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Role of 5-hydroxytryptamine 1B (5-HT_{1B}) receptors in the regulation of ethanol intake in rodents

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Abstract

Evidence indicates that the serotonergic system is important in mediating dependence on and craving for alcohol. Among serotonin receptors, 5-hydroxytryptamine 1B (5-HT_{1B}) receptors have been associated with drug abuse including alcohol. In this review, the neurocircuitry involving 5-HT_{1B} receptors in central reward brain regions related to alcohol intake are discussed in detail. Emphasis has been placed on the pharmacological manipulations of 5-HT_{1B} receptor-mediated alcohol intake. Furthermore, 5-HT_{1B} auto- and hetero-receptors regulate alcohol intake through the regulatory mechanism involving release of 5-HT, gamma-aminobutyric acid (GABA), dopamine, and glutamate is evaluated. Thus, interactions between 5-HT_{1B} receptors and these neurotransmitter systems are suggested to modulate alcohol-drinking behavior. This review on the role of 5-HT_{1B} receptors in neurotransmitter release and consequent alcohol intake provides important information about the potential therapeutic role of 5-HT_{1B} receptors for the treatment of alcohol dependence.

Keywords

5-HT_{1B} receptor; alcohol dependence; serotonin; GABA; dopamine

Introduction

Alcohol abuse and dependence continue to be significant public health problems (Harper, 2009; Heilig and Egli, 2006; Li, 2008; Room et al., 2005; Sullivan and Zahr, 2008; Volkow and Li, 2005). Alcohol dependence, known also as alcoholism, is considered one of the high severity disorders (Schuckit, 2009). Alcohol dependence is a cluster of cognitive behavior and physiological functions that can be developed after repeated use of alcohol. Chronic consumption of alcohol can induce alteration in neuronal function, which may lead to sensitization, tolerance, withdrawal, and dependence to alcohol (Diana et al., 2003). Emerging evidence indicates that many aspects of alcohol dependence involve the serotonergic system (for review, see Sari et al., 2011).

The serotonin (5-hydroxytryptamine (5-HT)) system is involved in alcohol intake, abuse and dependence (Ait-Daoud et al., 2009; LeMarquand et al., 1994a; LeMarquand et al., 1994b; Sari et al., 2011; Sellers et al., 1992). Decreased 5-HT function in central brain reward regions is associated with increased alcohol consumption (Balldin et al., 1994; LeMarquand et al., 1994a). 5-HT inversely mediates alcohol intake, such that an increase in 5-HT

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Conflicts of interest

The author declares that there is no conflict of interest.

function may lead to a decrease in alcohol intake and a decrease in 5-HT function may lead to an increase in alcohol intake (LeMarquand et al., 1994b). Dysfunction of the 5-HT system often occurs in individuals who either abuse alcohol or are alcohol-dependent (LeMarquand et al., 1994a). Brain imaging studies have shown reduced 5-HT transporter levels in alcoholics (Heinz et al., 1998; Heinz et al., 2001). It is noteworthy that the 5-HT transporter genotype has a significant influence on alcohol craving in alcoholic individuals. Alternatively, the concentration of 5-HT and its metabolite 5-hydroxy indole acetic acid (5-HIAA) in a central reward region such as the nucleus accumbens (NAc) were lower in selectively bred, high alcohol-drinking rats when compared with their low alcohol-drinking counterparts (McBride et al., 1995). This parallels a previous study, which also demonstrated that selectively bred, alcohol-preferring rats have reduced levels of 5-HT and 5-HIAA compared to alcohol-non-preferring rats (Murphy et al., 1982). Note that alcohol-preferring rats exhibit behavioral, physiological and neurochemical traits similar to those observed in alcoholic humans (Bell et al., 2005; Bell et al., 2006a; Bell et al., 2006b; McBride and Li, 1998; Murphy et al., 2002; Rodd et al., 2004).

Clinical studies indicate that selective serotonin reuptake inhibitors (SSRIs; e.g. fluoxetine and paroxetine) can be used to treat alcohol addiction in subgroups of alcoholics (Heinz et al., 1998; Pettinati, 2001). SSRI-induced decreases in 5-HT turnover are associated with a reduced reward response to excessive alcohol consumption in the dorsal raphe nuclei of non-human primates (Wrase et al., 2006). In addition, similar studies have demonstrated that the administrations of SSRIs decrease neuronal firing in the ventral tegmental area (VTA), a central brain reward region (Esposito, 1996; Prisco and Esposito, 1995). Together, these suggest that dysfunction in 5-HT neurotransmission might be a key player in the initiation and maintenance of alcoholism. Changes in the release of 5-HT are considered key factors in mediating the activation of several 5-HT receptors in central brain reward regions. Among these are the 5-HT1A, 5-HT1B and 5-HT3 receptors. The identification of these subtypes of 5-HT receptors which regulate alcohol intake in rodents might be of particular importance in developing pharmacotherapies for alcohol dependence. The present focus has been on the role of the 5-HT1B receptor in alcohol-drinking behavior because of its involvement in the release of several neurotransmitters mediating the regulation of alcohol intake (for review see Sari, 2004). Furthermore, quantitative trait analysis of Bithoraxoid (BXD) recombinant mice demonstrated that the 5-HT1B receptor gene is considered a potential candidate for influencing alcohol preference (Crabbe et al., 1999). Interestingly, polymorphisms of the 5-HT1B receptor gene have been linked to alcoholism (Lappalainen et al., 1998).

In recent decades, findings have demonstrated that 5-HT1B receptors are involved in multiple physiological functions, behaviors and psychiatric diseases (Fernandez-Guasti et al., 1992; Kaiyala et al., 2003; Lin and Parsons, 2002; Ramboz et al., 1996; Sari, 2004). The 5-HT1B receptor (human analog 5-HT1D β) contains seven transmembrane domains, of which one is composed of eight amino acids and acts as the binding site for a specific ligand (Findlay and Eliopoulos, 1990; Hibert et al., 1991; Trumpp-Kallmeyer et al., 1992). The 5-HT1B receptor is coupled to an intermediate inhibitory G protein, which acts as a second messenger that can lead to a decrease in the activity of adenylyl cyclase (Bouhelal et al., 1988; Hamblin and Metcalf, 1991; Maroteaux et al., 1992; Schoeffter and Hoyer, 1989; Seuwen et al., 1988).

It is important to note that 5-HT1B receptors have been demonstrated to play a key role in drug abuse reinforcement, including cocaine and alcohol (for review see Sari, 2004). Activation of 5-HT1B receptors potentiates the reinforcing effects of cocaine (Parsons et al., 1999). Studies using pharmacological, molecular, and genetic manipulations have demonstrated that 5-HT1B receptors play a key role in alcohol dependence (Crabbe et al., 1996; Hoplight et al., 2006; Maurel et al., 1999a; Maurel et al., 1999b; Miczek and De

Almeida, 2001; Risinger et al., 1999; Tomkins and O'Neill, 2000). Voluntary alcohol consumption appears to be mediated by the 5-HT_{1B} receptors innervating the mesocorticolimbic brain regions involved in the reward circuit. These central reward brain regions originate from VTA neurons and project to the NAc, olfactory tubercle, frontal cortex, and in particular, the amygdala complex (Asan, 1998). Dopaminergic VTA projections are most intensely concentrated in the central nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the NAc shell; these regions constitute the 'extended amygdala' (For review see Alheid, 2003).

