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Review

5-HT_3 receptors and the neural actions of alcohols: an increasingly exciting topic

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Abstract

The 5-HT_3 receptor is a ligand-gated ion channel activated by the neurotransmitter serotonin. Receptors of this subtype have been localized to several regions of the brain, and appear to be involved in many neuronal functions including responses to alcohol and other drugs of abuse. There is an extensive and growing literature indicating that 5-HT_3 receptors are involved in several facets of alcohol seeking behavior, alcohol intoxication and addiction. In addition, there is strong evidence that alcohols, including ethanol, alter the function of the 5-HT_3 receptor, possibly through actions on the receptor protein itself. In this article, our current understanding of the role of the 5-HT_3 receptor in alcohol abuse and alcoholism will be reviewed. In addition, an overview of current understanding of the mechanism of alcohol actions of the receptor is provided.

Contents

1. Introduction

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) has been implicated in several aspects of brain function including regulation of affective states, ingestive behavior and addiction. Serotonin is especially strongly implicated in alcohol abuse and addiction, as has been reviewed elsewhere (Grant, 1995; Lovinger, 1997a). For the purposes of this review, I will concentrate on one aspect of the role of 5-HT in alcohol abuse, namely, the involvement of one receptor for this neurotransmitter, the 5-HT_3 receptor.

Serotonin can activate a number of different receptor subtypes (at least 14 at last count). These receptors produce diverse neuronal responses, mostly through

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activation of G-protein-mediated signalling pathways. However, signalling through the 5-HT_3 receptor stands out from other effects of 5-HT because this receptor is a member of the ligand-gated ion channel superfamily which is not linked to G-proteins. Instead, the 5-HT_3 receptor contains an intrinsic ion channel that, when activated, allows cation flux through the neuronal membrane and depolarizes the membrane potential (Derkach et al., 1989; Maricq et al., 1991; Peters and Lambert, 1989). Thus, 5-HT_3 receptors may be thought of as excitatory receptors. However, as we will discuss in relation to alcohol effects, the net excitatory or inhibitory effect of an agent is not solely a consequence of its effect on an individual neuron, but is more accurately judged by its actions on neuronal circuits. Thus, if a receptor acts to stimulate the activity of inhibitory neurons, then it may be viewed as having a net inhibitory effect on brain function, at least within a given brain region. I will discuss evidence that 5-HT_3 receptors have such an inhibitory action.

2. 5-HT_3 receptors

Until very recently, the 5-HT_3 receptor was thought to be formed by a single protein subunit (termed the 5-HT_3RA) that was assembled in a pentameric configuration (Green et al., 1995; Maricq et al., 1991). However, recent evidence suggests that this subunit protein may assemble with subunits normally associated with the nicotinic acetylcholine receptor-channel (Van Hooft et al., 1998; but see also Fletcher et al., 1998), and with a newly discovered 5-HT_3 receptor subunit (Davies et al., 1999). Thus, a picture of the receptor as a heteropentamer, at least under some conditions, is beginning to emerge. The 5-HT_3RA subunit is expressed in several locations within the peripheral and central nervous systems, including the brain (Maricq et al., 1991; Morales et al., 1996; Morales and Bloom, 1997). Receptor function has been implicated in a variety of neural processes including pain perception, emesis, anxiety and the actions of drugs of abuse (Grant, 1995; Jackson and Yakel, 1995).

There is strong evidence supporting a role for 5-HT_3 receptors in the neural actions of EtOH (see Grant, 1995, and Parker et al., 1996, for reviews). There is compelling evidence that 5-HT_3 receptor antagonists reduce alcohol intake in free-choice animal models of drinking (Fadda et al., 1991; LeMarquand et al., 1994a; Sellers et al., 1994; Tomkins et al., 1995). In addition, studies of human alcoholics indicate that these antagonists reduce drinking and alter the subjective perception of intoxication (Johnson et al., 1993; LeMarquand et al., 1994b; Sellers et al., 1994). Recent studies using transgenic mice that overexpress the 5-HT_3 receptor in forebrain, indicate that chronic enhancement of receptor function can also reduce alcohol intake (Engel et al., 1998). Thus, there is solid evidence for a role of this receptor in alcohol consummatory behavior.

