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Editorial: Tonic for What Ails Us? High Affinity $GABA_A$ Receptors and Alcohol

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Abstract

Ethanol interactions with gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, play key roles in acute intoxication. However, the exact mechanisms of these ethanol interactions have been the subject of considerable confusion and controversy. Many studies suggest that ethanol potentiates the function of the type A GABA receptor ($GABA_A$-R). However, these findings have not been consistently replicated in experiments that directly examined ethanol effects on $GABA_A$-R-mediated ion current. Differences in ethanol sensitivity of different $GABA_A$-R subtypes have been invoked as a potential explanation for the inconsistent findings, and recent work suggests that $GABA_A$-Rs that contain the delta subunit and/or mediate tonic extrasynaptic GABA responses may be especially ethanol-sensitive. However, considerable disagreement has arisen over these findings. This special issue of Alcohol contains articles from eight research groups who are examining this issue. The authors present their work, their views on the present state of this area of alcohol research, and their ideas about how to proceed with future studies that may help to address the present confusion and controversy. This editorial provides an introduction to this line of research and the current findings and controversies.

Keywords

Ethanol; Synaptic Inhibition; Intoxication; RO15-4513

It is widely accepted that acute alcohol intoxication involves drug interactions with the major central nervous system (CNS) inhibitory neurotransmitter, namely γ-aminobutyric acid (GABA) (Aguayo et al., 2002;Diamond and Gordon, 1997;Grobin et al., 1998;Mihic and Harris, 1997;Siggins et al., 2005;Ueno et al., 2001). It has long been known that many of the behavioral effects of alcohol are very similar to those elicited by drugs that are known to exert their effects through GABA type A receptors ($GABA_A$-Rs) (e.g. benzodiazepines and barbiturates). Ethanol also interacts with these drugs to enhance acute intoxication. Furthermore, there is an abundance of evidence that acute ethanol exposure alters many aspects of GABAergic transmission in the brain.

Despite a vast literature linking the behavioral effects of alcohol to the GABAergic system, acute ethanol actions at the $GABA_A$ receptor remain one of the most perplexing and contentious issues in the alcohol research field. Recent studies of ethanol actions on $GABA_A$ receptors that

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contain the delta subunit, and $GABA_A$ receptors that mediate tonic ion current have rekindled both the interest and controversy in this research area (Borghese et al., 2006;Glykys et al., 2007;Hanchar et al., 2005,Hanchar et al., 2006;Mihalek et al., 2001;Wallner et al., 2003;Wallner et al., 2006;Wei et al., 2004). These new findings spurred us to plan the current special issue of Alcohol following suggestions and support from Alcohol Editorial Board members including Dr. Adron Harris.

A large body of studies over the last four decades using in vivo and in vitro electrophysiological and neurochemical approaches has produced an abundance of evidence both for and against ethanol alterations in neuronal responses to GABA (see Aguayo et al., 2002;Grobin et al., 1998;Mihic and Harris, 1997;Siggins et al., 2005;Ueno et al., 2001; for review). Indeed, ethanol potentiation of $GABA_A$ receptor function has proven notoriously variable when measured by the most direct method, recording of GABA-activated ion current in isolated neurons. Reports of potentiation (Aguayo, 1990;Aguayo et al., 1994;Celentano et al., 1988;Homanics et al., 1999;Reynolds et al., 1992;Sapp and Yeh, 1998;Sundstrom-Poromaa et al., 2002), inhibition (McCool et al., 2003) and lack of effect (Marszalec et al., 1998;White et al., 1990;Zhai et al., 1998) of ethanol at pharmacologically-relevant concentrations have all appeared in the literature and when potentiation is observed, the ethanol potency and concentration-response functions have differed greatly in different preparations and under different experimental conditions (Aguayo, 1990;Aguayo et al., 1994;Celentano et al., 1988;Homanics et al., 1999;Reynolds et al., 1992;Sapp and Yeh, 1998,Sundstrom-Poromaa et al., 2002). Ethanol potentiation of $GABA_A$ receptor-mediated synaptic current is perhaps more consistent (Ariwodola and Weiner, 2004;Carta et al., 2004;Marszalec et al., 1998;Nie et al., 2004;Proctor et al., 1992;Siggins et al., 2005;Wan et al., 1996;Weiner et al., 1994;Zhu and Lovinger, 2006, although see Gage and Robertson, 1985;Hanchar et al., 2005;Siggins et al., 1987), but these effects cannot always be attributed to ethanol actions on the $GABA_A$ receptor. Indeed, recent reports indicate potent presynaptic ethanol effects on GABA release (Ariwodola and Weiner, 2004,Nie et al., 2004;Roberto et al., 2003;Siggins et al., 2005,Wan et al., 1996;Zhu and Lovinger, 2006).