Within this neurocircuitry, pharmacological and ligand binding studies show lower densities of 5-HT_{1B} receptors in the central nervous system of alcohol-preferring rats compared to alcohol-non-preferring rats (McBride et al., 1997). In addition, pharmacological studies suggest that both 5-HT_{1B} auto- and hetero-receptors are involved in the modulation of alcohol-drinking behavior. The 5-HT_{1B} receptor mRNA and its protein, 5-HT_{1B} hetero-receptors, are expressed in the NAc (Bruinvels et al., 1993; Bruinvels et al., 1994; Mengod et al., 1990), suggesting that 5-HT_{1B} auto-receptors located at the terminals of dorsal raphe serotonergic neurons in the NAc and VTA may play a significant role in drug reinforcement, including that of alcohol (for review see Sari, 2004). It is noteworthy that there are no structural differences between 5-HT_{1B} auto- and hetero-receptors. However, studies have shown that there exists differential sensitivity between 5-HT_{1B} auto- and hetero-receptors (Rossetti and Carboni, 1995). This differential sensitivity between 5-HT_{1B} auto- and hetero-receptors may be due to differences in the level of receptors at different synapses which may influence sensitivity under conditions such as partial occupancy.

In this review, the pharmacological manipulations of 5-HT_{1B} receptors and the use of 5-HT_{1B} receptor knockout mice have been discussed in detail. The discussion focuses also on the role of 5-HT_{1B} auto- and hetero-receptors in alcohol intake. In addition, the interactions between 5-HT_{1B} receptors and other neurotransmitters, including dopamine, gamma-aminobutyric acid (GABA) and glutamate, in the modulation of alcohol intake have been assessed in this review. Emphasis has been on the role of 5-HT_{1B} receptors in neurotransmitter release for the regulation of alcohol intake.

Animal models and pharmacological manipulations of 5-HT_{1B} receptor-mediated alcohol consumption

Knockout models, alcohol-preferring animal models, and pharmacological manipulations of 5-HT_{1B} receptors in alcohol-drinking behavior—The role of 5-HT_{1B} receptors in alcohol consumption has been investigated in 5-HT_{1B} knockout mice (genotype $-/-$). The results generated by several studies suggest that 5-HT_{1B} receptors mediate alcohol intake: however, some controversy still exists. Although 5-HT_{1B} receptor knockout mice phenotypically consumed alcohol at an increased rate in initial studies (Crabbe et al., 1996; Risinger et al., 1996), later studies using different substrains of knockout mice have failed to reproduce this phenotypic characteristic (Bouwknicht et al., 2000; Crabbe et al., 1999; Risinger et al., 1999). For example, in one study, 5-HT_{1B} receptor knockout mice showed greater levels of alcohol consumption for unsweetened 10% ethanol but showed moderate alcohol self-administration overall (Risinger et al., 1999). Contrastingly, other studies demonstrated that alcohol intake (g/kg body weight) was similar for wild type and 5-HT_{1B} receptor knockout mice (Bouwknicht et al., 2000). However, in the latter case, body weights and water intake were elevated in these knockout mice which suggests that the initial finding of elevated ethanol consumption might actually be related to differences in fluid intake. Although alcohol intake is not consistent in knockout mice, these differences might be due to substantial genetic drift over generations, including population adaptations.

Variant results related to 5-HT_{1B} receptor knockout mice in alcohol consumption studies suggest that phenotypic differences in mutants may exist (Gerlai, 1996; Phillips et al., 1999). Previous studies suggest the possibility of genetic drift and genetic crossover from multiple substrains of knockout mice during the course of breeding (Phillips et al., 1999). Additionally, dissimilarities in each experimental design may explain the discrepancies in alcohol consumption in 5-HT_{1B} receptor knockout mice. For example, studies performed in multiple laboratories showed low alcohol intake (6%, v/v) in 5-HT_{1B} receptor knockout mice tested for four days (Crabbe et al., 1999), while other studies showed high alcohol intake (for multiples concentrations of alcohol 3–20%, v/v) in mice tested for 12 days (Crabbe et al., 1996).

The involvement of 5-HT_{1B} receptors in alcohol-drinking behavior has also been supported by pharmacological studies conducted with divergent animal strains (Tables 1 and 2). Administration of CGS12066B, a partial 5-HT_{1B} receptor agonist, in the NAc core decreased ethanol intake in Long-Evans rats (Czachowski, 2005). There are 5-HT_{1B} autoreceptors located at the terminals of the dorsal raphe-NAc pathway and 5-HT_{1B} heteroreceptors located at the terminals of the glutamatergic cortico-accumbal pathway. Therefore, the infusion of 5-HT_{1B} receptor agonist in the NAc may lead to inhibition of glutamate release and in turn lead to disinhibition of dopamine neurons in the VTA-NAc pathway. This regulatory mechanism would lead to a reduction in alcohol consumption.

In an operant oral self-administration of alcohol (10%, v/v) study, intraperitoneal (i.p.) injections of CP-94,253, a 5-HT_{1B} receptor agonist, reduced ethanol-reinforced lever pressing (Maurel et al., 1999b). In addition, the 5-HT_{1B} receptor agonist m-chlorophenylpiperazine (mCPP) induced a general decrease in alcohol intake in the Cologne Alcohol-Addicted (cAA) rat model of alcoholism (Maurel et al., 1999a). However, this effect may be relatively nonselective for alcohol consumption because mCPP binds non-selectively to 5-HT_{1B} and 5-HT_{2C} receptors. Thus, it is unclear whether these effects of mCPP are due to stimulation of 5-HT_{2C} receptors, 5-HT_{1B} receptors, or both. Furthermore, studies using Wistar rats have demonstrated that i.p. administration of a partial 5-HT_{1B} receptor agonist, CGS12066B, also reduced oral ethanol self-administration (12%, v/v ethanol) (Tomkins and O'Neill, 2000). Moreover, 5-HT_{1B} receptor agonist, RU24969, is the most commonly used agonist in investigating different behavioral paradigms and neurochemical consequences of 5-HT_{1B} receptor activation (Fletcher et al., 1992; Halford and Blundell, 1996; O'Neill et al., 1996; Oberlander et al., 1987). In Wistar rats, i.p. administration of RU24969 reduced oral ethanol self-administration (12% v/v ethanol) (Tomkins and O'Neill, 2000). Regarding the selectivity of RU24969, this compound has similar affinity for both 5-HT_{1B} and 5-HT_{1A} receptors (Middlemiss and Tricklebank, 1992), but several studies have suggested that the action of RU24969 is more specific to 5-HT_{1B} receptors (Fernandez-Guasti et al., 1992; Fletcher et al., 1992; O'Neill et al., 1996; Oberlander et al., 1987). The action of RU24969 is reversed by the 5-HT_{1B} receptor antagonist GR127935 but not by the 5-HT_{1A} receptor antagonist WAY100135 (O'Neill et al., 1996). GR127935 is a potent and selective 5-HT_{1B/1D} antagonist that shows about 1000-fold selectivity for the 5-HT_{1B} receptor compared to the 5-HT_{1A}, 5-HT_{2C}, and 5-HT_{2A} receptors (Skingle et al., 1996).