3. Alcohol actions on the 5-HT_3 receptor: possible role in intoxication

Numerous studies have documented that alcohols alter the function of 5-HT_3 receptors (Barann et al., 1995; Jenkins et al., 1996; Lovinger, 1991; Lovinger and Zhou, 1993, 1994; Machu and Harris, 1994; Parkier et al., 1996). The most consistent finding is that EtOH and other small to moderate chain length n-alkanols potentiate receptor function. Potentiation is also observed upon exposure to halogenated alcohols such as trichloroethanol (TCEt, the active metabolite of the general anesthetic chloral hydrate: Lovinger and Zhou, 1993; Downie et al., 1995; Zhou and Lovinger, 1996). Potentiation is observed in the presence of these alcohols at concentrations that are within the range of the blood and brain alcohol concentrations present during acute intoxication. Thus, it is possible that alcohol effects on the receptor contribute to intoxication. However, a strong link between effects at the receptor level and the aforementioned behavioral evidence for 5-HT_3 receptor involvement in intoxication has not yet been forged.

Despite the lack of a linkage between findings at these two levels of analysis, it is worth considering the ways in which alcohol potentiation of receptor function might play a role in the neural actions of acute alcohol. One possibility that was touched on in the foregoing discussion is enhanced neuronal inhibition. As mentioned above, the inhibitory effect for the 5-HT_3 receptor would appear to conflict with the apparent excitatory nature of the current produced by receptor activation. However, the observation that 5-HT_3 receptors are often expressed by inhibitory interneurons in the forebrain may help to explain this role. Immunocytochemical evidence indicates that GABAergic interneurons in the cerebral cortex and some limbic regions express 5-HT_3 receptors (Morales et al., 1996; Morales and Bloom, 1997). Furthermore, electrophysiological analysis of 5-HT_3 receptor function in the hippocampal formation indicates that receptors residing on GABAergic inhibitory interneurons in the dentate and hippocampal gyri can stimulate interneuron activity (Kawa, 1994; McMahon and Kauer, 1997; Ropert and Guy, 1991). This leads to increased release of the inhibitory neurotransmitter GABA, and net inhibition of hippocampal circuitry. Thus, enhancement of inhibitory synaptic transmission by 5-HT_3 receptors may contribute to some of the neural inhibitory actions of alcohols.

There is also accumulating evidence supporting a role for 5-HT_3 receptors in neurotransmitter release from presynaptic terminals. Studies have utilized neurochemical and electrophysiological techniques to demonstrate that 5-HT_3 receptors stimulate the release of neurotransmitters. Microdialysis and coulometric measurements indicate that the receptors can stimulate release of dopamine in the mesocortical and mesolimbic systems (Chen et al., 1991, 1992; Costall et al., 1987; Hagan et al., 1987; Jiang et al., 1990; Tanda et al., 1995). However, it is not clear if these effects result from activation of receptors located on dopaminergic terminals or via secondary effects of receptor activation (Campbell et al., 1995; Crespi et al., 1997). Activation of 5-HT_3 receptors on presynaptic terminals in the nucleus tractus solitarius appears to increase release of the neurotransmitters GABA and glutamate (Glaum et al., 1992). It is possible that activation of receptors on axon terminals may generate increased intraterminal calcium that directly stimulates neurotransmitter release or works in concert with calcium signals generated by other sources to stimulate release.

