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Commentary: Targeting NMDA receptor and serotonin transporter for the treatment of comorbid alcohol dependence and depression

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Abstract

This commentary addresses some of the important outcomes of the published study by Ho and colleagues, titled “Combined effects of acamprosate and escitalopram on ethanol consumption in mice”, published in Alcohol Clin Exp Res. 2016 Jul;40(7):1531–1539. Ho and colleagues reported that the combination of acamprosate and escitalopram was able to reduce ethanol intake in both stressed and non-stressed mice during treatment. However, escitalopram alone reduced ethanol intake only in non-stressed mice. Acamprosate treatment did not induce any changes in ethanol intake. This commentary addresses the important roles of glutamatergic and serotonergic systems in ethanol intake and dependence. The differential effects of combined drugs or a drug administered alone on ethanol intake have been addressed with a focus on stressed versus non-stressed mice exposed to two-bottle choice limited-access drinking of 15% ethanol and tap water. The interactive role of glutamate and serotonin in ethanol intake is also discussed in this commentary.

Keywords

SSRI; NMDA; alcohol; glutamate; serotonin; depression

This commentary discusses the work published by Ho and colleagues (Ho et al., 2016), which reports the potential uses of combined drugs (acamprosate and escitalopram) for the treatment of alcohol dependence in stressed and non-stressed C57BL/6J mice. Emerging evidence indicates that many aspects of alcohol dependence involve changes in multiple neurotransmitters. In fact, ethanol may interact with several neurotransmitter systems in the brain, and dysregulates both inhibitory and excitatory neurotransmitters (For a review see (Sari et al., 2011). Alterations of the function of neurotransmitters are critical for the development of alcohol dependence and abuse. Among neurotransmitters affected by chronic abuse of ethanol are glutamatergic and serotonergic systems. Serotonin (5-HT) can

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Conflict of interest:

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modulate the transmission of glutamate in several brain reward regions (For a review see (Sari et al., 2011). Glutamate release might be regulated through presynaptic 5-HT1B receptors located at the glutamatergic terminals in the nucleus accumbens (NAc) (Muramatsu et al., 1998) or through 5-HT1A receptors in the prefrontal cortex (PFC) (Puig et al., 2010). Furthermore, activation of 5-HT3 in the ventral tegmental area attenuated alcohol-induced increases in extracellular dopamine concentrations in the mesocorticolimbic regions (Ding et al., 2011).

The development of therapies for alcohol abuse and dependence is still challenging due to the complexity of the pharmacological actions of ethanol in the brain and the small number of existing therapeutic options. There are only a few FDA-approved medications for the treatment of alcohol addiction. These medications include naltrexone (opioid antagonist) and acamprosate (NMDA and calcium channel dependent activity) (Johnson et al., 2003; Kranzler and Van Kirk, 2001). Targeting serotonergic system is another therapeutic option for the treatment of alcohol dependence For a review see (Sari et al., 2011). An example of this is the uses of selective serotonin reuptake inhibitors (SSRIs), which are 5-HT transporter blockers to treat certain populations of alcohol addicts. The article by Ho and colleagues (2016) tested the effects of targeting serotonergic (5-HT transporter) and glutamatergic (NMDA receptor) systems using escitalopram (SSRI) and acamprosate, respectively, for the treatment of alcohol dependence in stressed and non-stressed C57BL/6J mice with two-bottle choice limited-access drinking of 15% ethanol and tap water for two weeks (Ho et al., 2016). This study reports data related to the use of acamprosate to modulate glutamate homeostasis and the use of SSRI and escitalopram to module 5-HT turnover, which are critical in stress and depressive states. This commentary discusses data that reveal the important role of targeting glutamatergic and serotonergic systems in the treatment of alcohol dependence with comorbidity to depression and to relate them to the new and exciting findings from Ho and colleagues (2016).

