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Invited review

Neuroimaging insights into the role of cortical GABA systems and the influence of nicotine on the recovery from alcohol dependence

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ABSTRACT

This paper reviews evidence suggesting that nicotine and tobacco smoke profoundly modulate the effects of alcohol on γ-aminobutyric acid (GABA) neuronal function, specifically at the $GABA_A$-benzodiazepine receptor ($GABA_A$-BZR). The focus of this paper is on recent neuroimaging evidence in preclinical models as well as clinical experiments. First, we review findings implicating the role of alcohol at the $GABA_A$-BZR and discuss the changes in $GABA_A$-BZR availability during acute and prolonged alcohol withdrawal. Second, we discuss preclinical evidence that suggests nicotine affects GABA neuronal function indirectly by a primary action at neuronal nicotinic acetylcholine receptors. Third, we show how this evidence converges in studies that examine GABA levels and $GABA_A$-BZRs in alcohol-dependent smokers and nonsmokers, suggesting that tobacco smoking attenuates the chemical changes that occur during alcohol withdrawal. Based on a comprehensive review of literature, we hypothesize that tobacco smoking minimizes the changes in GABA levels that typically occur during the acute cycles of drinking in alcohol-dependent individuals. Thus, during alcohol withdrawal, the continued tobacco smoking decreases the severity of the withdrawal-related changes in GABA chemistry.

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1. Introduction

γ-aminobutyric acid (GABA) neuronal function is modulated by ethanol and nicotine (Kumar et al., 2009; Markou, 2008). Neuroadaptations within GABA neurons contribute to the development of both ethanol and nicotine dependence, as well as complications associated with the abrupt discontinuation of ethanol or nicotine in dependent individuals (Hughes, 2009). Similarly, GABA systems have been implicated in the recovery from ethanol and nicotine dependence (Mason et al., 2006; Staley et al., 2005). Given the high rate of alcohol and nicotine dependence comorbidity (Grant et al., 2004), studying the convergent effects of acute and chronic exposure to these substances might provide clinically relevant insights about the underlying mechanistic interactions of ethanol and nicotine. In this review we examine evidence suggesting that GABA neuronal function, and specifically the $GABA_A$-benzodiazepine receptor ($GABA_A$-BZR), is a major neurochemical target mediating the comorbidity of alcohol and nicotine dependence. We hypothesize that nicotine profoundly alters both the acute and chronic effects of ethanol on $GABA_A$ receptors and thus increases the risk for both alcoholism (by suppressing ethanol neuroadaptations and withdrawal) and nicotine dependence (because the increased tolerability of ethanol and ethanol withdrawal serves as a negative reinforcer for continued smoking). Important contributions of neuroadaptions associated with $GABA_A$ receptors to ethanol dependence have been reviewed previously (Krystal et al., 2006) and we refer readers to other recently published reviews on the interaction of nicotine and alcohol such as genetic components (Flatscher-Bader and Wilce, 2009; Schlaepfer et al., 2008) and reward mechanisms (Schlaepfer et al., 2008) that contribute to the comorbidity.

2. Comorbidity of alcohol and nicotine dependence

The high rate of comorbidity between alcohol and nicotine dependence is well established. While in the general population it is estimated that 25% of people are current cigarette smokers, up to 45% of alcohol-dependent individuals smoke, and as many as 14% of smokers are also alcohol-dependent (Grant et al., 2004). Smokers consume twice as much alcohol as nonsmokers (Carmody et al., 1985), alcohol problems are approximately 10 times more prevalent in smokers vs. nonsmokers (DiFranza and Guerrera, 1990), and alcohol-dependent smokers use more cigarettes per day than non-alcohol-dependent smokers (Dawson, 2000). Unfortunately,