Stimulation of dopamine release may be of particular significance in the neural actions of drugs of abuse. Dopamine is thought to be a major chemical mediator of brain 'reinforcement' systems, particularly those that are engaged by drugs of abuse, including EtOH. Thus, 5-HT_3 receptors involved in stimulation of dopamine release may be especially well poised to participate in regulation of brain reward systems. Indeed, there is some evidence that 5-HT_3 receptors in the basal ganglia are crucial for increases in dopamine release stimulated by local EtOH application (Wozniak et al., 1990), and may also participate in increases produced by peripheral EtOH administration (Campbell and McBride, 1995). However, it is not clear if these local effects of EtOH accurately reflect the actions of EtOH in vivo that lead to enhanced dopamine release. Thus, it is not yet clear if 5-HT_3 receptor-mediated stimulation of dopamine release is an important step in the neural mechanisms underlying the reinforcing effects of EtOH.

Some alcohols also have inhibitory actions on 5-HT_3 receptor function. These effects are particularly prominent during exposure to long-chain n-alkanols and high concentrations of TCEt (Jenkins et al., 1996; Zhou et al., 1998). However, inhibitory actions are not generally observed upon exposure to EtOH and other short-chain n-alkanols. Furthermore, these inhibitory effects appear to occur mainly at concentrations of TCEt that are higher than those encountered clinically. Thus, one cannot make a compelling case that alcohol inhibition of 5-HT_3 receptors plays a role in alcohol-induced intoxication or anesthesia.

4. Mechanisms of alcohol action on the 5-HT_3 receptor

Potentiation of 5-HT_3 receptor function is associated with an apparent increase in the potency of 5-HT for receptor activation. This can be seen as a leftward shift in the 5-HT concentration-response curve. Recent studies indicate that alcohols enhance the likelihood that the channel associated with the receptor will remain in the open, ion conducting state (Zhou et al., 1998). Detailed analysis of receptor-channel kinetics indicates that alcohols favor the opening state of the channel by increasing the rate constants into the open state, while stabilizing the open state by decreasing rate constants leading to closed and desensitized, non-conducting channel states.

The enhanced agonist potency and increased time spent in the open state that are brought about by alcohols could be the result of a direct increase in the affinity of the receptor for agonist. Conversely, increased efficacy (i.e. increased ease of channel gating) might also contribute to these effects. We have used a partial agonist for the receptor to help sort out the roles of these different mechanisms. Our findings indicate that EtOH and TCEt potentiate receptor function even when the receptor agonist binding site is fully occupied by the weak partial agonist dopamine (Lovinger and Zhou, 1997). This finding indicates that alcohol effects on channel gating, most likely involving increased probability of channel opening, contribute to alcohol potentiation of receptor function.

5. Mechanism of alcohol-induced receptor inhibition

There is not a great deal of evidence indicating what mechanisms underlie alcohol inhibition of the 5-HT_3 receptor. It is clear that the potency of the inhibitory actions of alcohols increases with increasing n-alkanol carbon chain length (Jenkins et al., 1996). This indicates that the site of the alcohol inhibitory action is hydrophobic. Studies of the nicotinic ACh receptor, which is part of the same molecular family as the 5-HT_3R, indicate that long-chain alcohols inhibit receptor function via a use-dependent, channel blocking action in which the alcohol appears to physically occlude the ion pore (Forman, 1997; Forman et al., 1995). This mechanism may well underlie the inhibitory actions of TCEt and long-chain alcohols on the 5-HT_3 receptor, but further tests of this hypothesis are needed. One useful set of information would be to determine if alcohols produce apparent 'flickering' behavior in single 5-HT_3 receptor-channels. This is a common feature of channels undergoing rapid block and unblock. However, this behavior will not be easy to measure in the small-conductance 5-HT_3R channels observed in many preparations. More useful infor-

mation may come from preparations, such as peripheral neurons, that express channels with large conductance (Peters et al., 1993).