The failure to observe consistent results has led many to postulate that $GABA_A$-R subunit composition is the key to ethanol responsiveness. $GABA_A$ receptors are formed by the co-assembly of numerous subunits, many of which are subject to posttranslational modification by molecular processes such as protein phosphorylation. This has led many laboratories to investigate the subunit requirements that dictate $GABA_A$-R potentiation by ethanol (Borghese et al., 2006;Glykys et al., 2007;Hanchar et al., 2006;Marszalec et al., 1994;McCool et al., 2003;Mihic et al., 1994,1997;Sigel et al., 1993;Sundstrom-Poromaa et al., 2002;Ueno et al., 2001;Wafford et al., 1991;Wallner et al., 2003,2006;Wei et al., 2004). Of particular interest are those receptor combinations that are sensitive to low concentrations of ethanol (3–30mM) that cause mild behavioral effects (for comparison, the legal limit of blood ethanol for driving in many states is 17mM).

Studies of recombinant $GABA_A$-Rs expressed in heterologous cells, such as *Xenopus laevis* oocytes and human embryonic kidney 293 cells have not provided much help in resolving this issue. Ethanol potentiation of GABA-activated ion current has been consistently observed in oocytes, but the majority of these studies have reported potentiation only at high concentrations (50–200 mM) that are associated with severe intoxication and acute alcohol toxicity in humans (Borghese et al., 2006;Mihic et al., 1994,1997;Sigel et al., 1993;Ueno et al., 2001;Wafford et al., 1991;Wallner et al., 2003,2006). Past attempts to use the oocyte system to resolve the mechanisms underlying the variability in alcohol actions in different neuronal preparations have not resulted in reliable, replicable findings (Wafford et al., 1991;Sigel et al., 1993;Marszalec et al., 1994;Mihic et al., 1994). Examination of recombinant $GABA_A$ receptors in mammalian expression systems has provided even less support for the idea that a specific

$GABA_A$ receptor subtype has high sensitivity to ethanol potentiation. Indeed, very few studies have reported potentiation of any $GABA_A$ receptor subtype when using electrophysiological techniques to examine heterologously expressed receptors in mammalian cells (Marszalec et al., 1994;McCool et al., 2003). Thus, the question of the role of $GABA_A$ receptors in ethanol-GABA interactions, and the molecular basis of potent ethanol actions on the $GABA_A$ receptor remains open.

Against this background of conflicting and confusing research, two recent lines of evidence have suggested a potential $GABA_A$ receptor subtype that is a target for potent ethanol actions. Studies in the Xenopus oocyte expression system indicate that ethanol at concentrations as low as 1 mM enhances the function of $GABA_A$ receptors that contain the alpha 4 or alpha 6 subunit in combination with beta 2 or 3 subunits and the delta subunit (Sundstrom-Poromaa et al. 2002;Wallner et al. 2003). A parallel line of research indicates that ethanol enhances “tonic” $GABA_A$ receptor-mediated current in neurons found in a variety of brain regions (Glykys et al., 2007;Hanchar et al., 2005;Wei et al., 2004). This tonic current is not dependent on synaptic release of GABA, and is observable as a stable Cl^- current present in neurons at their resting membrane potential (Chandra et al., 2006;Cope et al., 2005;Glykys et al., 2007;Hanchar et al., 2005;Jia et al., 2005;Stell et al., 2003;Wei et al., 2004). The presence of this tonic current is normally revealed by a decrease in resting conductance upon application of $GABA_A$ receptor antagonists, indicating that it is mediated by this class of receptor. Recent studies have provided evidence that $GABA_A$-Rs containing the delta subunit mediate the tonic current in cerebellar, hippocampal and thalamic neurons (Brickley et al., 2001;Chandra et al., 2006;Cope et al., 2005;Jia et al., 2005;Stell et al., 2003). The possibility that ethanol enhancement of the tonic $GABA_A$-R -mediated current involves potentiation of the function of delta subunit-containing receptors suggests a convergence point for these two lines of research, and points to a possible solution of the ethanol / $GABA_A$-R dilemma.