Role of glutamatergic system in alcohol consumption

Acamprosate appears to block the effect of ethanol-induced increases in extracellular glutamate in the brain, particularly in the NAc (Dahchour et al., 1998). Ho and colleagues found no effect of acamprostate treatment on ethanol intake in C57BL/6J mice. This is probably due to the fact that Ho and colleagues tested a dose that is considered ineffective in reducing ethanol intake in C57BL/6J mice. However, it has been previously shown by this group that a similar dose of acamprostate reduced ethanol intake in mice lacking the type 1 equilibrative nucleoside transporter (Lee et al., 2011). It is important to note that a previous study demonstrated a dose-dependent effect of acamprosate in the reduction of ethanol intake (Gupta et al., 2008). Ho and colleagues suggested that the dose tested in their study was lower than that tested by Gupta and colleagues.

Acamprosate may also regulate extracellular glutamate in the brain (Dahchour et al., 1998). Recent evidence suggests that many aspects of neuroplasticity associated with alcohol/drug addiction involve changes in glutamatergic neurotransmission. It is important to note that ethanol exposure alters glutamate transport and can lead to a reduction in the expression of key glutamate transporters in several brain reward regions. Our lab revealed that chronic

ethanol intake reduced the expression of major glutamate transporter type 1 (GLT-1; its human homolog is excitatory amino acid transporter 2, EAAT2) and cystine/glutamate exchanger (xCT), and increased extracellular glutamate concentration in the NAc in male alcohol-preferring (P) rats (Alhaddad et al., 2014; Das et al., 2015). These studies showed that ceftriaxone, a β-lactam antibiotic known to upregulate GLT-1 and xCT, restored these effects. Together, regulating glutamate homeostasis through the upregulation of GLT-1 and xCT expression is critical in the attenuation of ethanol consumption. Chronic ethanol exposure increases the density of glutamate and NMDA antagonist (MK801) binding sites in the brains of rats and mice (Grant et al., 1990). In rats, the effects of ethanol are associated with an increased extracellular glutamate concentration in the NAc and enhanced NMDA receptor sensitivity in this brain region (Siggins et al., 2003). Acamprosate is believed to maintain abstinence by blocking the negative craving that alcohol-dependent patients experience in the absence of alcohol (Mann, 2004). This suggests that the NMDA receptor has a crucial role in the development of alcohol dependence. Although the mechanisms of action of acamprosate are still unclear, it blocked ethanol's increase in extracellular glutamate in the NAc (Dahchour et al., 1998). Ho and colleagues described several possible mechanisms of action of this drug, including its modulatory effect on NMDA receptor function (Ho et al., 2016). In fact, the main mechanism of action of acamprosate may be to modulate extracellular glutamate concentration so as to normalize a hyperglutamatergic state in several brain reward regions, including the NAc (Dahchour et al., 1998) and thereby attenuate alcohol dependence.

Role of serotonergic system in alcohol consumption

Ho and colleagues (2016) showed that escitalopram treatment reduced ethanol intake in non-stressed mice but the drug had no effect in stressed mice. Escitalopram is a drug that blocks the 5-HT transporter, which increases 5-HT concentration in the synaptic cleft. Changes in 5-HT uptake and its release may affect alcohol-drinking behavior. A deficit in 5-HT was observed in patients who suffered either alcohol abuse or dependence, and the concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) were lower in abstinent alcoholics (For a review see (Sari et al., 2011). Importantly, the presence of the short allele of the 5-HT transporter promoter-linked polymorphism was correlated with higher ethanol intake in human alcoholics (For a review see (Sari et al., 2011). Furthermore, decreased expression of the 5-HT transporter was found in the raphe nuclei of alcoholics, and this effect was correlated with lifetime ethanol intake and ratings of depression and anxiety during periods of withdrawal (Heinz et al., 1998). Consistent with these findings, studies in animal models showed a reduction in the functional capacity of the 5-HT transporter, which was postulated to be a key factor in the development of alcohol dependence (Goldman, 1996). Clinical findings demonstrated that the use of SSRIs such as fluoxetine and paroxetine may help to reduce ethanol intake only in some subgroups of alcoholics (For a review see (Sari et al., 2011). In addition, studies decreases in 5-HT turnover rate and greater availability of the 5-HT transporter were associated with a reduction in heavy drinking, anxiety and impulsive aggression (Johnson et al., 2008; Wrase et al., 2006). Anxiety is a phenotype of P rats, which also display 5-HT deficits (Stewart et al., 1993). Deficits in the concentrations of 5-HT and 5-HIAA have been found in several