6. Molecular determinants of alcohol actions on the 5-HT_3 receptor

The primary molecular site of alcohol interactions with neuronal membranes that leads to alterations in receptor function is not known. Although past investigations suggested a lipid site for alcohol actions, more recent studies have provided good evidence that alcohols and general anesthetics produce their actions through interactions with protein targets (see Franks and Lieb, 1994, for a review).

Recent studies have provided evidence consistent with the idea that alcohols interact with the 5-HT_3 receptor itself rather than acting on the receptor indirectly through effects on membrane lipids. The potentiating effects of alcohols are absent at chain lengths longer than 6 carbons (Jenkins et al., 1996). This observation is consistent with the idea that this action of alcohols involves hydrophobic sites associated with the protein itself, since alcohols with chain lengths longer than this 'cutoff' point perturb lipid bilayers but do not potentiate receptor function. Furthermore, allosteric interactions between the actions of different alcohols on the receptor have been observed (Zhou and Lovinger, 1996), and these interactions would be difficult to explain by interactions solely with lipid components of the membrane. However, there is little information about which portions of the receptor are critical for conferring alcohol sensitivity on the receptor.

One approach that has been taken to this question is to create chimeric receptors that combine portions of the 5-HT_3 receptor with portions of the α7 nicotinic ACh receptor, a receptor that appears to be inhibited by EtOH (Yu et al., 1996). Receptors that contain the n-terminal portion of the nicotinic receptor retain their sensitivity to EtOH inhibition. This suggests that amino acids within the n-terminal, presumed extracellular, portion of the receptor play a critical role in determining alcohol sensitivity. The results of this experiment cannot be completely disentangled from issues arising from the very fast desensitization of the nicotinic receptor-channel. It is possible that alcohol exposure appears to inhibit the receptor due to rapid movement of channels into the desensitized state resulting from increased receptor activation rate (Zhou et al., 1998). However, the results of this chimeric receptor analysis provide an intriguing first piece of evidence indicating a possible locus of an alcohol interaction site on the receptor. It will be interesting to determine if any point mutations of amino acids in this region will alter alcohol effects on the receptor.

Examination of close molecular relatives of the 5-HT_3 receptor may also yield information that indicates sites of alcohol action on the receptor. Recent studies of recombinant GABAρ and glycine receptors used a chimeric receptor approach combined with site-directed mutagenesis to provide evidence that alcohol actions involve particular amino acids near the extracellular side of the TM2 and TM3 membrane-spanning portions of these receptors (Mihic et al., 1997; Wick et al., 1998). While these amino acids are not strictly conserved in the 5-HT_3 receptor, it is thought that there is a good deal of conservation of protein secondary structure among these members of the nACh receptor subfamily of ligand-gated ion channels. Thus, residues in the same positions within the TM regions may be positioned similarly in the holoprotein. If this is the case, then alcohol effects on the 5-HT_3 receptor may involve actions at residues in the TM2 and TM3 regions at sites corresponding to those implicated in alcohol actions on GABAA and glycine receptors.

Residues that are thought to line the ion pore of the nACh receptor appear to contribute to the inhibitory actions of alcohols on that close molecular cousin of the 5-HT_3 receptor (Forman, 1997; Forman et al., 1995; Forman and Zhou, 1999). It is currently thought that alcohols directly interact with residues within the pore to produce open-channel block. It will be interesting to determine if analogous residues within the 5-HT_3 receptor putative pore-lining regions of TM2 are involved in the inhibitory actions of alcohols.

Ultimately, strong evidence of direct alcohol-protein interactions will be needed to support the hypothesis that alcohols alter receptor function by interacting with key amino acids on the 5-HT_3 receptor. This sort of information will have to come from the studies using biophysical techniques that allow for direct examination of protein structural features. These approaches to examination of ligand-gated ion channels are just being refined, and there is a great deal to be learned about the basic structural features of the receptor prior to beginning examination of interactions with alcohols. However, it should be possible in the not-too-distant-future to begin examining alcohol interactions with proteins more directly.

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