Lastly, administration of anpirtoline, another 5-HT_{1B} receptor agonist, significantly decreased ethanol-reinforced behavior in Swiss Webster mice (Miczek and De Almeida, 2001). Anpirtoline binds to both 5-HT_{1B} and 5-HT_{1A} receptors, with higher affinity for 5-HT_{1B} receptors. Again, it is unclear whether its effect on alcohol reinforcement is dependent on 5-HT_{1B} receptors, 5-HT_{1A} receptors, or both. In male ejaculatory behavior study, anpirtoline's effects were prevented by the application of 5-HT_{1B} receptor antagonists (Hillegaart and Ahlenius, 1998). In addition, a study that investigated the

metabolism and synthesis of 5-HT has shown similar effects (Stenfors et al., 2000). This suggests that anpirtoline selectively acts on 5-HT_{1B} receptors, at least in some behavioral and chemical assays. These findings show that ethanol-reinforced behavior is inhibited by selective activation of 5-HT_{1B} receptors (Tomkins and O'Neill, 2000) and reduced alcohol intake. The following mechanism of action is suggested: when 5-HT_{1B} receptor agonist is administered i.p., it deactivates the release of glutamate at either the cortico-NAc or cortico-VTA pathway since the 5-HT_{1B} receptor has an inhibitory effect on glutamate release in these pathways. Alternatively, 5-HT_{1B} receptor agonist may decrease 5-HT release (through 5-HT_{1B} auto-receptors) in the central reward regions NAc and VTA which can lead to increased GABA release and indirectly decrease dopamine release. The consequence of these actions is the reduction of alcohol intake.

Viral vector overexpression of 5-HT_{1B} receptors in the regulation of alcohol-drinking behavior

—Studies have utilized herpes simplex virus (HSV) viral vector to overexpress 5-HT_{1B} receptors in the investigation of alcohol consumption. Both hemagglutinin-tagged and green fluorescent protein-tagged (HA1B/GFP) 5-HT_{1B} receptors have been overexpressed using HSV vectors (Clark et al., 2002; Clark et al., 2004; Hoplight et al., 2006). Viral vector gene expression is advantageous due to its high selectivity and low toxicity for target neurons (Carlezon et al., 2000). Bilateral microinjections of HSV vectors carrying 5-HT_{1B} receptors in the medial NAc shell increased voluntary alcohol consumption in Long-Evans rats in a two-week free-choice alcohol (6% or 12%) drinking protocol (Hoplight et al., 2006). Groups that had received the viral vector HA1B/GFP showed an increase in alcohol intake compared to the control groups. Viral vector overexpression of 5-HT_{1B} receptors specifically targets the medium spiny neurons in the NAc shell which express 5-HT_{1B} receptors. Interestingly, the expression of 5-HT_{1B} receptors on 5-HT projections from the dorsal raphe nucleus innervating the NAc were not affected (Clark et al., 2002). This suggests that overexpression is specific for 5-HT_{1B} heteroreceptors located at the terminals of the VTA-NAc pathway. Importantly, a recent study showed that over-expression of 5-HT_{1B} receptors in the NAc shell alters the preference for low versus high ethanol concentration and also alters the drinking behavior pattern during both initiation and maintenance phases of ethanol consumption (Furay et al., 2011).

Pharmacological actions of 5-HT_{1B} receptors in neurotransmitter release and subsequent modulation of alcohol-drinking behavior

—Although the mechanism by which 5-HT_{1B} ligands regulate alcohol self-administration is not fully known, it is possible that the regulatory effect is achieved through indirect manipulation of dopamine neurotransmission via GABAergic activity (Figure 1). Previous studies showed that intrategmental administration of a 5-HT_{1B} receptor agonist, CP-93,129, increased dopamine release in both the VTA and the NAc (Yan and Yan, 2001; Yan et al., 2004). In contrast, infusion of a 5-HT_{1B} receptor antagonist, SB-216641, in the VTA attenuated ethanol-induced (i.p.) increases in extracellular dopamine in both VTA and NAc (Yan et al., 2005). This suggests that 5-HT_{1B} receptors interact indirectly with mesolimbic dopamine systems during alcohol intake. It is postulated here that activation of 5-HT_{1B} receptor in the VTA may induce inhibition of GABA release, which consequently leads to increases in dopamine release in both the VTA and NAc; this regulatory mechanism would be a key factor mediating increased alcohol intake. However, administration of the 5-HT_{1B} receptor agonist, CGS12066B, in the NAc core decreases ethanol-intake (Czachowski, 2005). It is possible that administering a 5-HT_{1B} receptor agonist directly into the NAc may induce decreased neuronal activity by binding to the 5-HT_{1B} receptor subtype and inhibiting presynaptic release of glutamate in the NAc ((Hoyer et al., 1994; Johnson et al., 1992a; Morikawa et al., 2000; Muramatsu et al., 1998), Figure 1). Therefore, 5-HT_{1B} receptor

agonist infusion into NAc may bind to 5-HT_{1B} receptors located at the terminals of cortico-accumbal glutamatergic projections and thus inhibit glutamate release, which consequently decreases dopamine release in the NAc, reducing ethanol-associated reward and leading to reduction in alcohol intake.

Serotonergic projections from the dorsal raphe innervate the VTA and the NAc (Conrad et al., 1974; Li et al., 1993; Moore et al., 1978; Parent et al., 1981). Importantly, serotonergic projections from the dorsal raphe nucleus to the NAc are suggested to be involved with alcohol reinforcement in alcohol-preferring rats (McBride et al., 1989). These serotonergic projections make synaptic contact with pre- and postsynaptic sites in the NAc (Van Bockstaele et al., 1996; Van Bockstaele and Pickel, 1993). At the ultrastructural level, serotonergic terminals are often found adjacent to GABA-containing neurons in the NAc (Van Bockstaele et al., 1996) and these serotonergic terminals may regulate, or be regulated by, presynaptic inputs with excitatory axons forming asymmetric junctions and also by catecholaminergic afferents (Van Bockstaele and Pickel, 1993). Thus, dendrites of medium spiny neurons which are GABAergic form synaptic contacts with 5-HT, dopamine, and glutamate terminals (Gonzales and Weiss, 1998; Muramatsu et al., 1998; Van Bockstaele et al., 1996; Van Bockstaele and Pickel, 1993; Weiss et al., 1993; Yan, 1999; Yan and Yan, 2001; Yan et al., 2004). Both 5-HT_{1B} receptor mRNA and its protein are expressed in the NAc (Bruinvels et al., 1993; Bruinvels et al., 1994; Mengod et al., 1990) suggesting that 5-HT_{1B} auto-receptors located at the terminals of dorsal raphe serotonergic neurons in the NAc and VTA, and hetero-receptors located at the terminal of medium spiny neurons in the VTA, may play a significant role in drug reinforcement, including alcohol.

It is important to note that there are some differences in sensitivity between presynaptic 5-HT_{1B} auto- and hetero-receptors for a particular agonist (Rossetti and Carboni, 1995). This study investigated the effects of selective 5-HT_{1B} receptor agonists (5-HT and CP93,129) on the K⁺-evoked overflow of [³H]5-HT, [³H]dopamine and [³H]acetylcholine in the striatum or hippocampus. The 5-HT_{1B} receptor agonists show higher potencies in the inhibition of the K⁺-evoked overflow of [³H]5-HT from striatal synaptosomes as compared to the inhibition of the K⁺-evoked overflow of [³H]dopamine in the striatum or [³H]acetylcholine in the hippocampus (Sarhan and Fillion, 1999). These findings demonstrated that 5-HT_{1B} auto- and hetero-receptors located at the terminals of dopaminergic and cholinergic neurons show differences in sensitivity for a 5-HT_{1B} receptor agonist or even antagonist. There appear to be no structural differences between 5-HT_{1B} auto- and hetero-receptors but differences in sensitivity to a selected agonist or antagonist might occur because these receptors might be coupled differently to their effectors. This assumption is based on findings from investigations of D₂ receptor function. Thus, studies have shown that D₂ receptor agonists display different efficacies in the activation of D₂ auto- versus hetero-receptors (Martin et al., 1984; Rosenzweig-Lipson and Barrett, 1995; Rosenzweig-Lipson and Bergman, 1993; Skirboll et al., 1979). In general, D₂ receptor agonists displayed dose-dependent effects on the activation of auto- versus hetero-receptors. It was suggested that low doses of D₂ receptor agonists may activate only D₂ auto-receptors, leading to the inhibition of dopamine release (Rosenzweig-Lipson and Barrett, 1995). This phenomenon may apply to 5-HT_{1B} auto-receptors as well. Studies are needed to investigate this possibility.