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individuals with a current or past alcohol problem have a more difficult time quitting smoking than non-alcoholics (Bobo et al., 1987; Kahler et al., 2010a; Romberger and Grant, 2004) and they are more likely to lapse to smoking while they are drinking (Kahler et al., 2010b). However, quitting smoking does not appear to affect rates of heavy drinking (Kahler et al., 2010a), suggesting that quitting smoking and drinking must both be targeted in vulnerable individuals. There are several factors that may underlie the high comorbidity of smoking and drinking (reviewed in Meyerhoff et al., 2006). First, the effects of the drugs, when used together, may be additive or synergistic with regard to the reinforcing properties. Second, pharmacological effects or interactions of the drugs, such as changes in metabolism or cross-tolerance, may lead to co-abuse. Third, genetic factors likely contribute to this comorbidity.

We suggest that there is a critical influence of nicotine on alcohol's actions at the $GABA_A$ receptor, as an additional factor that may contribute to the comorbidity of these disorders. The cycle of addiction begins with acquisition or initiation of drug taking, which escalates to a steady-state maintenance phase and then cycles of withdrawal and relapse typically occur. It is likely that during these phases, discrete brain areas and neurochemical systems are recruited. Traditionally, the initiation phase is characterized by positive reinforcement, which is critically tied to the mesolimbic dopamine system (Di Chiara and Imperato, 1988). The shift from controlled to uncontrolled use can be associated with a shift from positive to negative reinforcement, i.e., when addicted individuals switch from taking drugs for the euphoric effects to taking drugs to prevent withdrawal symptoms. At that point it becomes critical to maintain homeostasis between the inhibitory (GABAergic) and excitatory (glutamatergic) systems. During alcohol withdrawal, the drug-maintained homeostasis is severely disrupted, most clearly evidenced by seizures, and it is at this critical juncture that nicotine may be conferring protection against changes in neurochemicals and in alcohol withdrawal symptoms. Specifically, the profound effects of nicotine on alcohol-induced alterations of $GABA_A$ receptors may drive the continued use of both substances.

3. Effects of alcohol and alcohol withdrawal on $GABA_A$ receptors

$GABA_A$ receptors are ligand-gated ion channels that are the primary mechanism for modulating inhibitory synaptic transmission in the brain and have a central role in modulating the effects of alcohol in the central nervous system (Davies, 2003; Krystal et al., 2006; Kumar et al., 2004). GABA plays a number of important roles in the brain, including maintaining homeostatic balance between excitation and inhibition (Sivilotti and Nistri, 1991), tuning the activity of glutamate neurons (Sesack et al., 2003), and entraining the coherent oscillatory interactions within cortical networks (Mann and Paulsen, 2007; Wang and Buzsaki, 1996). The $GABA_A$ receptor is a member of a family of homologous transmitter-gated ion channels along with the nicotinic acetylcholine receptor (nAChR), glycine and 5-HT_3 receptors (Sigel and Buhr, 1997). $GABA_A$ receptors are pentamers typically comprised of two $\alpha_{1\text{-}6}$, two $\beta_{1\text{-}3}$, and one $\gamma_{1\text{-}3}$ subunit. Benzodiazepines bind to a distinct site at the interface between an α and γ subunit on the $GABA_A$ receptor, a site commonly referred to as the $GABA_A$-benzodiazepine receptor ($GABA_A$-BZR).

