The neuropharmacology of the age-old sedative/hypnotic, ethanol

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A commentary on

Ethanol activation of protein kinase A regulates GABA<sub>A</sub> receptor subunit expression in the cerebral cortex and contributes to ethanol-induced hypnosis

During the past several decades, there has been a concerted effort to determine the neuropharmacological mechanism of action(s) of ethanol. Ethanol has been reported to produce its effects via modulation of neural cell membrane fluidity as well as modulation of several neurotransmitter systems, including γ-amino butyric acid (GABA), glutamate, dopamine, and opioid systems (for reviews, see Koob et al., 1998; Kumar et al., 2009). GABA is an inhibitory amino acid neurotransmitter that is ubiquitously distributed in the mammalian brain, and ethanol’s effects on the GABA system are thought to be mediated primarily by activating the GABA_A receptor, a 5-subunit receptor that gates Cl⁻ ions (for a review, see Kumar et al., 2009). Thus, GABA receptor activation produces CNS inhibition via Cl⁻ influx. It has also been reported that specific GABA_A receptor subunits mediate specific effects. For example, the α1 subunit is associated with sedation, whereas the α2 and α3 subunits are associated with anti-anxiety effects (Licata and Rowlett, 2008; Ator et al., 2010).

Many types of sedative-hypnotic compounds (drugs producing dose-dependent sedation and ultimately sleep), including the benzodiazepines, barbiturates, and ethanol, bind to and activate the GABA_A receptor, and it is reasonable to assume that the sedative effects of these agents are mediated, at least in part, by the α1 subunit.

It is known that neurotransmitters, including GABA, bind to their receptors as “first messengers,” and initiate a complex cascade of intra-cellular events. In the case of GABA, part of this cellular cascade includes modulation of the “second messenger” systems Ca²⁺ and cAMP that ultimately modulate two protein kinases, PKC and PKA, resulting in myriad effects in the cell, including changes to gene expression (Moss et al., 1992; Diamond and Gordon, 1997; Brandon et al., 2000 for a review, see Kumar et al., 2009).

Leslie Morrow and colleagues have been exploring the complex cascade of downstream cellular events mediated by ethanol-induced GABA_A receptor activation. In their recent Frontiers in Neuroscience report (Kumar et al., 2012), this research team determined the effects of acute ethanol exposure on PKA-mediated GABA_A receptor expression. Although chronic ethanol exposure has been reported to produce down-regulation and/or desensitization of GABA_A receptors, Morrow and colleagues reported an interesting finding of acute ethanol exposure. Specifically, acute intracerebroventricular administration of ethanol produced dose-dependent increases in expression of PKA and GABA_A receptor α1 subunits. In addition, antagonism studies revealed that blockade of PKA blocked the ethanol-induced increases in GABA_A receptor α1 subunit expression, providing further evidence for a PKA-GABA_A receptor network communication. An additional manipulation showed that enhancing PKA activity actually enhanced ethanol-induced loss of righting reflex. Together with earlier reports from this research group, these data indicate that PKA (Kumar et al., 2012) and PKC (Kumar et al., 2006) may have antagonistic effects on GABA_A receptor α1 subunit expression, thus delineating specific potential pathway(s) for mediation of ethanol effects on cell function and overt organismal behavior. This group’s current report represents a comprehensive analysis of the specific effects of ethanol on kinase activity and receptor subunit expression levels, and adds another layer of knowledge about the neuropharmacological mechanisms of ethanol. It is quite possible that further elucidation of the complex molecular “systems level” analysis of ethanol’s actions in nerve cells may yield important “systems level” approaches and advances for the treatment of alcohol abuse and dependence.

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References


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Sedative-Hypnotic Drugs. Anxiety Term used to describe both symptoms and disorders Occurs normally as signal of impending danger or threat Very common, occurs in many disorders in addition to the anxiety. More information. MEDICATION ABUSE IN OLDER ADULTS Clifford Milo Singer, MD Adjunct Professor, University of Maine, Orono ME Chief, Division of Geriatric Mental Health and Neuropsychiatry The Acadia Hospital and Eastern. More information. Can’t sleep? The Neuropharmacology of Drugs of Abuse 3 rugs of abuse interact with the neurochemical mechanisms of the brain. Some of these interactions are directly related to the reinforcing properties of a drug. More information.