Interactions between 5-HT_{1B} receptors and the dopaminergic system involving GABAergic activity in the modulation of alcohol-drinking behavior

The excitatory action of ethanol on dopaminergic neurons in the VTA is potentiated by 5-HT (Rossetti and Carboni, 1995). The 5-HT_{1B} receptors play a key role in the activation of dopaminergic neurons in the VTA. This excitatory effect is further influenced by GABAergic projections (NAc-VTA feedback loop). For example, activation of 5-HT_{1B}

receptors in the VTA indirectly disinhibited dopaminergic neurons which reduced alcohol-associated reward and subsequently reduced alcohol intake (Yan et al., 2004; Yan et al., 2005). Thus, the interactions between these reciprocal pathways in the NAc and the VTA regulate alcohol consumption.

Numerous pharmacological studies have demonstrated the role of dopamine in alcohol-drinking behavior using rat models. It has been shown that i.p. injections of D1 and D2 receptor agonists decreased alcohol intake (McBride et al., 1990; Weiss et al., 1990). In addition, systemic administration of D1 and D2, as well as D3, receptor agonists dose-dependently decreased oral self-administration of ethanol (Cohen et al., 1998, 1999). Local injections of D2 receptor antagonists (sulpiride or quinpirole) in the VTA increased alcohol intake (Melendez et al., 2005; Nowak et al., 2000). Furthermore, local injections of sulpiride in the NAc increased ethanol intake in a dose-dependent manner (Levy et al., 1991). Note that any variances in alcohol intake between studies may be due to the specific type of targeted dopamine receptor, the doses of dopamine receptor agonists and antagonists, or differences in injection sites. Furthermore, dense dopaminergic projections from the VTA to the NAc are key players in the rewarding properties of alcohol (Hernandez and Hoebel, 1988; Pfau et al., 1995). Increases in extracellular dopamine in the NAc are a consequence of obtaining these rewards (Bozarth, 1991; Wise and Rompre, 1989). Drugs of abuse, including alcohol, increased the concentration of extracellular dopamine in the NAc (Di Chiara and Imperato, 1986; Di Chiara and Imperato, 1988; Melendez et al., 2002; Thielen et al., 2004), and caudate putamen (Budygin et al., 2007). It is also apparent that multiple brain structures and neurotransmitter systems, including the serotonergic system, regulate these dopaminergic pathways (McBride, 2002; McBride and Li, 1998). It is noteworthy that innate differences in the mesocorticolimbic dopaminergic system are associated with high ethanol consumption (McBride and Li, 1998; Murphy et al., 2002). In particular, alcohol-preferring rats have lower levels of dopamine and its metabolites in the NAc and anterior striatum, compared to alcohol-non-preferring rats (Murphy et al., 1982; Murphy et al., 1987). Alcohol-preferring rats also have fewer D2 receptors in the VTA and NAc compared to alcohol-non-preferring rats (McBride et al., 1993). Furthermore, chronic alcohol consumption decreases dopamine transporter activity at dopamine terminals in the NAc (Yoshimoto et al., 2000). Recently, we have shown that chronic and repeated deprivation in alcohol consumption increased the densities of D1 and D2 receptors in the anterior portion of the NAc in ethanol-experienced alcohol-preferring rats compared with naïve alcohol-preferring rats (Sari et al., 2006).

The 5-HT_{1B} receptors located at the terminals of NAc GABAergic projections to the VTA are found to be involved in the modulation of mesolimbic dopamine activity (Yan and Yan, 2001; Yan et al., 2004). Pharmacological studies revealed that activation of 5-HT_{1B} receptors in the VTA lead to increased dopamine release in both the VTA and NAc (Yan et al., 2005; Yan et al., 2004). Thus, it is suggested here that activating 5-HT_{1B} receptors in the VTA may potentiate the rewarding effects of ethanol, whereas deactivating 5-HT_{1B} receptors may attenuate the effects of ethanol. This regulation of dopamine release by 5-HT_{1B} receptors in the VTA may result from GABAergic activity. Studies suggest that 5-HT_{1B} receptors indirectly affect the release of dopamine in the VTA and the NAc through GABA release (O'Dell and Parsons, 2004; Parsons and Justice, 1993a; Parsons and Justice, 1993b; Yan and Yan, 2001; Yan et al., 2004). In addition, serotonergic neurons in the dorsal raphe nucleus regulate VTA dopaminergic projections to the NAc (Yoshimoto and McBride, 1992). This suggests that 5-HT affects ethanol-drinking behavior via 5-HT_{1B} auto-receptors located on these dopaminergic projections in the brain regions of drug reward (Czachowski, 2005). In alcohol-preferring rats, imbalances in 5-HT availability may affect the activity of the dopaminergic system in the NAc and VTA. From a therapeutic standpoint, if 5-HT_{1B} auto-receptors are key players in the regulation of dopamine activity to modulate alcohol

intake, therefore, targeting the sensitivity of these receptors would be an important step toward developing a treatment for alcohol dependence. As discussed in this review, the doses of 5-HT_{1B} receptor agonists or antagonists administered are important in the apparent differential effects of 5-HT_{1B} auto- or hetero-receptors.

Interactions between the serotonergic and the glutamatergic systems in the modulation of alcohol-drinking behavior—Glutamatergic projections innervating the NAc and the VTA bear 5-HT_{1B} hetero-receptors at their terminals and are critical modulators of alcohol intake. These glutamatergic projections modulate alcohol-drinking behavior in response to inputs from 5-HT_{1B} auto-receptors on dorsal raphe 5-HT neurons. Changes in glutamatergic neurotransmission affect many aspects of neuroplasticity associated with alcohol/drug dependence. Neuroadaptations in both presynaptic and postsynaptic aspects of mesocorticolimbic glutamatergic neurotransmission indicate that the regulation of protein expression is involved in alcohol dependence. Chronic alcohol exposure increased the density of glutamate and N-Methyl-D-aspartic acid (NMDA) antagonist (MK801) binding sites in the rat and mouse brain regions, including the hippocampus and cerebellum (Chen et al., 1997; Grant et al., 1990; Sanna et al., 1993; Snell et al., 1996). Also, cortical glutamatergic projections bearing 5-HT_{1B} heteroreceptors that target the NAc region (Muramatsu et al., 1998) may play a role in the regulation of alcohol-drinking behavior. The exact relationship between the glutamatergic system and 5-HT_{1B} receptors in the central reward regions is not fully defined. Although the glutamatergic projections bearing 5-HT_{1B} hetero-receptors have not been fully delineated, afferent regions in the NAc, VTA, neocortex, and thalamus display high levels of 5-HT_{1B} receptor mRNA (Bruinvels et al., 1994). This may provide a source for 5-HT_{1B} receptors on glutamatergic terminals in the mesocorticolimbic system. If these 5-HT_{1B} hetero-receptors play a role in the regulation of glutamate release (Muramatsu et al., 1998), the aforementioned glutamatergic projections may regulate the activity of associated GABAergic and dopaminergic neurons (Bonci and Malenka, 1999; Johnson et al., 1992b; Sesack et al., 1989). It is noteworthy that 5-HT inhibits synaptic glutamate release in NAc neurons through presynaptic 5-HT_{1B} receptors (Muramatsu et al., 1998). The glutamatergic inputs to the NAc and VTA that bear 5-HT_{1B} hetero-receptors (Figure 1) may be regulated as a consequence of changes in 5-HT release availability. The projections from the dorsal raphe nuclei are considered to be a potential source for 5-HT release in the synaptic clefts (for review see Sari, 2004) (Figure 1) which would subsequently control dopaminergic, glutamatergic and GABAergic release in the control of alcohol-drinking behavior. Therefore, both 5-HT_{1B} auto- and hetero-receptors might be involved in the regulation of glutamate neurotransmission, which leads to the modulation of alcohol intake.