Although acute ethanol exposure has been reported to potentiate GABA-gated currents (Suzdak and Paul, 1987; Tatebayashi et al., 1998), direct ethanol effects on synaptic $GABA_A$ receptors only occur at ethanol levels that are lethal in humans (Koski et al., 2002, 2005). Potent effects of ethanol *in vivo* likely reflect direct actions of ethanol at extrasynaptic $GABA_A$ receptors (Krystal et al., 2006; Sundstrom-Poromaa et al., 2002; Wallner et al., 2003). Acute ethanol may also act indirectly at synaptic $GABA_A$ receptors (via increased glutamate release), thereby increasing the synaptic release of GABA (Ariwodola and Weiner, 2004; Carta et al., 2004; Moghaddam and Bolinao, 1994). Of interest is the capacity of ethanol to raise levels of neurosteroids that interact with $GABA_A$ receptors (Barbaccia et al., 1999; Morrow et al., 1999) in a manner similar to other $GABA_A$-receptor positive modulators that may influence tolerance to alcohol (Morrow et al., 2006). Importantly, GABAergic neurosteroids do not exhibit cross-tolerance like benzodiazepines, and have been shown to be protective during ethanol withdrawal (Devaud et al., 1996, 1995). Neurosteroids act at extrasynaptic $GABA_A$ receptors that mediate tonic inhibition, rather than at synaptic $GABA_A$ receptors that mediate phasic inhibition (Stell et al., 2003; Wohlfarth et al., 2002). This is important because as previously mentioned the extrasynaptic $GABA_A$ receptors have been proposed as a high-affinity target for ethanol (Sundstrom-Poromaa et al., 2002; Wallner et al., 2003). Long-term ethanol exposure stimulates changes in $GABA_A$ receptor subunit composition (Charlton et al., 1997; Devaud et al., 1997; Petrie et al., 2001), and the consequence of this adaptation is that $GABA_A$ receptors show higher affinity for GABA, but disrupted chloride channel conductance (Liang et al., 2007; Morrow et al., 1988; Sanna and Harris, 1993). When ethanol is removed, the lowered functionality of the $GABA_A$ receptors contributes to the heightened excitatory tone (Kang et al., 1996), which is clearly evidenced by irritability, sympathetic activation, seizure activity, and neurotoxicity associated with the ethanol withdrawal syndrome (Hoffman, 1995; Kokka et al., 1993).

Several postmortem studies have been conducted to determine potential differences in numbers of $GABA_A$-BZRs between individuals with alcohol dependence and controls; however, the results are conflicting. The studies report decreases in $GABA_A$-BZRs of 30% in hippocampus and 25% in frontal cortex (Freund and Ballinger, 1991), no difference in $GABA_A$-BZR density in frontal cortex or cerebellum (Korpi and Uusi-Oukari, 1992), and increases in $GABA_A$ receptor density (Tran et al., 1981) in alcohol-dependent subjects vs. controls. This variability may be due to the lack of control for smoking status, and/or to other caveats associated with the study of postmortem specimens such as postmortem interval, freezer storage time and insufficient information about the chronicity and intensity of drug use over the lifetime.

The use of receptor imaging (single photon emission computed tomography, SPECT, and positron emission tomography, PET) has significantly advanced the field of drug addiction research by allowing us to probe and quantify receptors of interest in the living human brain. SPECT in combination with the radiotracer [^{123}I] iomazenil, a $GABA_A$-BZR inverse agonist, and PET with [^{11}C]flumazenil, a $GABA_A$-BZR antagonist, provide a way to quantify numbers of $GABA_A$-BZRs in human subjects. SPECT and PET studies consistently demonstrate *decreased* $GABA_A$-BZRs in alcohol-dependent subjects at approximately 1 month (Abi-Dargham et al., 1994), 3 months (Lingford-Hughes et al., 2000, 1998) and 7 months (Lingford-Hughes et al., 2005) of abstinence. The reductions in $GABA_A$-BZR availability were consistently reported in the medial frontal cortex (Abi-Dargham et al., 1998; Lingford-Hughes et al., 1998) and cerebellum (in alcoholic women only)(Lingford-Hughes et al., 2000). The most recent study, which was the first to evaluate $GABA_A$-BZRs longitudinally within subjects while controlling for smoking status, demonstrated *increased* $GABA_A$-BZRs at about 1 week withdrawal in alcohol-dependent nonsmokers ($n = 8$) compared to alcohol-dependent smokers ($n = 15$) and controls ($n = 15$), that normalized to control levels by 4 weeks of abstinence (Staley et al., 2005). The acute increases were predominantly in the cortical regions (Staley et al., 2005). These preliminary findings during acute abstinence highlight a temporal change in $GABA_A$-BZRs during the recovery