). There is no recognized treatment to slow or prevent this kindling process. In animals, benzodiazepines have yielded variable effects, in some cases slowing withdrawal-induced kindling, and in other cases, causing paradoxical worsening (65,66,89). Whether other agents used in the treatment of alcohol withdrawal have antiepileptogenic potential remains to be determined.

Conclusions

In the past several years, dramatic advances have been made in understanding the short- and long-term effects of alcohol on the central nervous system. These advances have provided new insight into the pathophysiology of alcohol withdrawal seizures. In contrast to epileptic seizures, alcohol withdrawal seizures originate in brainstem systems and involve unique cellular and molecular mechanisms. Older antiepileptic drugs, such as phenytoin and carbamazepine, are not useful in the prophylaxis of alcohol withdrawal seizures, and even benzodiazepines, the current mainstay of therapy in the United States, may not be optimal. Newer agents, such as chlormethiazole, topiramate, gabapentin, and valproate are promising, but validation in controlled clinical trials is necessary. The emerging understanding of the neurobiology of alcohol withdrawal suggests additional treatment approaches. For example, because NMDA-receptor antagonists are highly effective in animal models of alcohol withdrawal seizures (59) and, in addition, have antiepileptogenic activity in kindling models (90), it will be of interest to determine whether such agents will be clinically useful in prophylaxis against acute withdrawal seizures or in the kindling that occurs with multiple detoxifications.

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