Conclusion

We conclude here that 5-HT_{1B} receptors are involved in the release of at least four neurotransmitters (GABA, dopamine, glutamate and 5-HT) in the central reward brain regions and dorsal raphe nuclei. Pharmacological studies suggested that activation of 5-HT_{1B} receptors in these regions inhibits the release of these neurotransmitters and, by extension, regulates alcohol-drinking behavior. For example, activation of 5-HT_{1B} receptors in VTA can induce inhibition of GABA release, which can consequently lead to increases in dopamine release in both VTA and NAc. This regulatory mechanism would mediate increased alcohol intake. Alternatively, activation of 5-HT_{1B} receptors in the NAc induced decrease in alcohol intake which could be mediated through inhibition of glutamate release in the cortico-accumbal glutamatergic projections. Consequently, this can lead to a reduction in dopamine release in the NAc.

It is suggested here that 5-HT_{1B} auto- or hetero-receptors expressed on serotonergic, glutamatergic, or GABAergic neurons in the central reward regions regulate alcohol-drinking behavior in response to the inhibition of the release of neurotransmitters. The natural 5-HT may have different potencies for 5-HT_{1B} receptors that can lead primarily to the activation of 5-HT release; however, the activation of other neurotransmitters such as glutamate and GABA may occur when there is excessive release of 5-HT. Importantly, differences in sensitivity caused by 5-HT_{1B} auto- or hetero-receptors for the natural agonist 5-HT or a selective agonist or antagonist may lead to the reduction of alcohol intake. Pharmacological manipulations for the determination of lower or higher doses of selective 5-HT_{1B} receptor agonists or antagonists are important for determining doses in treatments for alcohol dependence.

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References

- Ait-Daoud N, Roache JD, Dawes MA, et al. Can serotonin transporter genotype predict craving in alcoholism? *Alcohol Clin Exp Res*. 2009; 33:1329–1335. [PubMed: 19426172]
- Alheid GF. Extended amygdala and basal forebrain. *Ann N Y Acad Sci*. 2003; 985:185–205. [PubMed: 12724159]
- Asan E. The catecholaminergic innervation of the rat amygdala. *Adv Anat Embryol Cell Biol*. 1998; 142:1–118. [PubMed: 9586282]
- Balldin J, Berggren U, Engel J, et al. Neuroendocrine evidence for reduced serotonergic neurotransmission during heavy drinking. *Alcohol Clin Exp Res*. 1994; 18:822–825. [PubMed: 7978090]
- Bell RL, Rodd ZA, Lumeng L, et al. The alcohol-preferring P rat and animal models of excessive alcohol drinking. *Addict Biol*. 2006a; 11:270–288. [PubMed: 16961759]
- Bell, RL.; Rodd, ZA.; Murphy, JM., et al. Use of selectively bred alcohol-preferring rats to study alcohol abuse, relapse and craving. In: Preedy, VR.; Watson, RR., editors. *Comprehensive Handbook of Alcohol Related Pathology*. Academic Press, Elsevier Science; New York: 2005. p. 1515-1533.
- Bell RL, Rodd ZA, Sable HJ, et al. Daily patterns of ethanol drinking in peri-adolescent and adult alcohol-preferring (P) rats. *Pharmacol Biochem Behav*. 2006b; 83:35–46. [PubMed: 16442608]
- Bonci A, Malenka RC. Properties and plasticity of excitatory synapses on dopaminergic and GABAergic cells in the ventral tegmental area. *J Neurosci*. 1999; 19:3723–3730. [PubMed: 10234004]
- Bouhelal R, Smounya L, Bockaert J. 5-HT_{1B} receptors are negatively coupled with adenylyl cyclase in rat substantia nigra. *Eur J Pharmacol*. 1988; 151:189–196. [PubMed: 2971554]
- Bouwknicht JA, Hijzen TH, van der Gugten J, et al. Ethanol intake is not elevated in male 5-HT_{1B} receptor knockout mice. *Eur J Pharmacol*. 2000; 403:95–98. [PubMed: 10969149]
- Bozarth, MA. The mesolimbic dopamine system as a model reward system. In: Willner, P.; Scheel-Hruger, J., editors. *The Mesolimbic Dopamine System: From Motivation to Action*. Chichester: Wiley Press; 1991. p. 301-330.
- Bruinvels AT, Landwehrmeyer B, Gustafson EL, et al. Localization of 5-HT_{1B}, 5-HT_{1D} alpha, 5-HT_{1E} and 5-HT_{1F} receptor messenger RNA in rodent and primate brain. *Neuropharmacology*. 1994; 33:367–386. [PubMed: 7984275]