The delta subunit-containing $GABA_A$-Rs are potently activated by GABA, exhibiting sensitivities that are markedly greater than receptors containing the γ2 subunit (Hanchar et al., 2005,2006;Sundstrom-Poromaa et al., 2002;Wallner et al., 2003,2006). This property is also shared by the tonic GABA-activated current in neurons that is believed to be mediated by receptors that contain the delta subunit (Brickley et al., 2001;Chandra et al., 2006;Cope et al., 2005;Jia et al., 2005;Stell et al., 2003). These high affinity receptors are well suited to mediate tonic current given that ambient extracellular levels of GABA are believed to be low. In contrast, the synaptic $GABA_A$ receptors are likely to be of the lower affinity variety, such that they would not be activated by ambient GABA, but only when higher GABA concentrations are present in the synapse after vesicular release (Brickley et al., 2001;Chandra et al., 2006;Cope et al., 2005;Jia et al., 2005;Stell et al., 2003). The tonically active, high affinity $GABA_A$-Rs would be in a position to regulate neuronal excitability by providing a resting, net inhibitory conductance that would tend to resist depolarization by excitatory influences. Clearly, ethanol potentiation of such a current could provide a powerful influence on cell excitation.

Unfortunately, there is not uniform agreement on the ethanol sensitivity of delta subunit-containing $GABA_A$ receptors (Borghese et al., 2006). While the evidence for ethanol potentiation of tonic $GABA_A$-R-mediated current is somewhat more consistent, this effect has not been observed by all laboratories who have studied the issue (Carta et al., 2004). Thus, there is lingering doubt about the consistency of tonic current potentiation by ethanol.

Aside from the issue of whether or not acute ethanol exposure alters tonic current and the function of delta subunit-containing $GABA_A$-Rs, there are still questions about the role of these receptors in ethanol intoxication. Recently, pharmacological and genetic approaches have been used to examine this issue (Hanchar et al., 2005;Hanchar et al., 2006;Wallner et al., 2006).

This has led to the revival of the idea of using drugs targeted at a4/a6/d-containing $GABA_A$-Rs in pharmacotherapy for the neural actions of ethanol.

Indeed, the drug RO15-4513 has undergone a renaissance in these studies. Originally, this drug was touted as an anti-intoxication "amethesytic" drug based on its ability to decrease the severity of certain acute ethanol actions, especially motor impairment during intoxication (Suzdak et al., 1986;Hoffman et al., 1987). Administration of RO15-4513 also reduces the anxiolytic effects of ethanol (Becker and Hale, 1991) and reduces alcohol self-administration (June et al., 1991; but see also Schmitt et al., 2002). These findings constitute evidence that the receptors for this drug play a central role in many of ethanol's neural actions. The compound was found to have appreciable affinity for a variety of $GABA_A$-Rs, but the most notable action was binding to receptors containing the α6/β combination found in cerebellar granule neurons (Korpi et al., 1993,1999;Luddens et al., 1990). The actions of RO15-4513 at this receptor subtype take place at the benzodiazepine binding site. However, the α6-containing receptors are resistant to the actions of diazepam and other benzodiazepine agonists (Korpi et al., 1993,1999). Subsequent research indicated limits of the effectiveness of RO15-4513 in reversing some acute ethanol actions, and the compound was found to exacerbate ethanol-induced activity increases and alcohol withdrawal seizures (Becker and Anton, 1989;Becker and Hale, 1989;Hoffman et al., 1987;Mhatre and Gonzalez, 1999;Ticku and Kulkarni, 1988). Thus, the ardor for development of RO15-4513 as a pharmacotherapeutic for treatment of alcohol disorders cooled considerably. Nonetheless, the drug has enjoyed considerable use in laboratory experiments.