brain regions, including the NAc, cerebral cortex, striatum, septal nuclei, hippocampus and hypothalamus of selectively bred high alcohol drinking (HAD) rats compared to their low alcohol drinking (LAD) counterparts (Gongwer et al., 1989). This is in agreement with a study that revealed a reduction in the concentrations of 5-HT and 5-HIAA in several brain regions of selectively bred P rats compared to their alcohol-non-preferring (NP) counterparts (Murphy et al., 1982). It is noteworthy that the P rat has behavioral, physiological and neurochemical traits similar to those of some alcoholic individuals (Bell et al., 2006). Together, studies conducted in animals and humans indicate that deficits in the serotonergic system have a strong influence on alcohol dependence risk.

Ho and colleagues found that escitalopram reduced ethanol intake in non-stressed mice but not in stressed mice. The lack of effect in stressed mice may be due to the fact that chronic unpredictable stress exposure may lead to a decrease in the expression of glutamate receptors such as AMPA and NMDA receptors and alteration of glutamate-glutamine cycling (For a review see (Popoli et al., 2011). Thus, modulating 5-HT transmission alone may not be effective in reducing ethanol intake in stressed animals; however, modulating both glutamatergic and 5-HT neurotransmission might be effective in this animal model. In fact, these systems interact with one another to modulate neurotransmission. It has been shown that the activation of 5-HT1B receptors located at the terminals of glutamatergic neurons blocks the action of glutamate in the NAc (Muramatsu et al., 1998). It is important to note that 5-HT1B receptors regulate the release of glutamate and other neurotransmitters in several brain regions, including the NAc [For a review see ref. (Sari, 2004)]. This is consistent with an interactive effect of 5-HT and glutamate on ethanol intake in stressed animals, as reported by Ho and colleagues (Ho et al., 2016).

Conclusions and closing thoughts

Ho and colleagues report demonstrates in an animal model the potential clinical uses of acamprosate and escitalopram to treat individuals with co-occurring alcohol dependence and depression. These findings are clinically relevant, as it is well known that chronic heavy drinking can lead to a hyperglutamatergic state and dampening this state with acamprosate would have an attenuating effect on alcohol dependence. Ho and colleagues reported that combining acamprosate with escitalopram may have a beneficial effect in treating alcohol dependence following stress exposure or not involving it. We have previously discussed several SSRIs that may have beneficial effects in treating alcohol dependence, including fluoxetine, sertraline, escitalopram, zimelidine, and tianeptine (For a review see (Sari et al., 2011). It is important to note that differences may occur with the use of SSRIs as therapies for the treatment of alcohol dependence. For example, a study performed in a rat model demonstrated that escitalopram may be less effective than fluoxetine in reducing some withdrawal symptoms (Saglam et al., 2006). The choice of an SSRI may be important in treating specific subpopulations of alcoholics.

Clinical studies demonstrated that the efficacy of SSRIs differ between type A (or type I) and B (or type II) alcoholic populations. Type A alcoholics show less severe and later onset of alcohol dependence and are less likely to have comorbid drug use and psychiatric disorders (For a review see (Sari et al., 2011). In contrast, type B alcoholics show high levels

of stress, early onset of alcohol dependence and greater comorbidity with drug use and psychiatric disorders. Importantly, SSRIs might be beneficial for type A alcoholics. For example, fluoxetine was found to be harmful in treating alcohol-related drinking problems in type B but not type A alcoholics (Kranzler et al., 1996). Sertraline treatment was effective in type A but not in type B alcoholics (Pettinati et al., 2000). It is noteworthy that the preclinical study by Ho and colleagues (2016) using stressed mice confirmed the findings from several clinical studies that support the use of SSRIs to treat alcohol dependence with comorbid depression. This is most evident in the findings of Pettinati et al. (2010), who found that combining sertraline with naltrexone to treat depressed alcoholics produced a higher alcohol abstinence rate and a longer time to relapse to heavy drinking than naltrexone, sertraline, or placebo alone.

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