- Bruinvels AT, Palacios JM, Hoyer D. Autoradiographic characterisation and localisation of 5-HT1D compared to 5-HT1B binding sites in rat brain. *Naunyn Schmiedeberg's Arch Pharmacol.* 1993; 347:569–582. [PubMed: 8361548]
- Budygin EA, Oleson EB, Mathews TA, et al. Effects of chronic alcohol exposure on dopamine uptake in rat nucleus accumbens and caudate putamen. *Psychopharmacology (Berl).* 2007; 193:495–501. [PubMed: 17492432]
- Carlezon WA Jr, Nestler EJ, Neve RL. Herpes simplex virus-mediated gene transfer as a tool for neuropsychiatric research. *Crit Rev Neurobiol.* 2000; 14:47–67. [PubMed: 11253955]
- Chen X, Michaelis ML, Michaelis EK. Effects of chronic ethanol treatment on the expression of calcium transport carriers and NMDA/glutamate receptor proteins in brain synaptic membranes. *J Neurochem.* 1997; 69:1559–1569. [PubMed: 9326285]
- Clark MS, Sexton TJ, McClain M, et al. Overexpression of 5-HT1B receptor in dorsal raphe nucleus using herpes simplex virus gene transfer increases anxiety behavior after inescapable stress. *J Neurosci.* 2002; 22:4550–4562. [PubMed: 12040062]
- Clark MS, Vincow ES, Sexton TJ, et al. Increased expression of 5-HT1B receptor in dorsal raphe nucleus decreases fear-potentiated startle in a stress dependent manner. *Brain Res.* 2004; 1007:86–97. [PubMed: 15064139]
- Cohen C, Perrault G, Sanger DJ. Preferential involvement of D3 versus D2 dopamine receptors in the effects of dopamine receptor ligands on oral ethanol self-administration in rats. *Psychopharmacology (Berl).* 1998; 140:478–485. [PubMed: 9888624]
- Cohen C, Perrault G, Sanger DJ. Effects of D1 dopamine receptor agonists on oral ethanol self-administration in rats: comparison with their efficacy to produce grooming and hyperactivity. *Psychopharmacology (Berl).* 1999; 142:102–110. [PubMed: 10102789]
- Conrad LC, Leonard CM, Pfaff DW. Connections of the median and dorsal raphe nuclei in the rat: an autoradiographic and degeneration study. *J Comp Neurol.* 1974; 156:179–205. [PubMed: 4419253]
- Crabbe JC, Phillips TJ, Feller DJ, et al. Elevated alcohol consumption in null mutant mice lacking 5-HT1B serotonin receptors. *Nat Genet.* 1996; 14:98–101. [PubMed: 8782828]
- Crabbe JC, Wahlsten D, Dudek BC. Genetics of mouse behavior: interactions with laboratory environment. *Science.* 1999; 284:1670–1672. [PubMed: 10356397]
- Czachowski CL. Manipulations of serotonin function in the nucleus accumbens core produce differential effects on ethanol and sucrose seeking and intake. *Alcohol Clin Exp Res.* 2005; 29:1146–1155. [PubMed: 16046869]
- Di Chiara G, Imperato A. Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with transcranial dialysis in freely moving rats. *Ann N Y Acad Sci.* 1986; 473:367–381. [PubMed: 3467628]
- Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A.* 1988; 85:5274–5278. [PubMed: 2899326]
- Diana M, Brodie M, Muntoni A, et al. Enduring effects of chronic ethanol in the CNS: basis for alcoholism. *Alcohol Clin Exp Res.* 2003; 27:354–361. [PubMed: 12605085]
- Esposito E. An indirect action for fluoxetine on the dopamine neurotransmitter system. *Trends Pharmacol Sci.* 1996; 17:400–402. [PubMed: 8990955]
- Fernandez-Guasti A, Escalante AL, Ahlenius S, et al. Stimulation of 5-HT1A and 5-HT1B receptors in brain regions and its effects on male rat sexual behaviour. *Eur J Pharmacol.* 1992; 210:121–129. [PubMed: 1534765]
- Findlay J, Eliopoulos E. Three-dimensional modelling of G protein-linked receptors. *Trends Pharmacol Sci.* 1990; 11:492–499. [PubMed: 1964255]
- Fletcher PJ, Ming ZH, Zack MH, et al. A comparison of the effects of the 5-HT1 agonists TFMPP and RU 24969 on feeding following peripheral or medial hypothalamic injection. *Brain Res.* 1992; 580:265–272. [PubMed: 1387034]
- Furay AR, Neumaier JF, Mullenix AT, et al. Overexpression of 5-HT(1B) mRNA in nucleus accumbens shell projection neurons differentially affects microarchitecture of initiation and maintenance of ethanol consumption. *Alcohol.* 2011; 45:19–32. [PubMed: 20843634]

- Gerlai R. Gene-targeting studies of mammalian behavior: is it the mutation or the background genotype? *Trends Neurosci.* 1996; 19:177–181. [PubMed: 8723200]
- Gonzales RA, Weiss F. Suppression of ethanol-reinforced behavior by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine levels in the nucleus accumbens. *J Neurosci.* 1998; 18:10663–10671. [PubMed: 9852601]
- Grant KA, Valverius P, Hudspeth M, et al. Ethanol withdrawal seizures and the NMDA receptor complex. *Eur J Pharmacol.* 1990; 176:289–296. [PubMed: 2158451]
- Halford JC, Blundell JE. The 5-HT_{1B} receptor agonist CP-94,253 reduces food intake and preserves the behavioural satiety sequence. *Physiol Behav.* 1996; 60:933–939. [PubMed: 8873272]
- Hamblin MW, Metcalf MA. Primary structure and functional characterization of a human 5-HT_{1D}-type serotonin receptor. *Mol Pharmacol.* 1991; 40:143–148. [PubMed: 1652050]
- Harper C. The neuropathology of alcohol-related brain damage. *Alcohol Alcohol.* 2009; 44:136–140. [PubMed: 19147798]
- Heilig M, Egli M. Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. *Pharmacol Ther.* 2006; 111:855–876. [PubMed: 16545872]
- Heinz A, Mann K, Weinberger DR, et al. Serotonergic dysfunction, negative mood states, and response to alcohol. *Alcohol Clin Exp Res.* 2001; 25:487–495. [PubMed: 11329486]
- Heinz A, Ragan P, Jones DW, et al. Reduced central serotonin transporters in alcoholism. *Am J Psychiatry.* 1998; 155:1544–1549. [PubMed: 9812115]
- Hernandez L, Hoebel BG. Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. *Physiol Behav.* 1988; 44:599–606. [PubMed: 3237847]
- Hibert MF, Trumpp-Kallmeyer S, Bruinvels A, et al. Three-dimensional models of neurotransmitter G-binding protein-coupled receptors. *Mol Pharmacol.* 1991; 40:8–15. [PubMed: 1649965]
- Hillegaart V, Ahlenius S. Facilitation and inhibition of male rat ejaculatory behaviour by the respective 5-HT_{1A} and 5-HT_{1B} receptor agonists 8-OH-DPAT and anpirtoline, as evidenced by use of the corresponding new and selective receptor antagonists NAD-299 and NAS-181. *Br J Pharmacol.* 1998; 125:1733–1743. [PubMed: 9886765]
- Hoplight BJ, Sandygren NA, Neumaier JF. Increased expression of 5-HT_{1B} receptors in rat nucleus accumbens via virally mediated gene transfer increases voluntary alcohol consumption. *Alcohol.* 2006; 38:73–79. [PubMed: 16839853]
- Hoyer D, Clarke DE, Fozard JR, et al. International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin). *Pharmacol Rev.* 1994; 46:157–203. [PubMed: 7938165]
- Johnson SW, Mercuri NB, North RA. 5-hydroxytryptamine_{1B} receptors block the GABAB synaptic potential in rat dopamine neurons. *J Neurosci.* 1992a; 12:2000–2006. [PubMed: 1578282]
- Johnson SW, Seutin V, North RA. Burst firing in dopamine neurons induced by N-methyl-D-aspartate: role of electrogenic sodium pump. *Science.* 1992b; 258:665–667. [PubMed: 1329209]
- Kaiyala KJ, Vincow ES, Sexton TJ, et al. 5-HT_{1B} receptor mRNA levels in dorsal raphe nucleus: inverse association with anxiety behavior in the elevated plus maze. *Pharmacol Biochem Behav.* 2003; 75:769–776. [PubMed: 12957218]
- Lappalainen J, Long JC, Eggert M, et al. Linkage of antisocial alcoholism to the serotonin 5-HT_{1B} receptor gene in 2 populations. *Arch Gen Psychiatry.* 1998; 55:989–994. [PubMed: 9819067]
- LeMarquand D, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: clinical evidence. *Biol Psychiatry.* 1994a; 36:326–337. [PubMed: 7993959]
- LeMarquand D, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: findings of animal studies. *Biol Psychiatry.* 1994b; 36:395–421. [PubMed: 7803601]
- Levy AD, Murphy JM, McBride WJ, et al. Microinjection of sulpiride into the nucleus accumbens increases ethanol drinking in alcohol-preferring (P) rats. *Alcohol Alcohol Suppl.* 1991; 1:417–420. [PubMed: 1845571]
- Li TK. Quantifying the risk for alcohol-use and alcohol-attributable health disorders: present findings and future research needs. *J Gastroenterol Hepatol.* 2008; 23:S2–S8. [PubMed: 18336658]
- Li YQ, Takada M, Matsuzaki S, et al. Identification of periaqueductal gray and dorsal raphe nucleus neurons projecting to both the trigeminal sensory complex and forebrain structures: a fluorescent retrograde double-labeling study in the rat. *Brain Res.* 1993; 623:267–277. [PubMed: 8221108]