Gene-targeted mice have also been used to address the roles of $GABA_A$-R subunits in acute ethanol intoxication. Both alpha6 and delta knockout mice have been subjected to extensive test batteries for intoxication and alcohol drinking behavior (Homanics et al., 1997,1998;Korpi et al., 1999;Mihalek et al., 2001). Studies of delta knockouts provide support for the involvement of alpha 4/6 delta subunit-containing receptors in some aspects of acute intoxication and drinking behavior, while many features of intoxication are still intact in these mice. Studies of alpha 6 knockouts did not reveal any differences in intoxication or drinking behavior (Homanics et al., 1997,1998). However, these results must be interpreted with caution because the global nature of the knockouts results in compensatory adaptations (Brickley et al., 2001;Tretter et al., 2001;Peng et al., 2002) that may mask the normal contribution of these receptor subunits to ethanol-induced behavioral effects.

Other groups have used rodents expressing a naturally-occurring polymorphism (R100Q) in the alpha 6 subunit to investigate the role these $GABA_A$-Rs play in ethanol action. This genetic variant was first found in the AT and ANT rats developed by selective breeding at Alko in Finland (Eriksson and Sarviharju, 1984;Korpi et al., 1993). One recent report indicates greater motor impairment in mice that express a more ethanol-sensitive variant of this subunit (Hanchar et al., 2005). However, other studies indicated that this polymorphism cannot account for the differential alcohol sensitivity of AT and ANT rats (Radcliffe et al., 2004), although it can influence benzodiazepine locomotor effects. The issue may hinge on the behavioral test used to assess acute ethanol sensitivity, and the role of polymorphisms that co-segregate with the 100Q/R variant and change the amino acid composition of other $GABA_A$-R subunits has not been fully explored (Congeddu et al., 2003). Thus, the role of this subunit in acute ethanol actions remains to be fully elucidated.

From the foregoing discussion it should be apparent that ethanol action at $GABA_A$-Rs is a topic of great current interest and importance in the alcohol research field. It should also be clear that the subject is filled with controversy and conflicting findings, and the importance and controversial nature of this research area contributed to our decision to put together this special issue of *Alcohol*. Submissions were solicited from laboratories specifically working on alcohol

actions on tonic GABA current and/or ethanol effects on delta-containing $GABA_A$-Rs. Authors were encouraged to submit new data pertinent to the subject, in addition to reviews of the field and their own conclusions from the existing literature. In addition, we encouraged the authors to provide suggestions as to how to resolve the controversies in this research area. We were gratified that eight groups of authors took this opportunity to submit manuscripts, and these papers have, to a greater or lesser degree, a mixture of the types of information we suggested.

This list necessarily excluded some investigators whose work has focused on the larger issue of ethanol and all types of $GABA_A$-Rs, as well as those who have investigated presynaptic effects of ethanol at GABAergic synapses. We may have failed to include investigators working in the specific area that is the subject of the special issue, and some authors declined to contribute or did not respond to our invitation. However, we welcome feedback from interested parties. If you have comments to make concerning any aspect of this Special Issue, these could be submitted either in the form of a letter to the editor or a guest editorial that would then be reviewed by the editorial staff and considered for publication.

The papers included in this special issue indicate several points of agreement between large subsets of authors, but there is also clear disagreement on certain points, particularly with respect to the ethanol sensitivity of delta subunit-containing receptors. Several authors have suggested ways to begin to bridge the gap between investigators who have evidence for high or low ethanol sensitivity of these receptors. However, no clear-cut solution to this vexing problem emerged from the papers in this issue. Still, we believe that these papers will stimulate others to think more deeply about this important issue and perhaps attempt to come up with solutions of their own. If so, then this special issue will have accomplished one of its major goals, namely to stimulate new research that can help advance this prominent topic in alcohol research.

We view this issue as the first of many potential special issues covering interesting, important and/or controversial areas of alcohol research. We welcome ideas for future special issues conceived with this same idea in mind.

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