- Lin D, Parsons LH. Anxiogenic-like effect of serotonin(1B) receptor stimulation in the rat elevated plus-maze. *Pharmacol Biochem Behav.* 2002; 71:581–587. [PubMed: 11888549]
- McBride WJ. Central nucleus of the amygdala and the effects of alcohol and alcohol-drinking behavior in rodents. *Pharmacol Biochem Behav.* 2002; 71:509–515. [PubMed: 11830185]
- McBride WJ, Bodart B, Lumeng L, et al. Association between low contents of dopamine and serotonin in the nucleus accumbens and high alcohol preference. *Alcohol Clin Exp Res.* 1995; 19:1420–1422. [PubMed: 8749804]
- McBride WJ, Chernet E, Dyr W, et al. Densities of dopamine D2 receptors are reduced in CNS regions of alcohol-preferring P rats. *Alcohol.* 1993; 10:387–390. [PubMed: 8216885]
- McBride WJ, Chernet E, Russell RN, et al. Regional CNS densities of monoamine receptors in alcohol-naïve alcohol-preferring P and -nonpreferring NP rats. *Alcohol.* 1997; 14:141–148. [PubMed: 9085714]
- McBride WJ, Li TK. Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. *Crit Rev Neurobiol.* 1998; 12:339–369. [PubMed: 10348615]
- McBride WJ, Murphy JM, Lumeng L, et al. Serotonin and ethanol preference. *Recent Dev Alcohol.* 1989; 7:187–209. [PubMed: 2648491]
- McBride WJ, Murphy JM, Lumeng L, et al. Serotonin, dopamine and GABA involvement in alcohol drinking of selectively bred rats. *Alcohol.* 1990; 7:199–205. [PubMed: 2184832]
- Maroteaux L, Saudou F, Amlaiky N, et al. Mouse 5HT1B serotonin receptor: cloning, functional expression, and localization in motor control centers. *Proc Natl Acad Sci U S A.* 1992; 89:3020–3024. [PubMed: 1557407]
- Martin GE, Williams M, Pettibone DJ, et al. Pharmacologic profile of a novel potent direct-acting dopamine agonist, (+)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO]. *J Pharmacol Exp Ther.* 1984; 230:569–576. [PubMed: 6433000]
- Maurel S, De Vry J, De Beun R, et al. 5-HT2A and 5-HT2C/5-HT1B receptors are differentially involved in alcohol preference and consummatory behavior in cAA rats. *Pharmacol Biochem Behav.* 1999a; 62:89–96. [PubMed: 9972850]
- Maurel S, De Vry J, Schreiber R. 5-HT receptor ligands differentially affect operant oral self-administration of ethanol in the rat. *Eur J Pharmacol.* 1999b; 370:217–223. [PubMed: 10334495]
- Melendez RI, Rodd-Henricks ZA, Engleman EA, et al. Microdialysis of dopamine in the nucleus accumbens of alcohol-preferring (P) rats during anticipation and operant self-administration of ethanol. *Alcohol Clin Exp Res.* 2002; 26:318–325. [PubMed: 11923583]
- Melendez RI, Rodd ZA, McBride WJ, et al. Dopamine receptor regulation of ethanol intake and extracellular dopamine levels in the ventral pallidum of alcohol preferring (P) rats. *Drug Alcohol Depend.* 2005; 77:293–301. [PubMed: 15734229]
- Mengod G, Pompeiano M, Martinez-Mir MI, et al. Localization of the mRNA for the 5-HT2 receptor by in situ hybridization histochemistry. Correlation with the distribution of receptor sites. *Brain Res.* 1990; 524:139–143. [PubMed: 2400925]
- Miczek KA, De Almeida RM. Oral drug self-administration in the home cage of mice: alcohol-heightened aggression and inhibition by the 5-HT1B agonist anpirtoline. *Psychopharmacology (Berl).* 2001; 157:421–429. [PubMed: 11605102]
- Middlemiss DN, Tricklebank MD. Centrally active 5-HT receptor agonists and antagonists. *Neurosci Biobehav Rev.* 1992; 16:75–82. [PubMed: 1553108]
- Moore RY, Halaris AE, Jones BE. Serotonin neurons of the midbrain raphe: ascending projections. *J Comp Neurol.* 1978; 180:417–438. [PubMed: 77865]
- Morikawa H, Manzoni OJ, Crabbe JC, et al. Regulation of central synaptic transmission by 5-HT(1B) auto- and heteroreceptors. *Mol Pharmacol.* 2000; 58:1271–1278. [PubMed: 11093763]
- Muramatsu M, Lapis MD, Tanaka E, et al. Serotonin inhibits synaptic glutamate currents in rat nucleus accumbens neurons via presynaptic 5-HT1B receptors. *Eur J Neurosci.* 1998; 10:2371–2379. [PubMed: 9749765]
- Murphy JM, McBride WJ, Lumeng L, et al. Regional brain levels of monoamines in alcohol-preferring and -nonpreferring lines of rats. *Pharmacol Biochem Behav.* 1982; 16:145–149. [PubMed: 6173885]

- Murphy JM, McBride WJ, Lumeng L, et al. Alcohol preference and regional brain monoamine contents of N/Nih heterogeneous stock rats. *Alcohol Drug Res.* 1987; 7:33–39. [PubMed: 2431698]
- Murphy JM, Stewart RB, Bell RL, et al. Phenotypic and genotypic characterization of the Indiana University rat lines selectively bred for high and low alcohol preference. *Behav Genet.* 2002; 32:363–388. [PubMed: 12405517]
- Nowak KL, McBride WJ, Lumeng L, et al. Involvement of dopamine D2 autoreceptors in the ventral tegmental area on alcohol and saccharin intake of the alcohol-preferring P rat. *Alcohol Clin Exp Res.* 2000; 24:476–483. [PubMed: 10798583]
- O'Dell LE, Parsons LH. Serotonin1B receptors in the ventral tegmental area modulate cocaine-induced increases in nucleus accumbens dopamine levels. *J Pharmacol Exp Ther.* 2004; 311:711–719. [PubMed: 15226384]
- O'Neill MF, Fernandez AG, Palacios JM. GR 127935 blocks the locomotor and antidepressant-like effects of RU 24969 and the action of antidepressants in the mouse tail suspension test. *Pharmacol Biochem Behav.* 1996; 53:535–539. [PubMed: 8866952]
- Oberlander C, Demassey Y, Verdu A, et al. Tolerance to the serotonin 5-HT1 agonist RU 24969 and effects on dopaminergic behaviour. *Eur J Pharmacol.* 1987; 139:205–214. [PubMed: 2443369]
- Parent A, Descarries L, Beaudet A. Organization of ascending serotonin systems in the adult rat brain. A radioautographic study after intraventricular administration of [3H]5-hydroxytryptamine. *Neuroscience.* 1981; 6:115–138. [PubMed: 6164006]
- Parsons LH, Justice JB Jr. Perfusate serotonin increases extracellular dopamine in the nucleus accumbens as measured by in vivo microdialysis. *Brain Res.* 1993a; 606:195–199. [PubMed: 8490716]
- Parsons LH, Justice JB Jr. Serotonin and dopamine sensitization in the nucleus accumbens, ventral tegmental area, and dorsal raphe nucleus following repeated cocaine administration. *J Neurochem.* 1993b; 61:1611–1619. [PubMed: 7693863]
- Parsons LH, Koob GF, Weiss F. RU 24969, a 5-HT1B/1A receptor agonist, potentiates cocaine-induced increases in nucleus accumbens dopamine. *Synapse.* 1999; 32:132–135. [PubMed: 10231132]
- Pettinati HM. The use of selective serotonin reuptake inhibitors in treating alcoholic subtypes. *J Clin Psychiatry.* 2001; 62(Suppl 20):26–31. [PubMed: 11584872]
- Pfaus JG, Damsma G, Wenkstern D, et al. Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats. *Brain Res.* 1995; 693:21–30. [PubMed: 8653411]
- Phillips TJ, Hen R, Crabbe JC. Complications associated with genetic background effects in research using knockout mice. *Psychopharmacology (Berl).* 1999; 147:5–7. [PubMed: 10591855]
- Prisco S, Esposito E. Differential effects of acute and chronic fluoxetine administration on the spontaneous activity of dopaminergic neurones in the ventral tegmental area. *Br J Pharmacol.* 1995; 116:1923–1931. [PubMed: 8528581]
- Ramboz S, Saudou F, Amara DA, et al. 5-HT1B receptor knock out--behavioral consequences. *Behav Brain Res.* 1996; 73:305–312. [PubMed: 8788525]
- Risinger FO, Bormann NM, Oakes RA. Reduced sensitivity to ethanol reward, but not ethanol aversion, in mice lacking 5-HT1B receptors. *Alcohol Clin Exp Res.* 1996; 20:1401–1405. [PubMed: 8947316]
- Risinger FO, Doan AM, Vickrey AC. Oral operant ethanol self-administration in 5-HT1b knockout mice. *Behav Brain Res.* 1999; 102:211–215. [PubMed: 10403028]
- Rodd ZA, Bell RL, Sable HJ, et al. Recent advances in animal models of alcohol craving and relapse. *Pharmacol Biochem Behav.* 2004; 79:439–450. [PubMed: 15582015]
- Room R, Babor T, Rehm J. Alcohol and public health. *Lancet.* 2005; 365:519–530. [PubMed: 15705462]
- Rosenzweig-Lipson S, Barrett JE. K-channel blockers attenuate the presynaptic effects of the D2/D3 agonist quinpirole in monkeys. *Pharmacol Biochem Behav.* 1995; 51:843–848. [PubMed: 7675867]

- Rosenzweig-Lipson S, Bergman J. Modification of the behavioral effects of the selective dopamine D2 agonist (+)-4-propyl-9-hydroxynaphthoxazine by dopamine antagonists in monkeys. *J Pharmacol Exp Ther.* 1993; 265:1039–1046. [PubMed: 8099614]
- Rossetti ZL, Carboni S. Ethanol withdrawal is associated with increased extracellular glutamate in the rat striatum. *Eur J Pharmacol.* 1995; 283:177–183. [PubMed: 7498307]
- Sanna E, Serra M, Cossu A, et al. Chronic ethanol intoxication induces differential effects on GABAA and NMDA receptor function in the rat brain. *Alcohol Clin Exp Res.* 1993; 17:115–123. [PubMed: 8383922]
- Sarhan H, Fillion G. Differential sensitivity of 5-HT1B auto and heteroreceptors. *Naunyn Schmiedebergs Arch Pharmacol.* 1999; 360:382–390. [PubMed: 10551275]
- Sari Y. Serotonin1B receptors: from protein to physiological function and behavior. *Neurosci Biobehav Rev.* 2004; 28:565–582. [PubMed: 15527863]
- Sari Y, Bell RL, Zhou FC. Effects of chronic alcohol and repeated deprivations on dopamine D1 and D2 receptor levels in the extended amygdala of inbred alcohol-preferring rats. *Alcohol Clin Exp Res.* 2006; 30:46–56. [PubMed: 16433731]
- Sari Y, Johnson VR, Weedman JM. Role of the serotonergic system in alcohol dependence: from animal models to clinics. *Prog Mol Biol Transl Sci.* 2011; 98:401–443. [PubMed: 21199778]
- Schoeffer P, Hoyer D. How selective is GR 43175? Interactions with functional 5-HT1A, 5-HT1B, 5-HT1C and 5-HT1D receptors. *Naunyn Schmiedebergs Arch Pharmacol.* 1989; 340:135–138. [PubMed: 2552330]
- Schuckit MA. Alcohol-use disorders. *Lancet.* 2009; 373:492–501. [PubMed: 19168210]
- Sellers EM, Higgins GA, Sobell MB. 5-HT and alcohol abuse. *Trends Pharmacol Sci.* 1992; 13:69–75. [PubMed: 1561716]
- Sesack SR, Deutch AY, Roth RH, et al. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leuco-agglutinin. *J Comp Neurol.* 1989; 290:213–242. [PubMed: 2592611]
- Seuwen K, Magnaldo I, Pouyssegur J. Serotonin stimulates DNA synthesis in fibroblasts acting through 5-HT1B receptors coupled to a Gi-protein. *Nature.* 1988; 335:254–256. [PubMed: 3045568]
- Skingle M, Beattie DT, Scopes DI, et al. GR127935: a potent and selective 5-HT1D receptor antagonist. *Behav Brain Res.* 1996; 73:157–161. [PubMed: 8788495]
- Skirboll LR, Grace AA, Bunney BS. Dopamine auto- and post-synaptic receptors: electrophysiological evidence for differential sensitivity to dopamine agonists. *Science.* 1979; 206:80–82. [PubMed: 482929]
- Snell LD, Nunley KR, Lickteig RL, et al. Regional and subunit specific changes in NMDA receptor mRNA and immunoreactivity in mouse brain following chronic ethanol ingestion. *Brain Res Mol Brain Res.* 1996; 40:71–78. [PubMed: 8840015]
- Stenfors C, Yu H, Ross SB. Enhanced 5-HT metabolism and synthesis rate by the new selective r5-HT1B receptor antagonist, NAS-181 in the rat brain. *Neuropharmacology.* 2000; 39:553–560. [PubMed: 10728876]
- Sullivan EV, Zahr NM. Neuroinflammation as a neurotoxic mechanism in alcoholism: commentary on “Increased MCP-1 and microglia in various regions of human alcoholic brain”. *Exp Neurol.* 2008; 213:10–17. [PubMed: 18625499]
- Thielen RJ, Engleman EA, Rodd ZA, et al. Ethanol drinking and deprivation alter dopaminergic and serotonergic function in the nucleus accumbens of alcohol-preferring rats. *J Pharmacol Exp Ther.* 2004; 309:216–225. [PubMed: 14718606]
- Tomkins DM, O'Neill MF. Effect of 5-HT(1B) receptor ligands on self-administration of ethanol in an operant procedure in rats. *Pharmacol Biochem Behav.* 2000; 66:129–136. [PubMed: 10837852]
- Trumpp-Kallmeyer S, Hoflack J, Bruinvels A, et al. Modeling of G-protein-coupled receptors: application to dopamine, adrenaline, serotonin, acetylcholine, and mammalian opsin receptors. *J Med Chem.* 1992; 35:3448–3462. [PubMed: 1328638]
- Van Bockstaele EJ, Chan J, Pickel VM. Pre- and postsynaptic sites for serotonin modulation of GABA-containing neurons in the shell region of the rat nucleus accumbens. *J Comp Neurol.* 1996; 371:116–128. [PubMed: 8835722]

- Van Bockstaele EJ, Pickel VM. Ultrastructure of serotonin-immunoreactive terminals in the core and shell of the rat nucleus accumbens: cellular substrates for interactions with catecholamine afferents. *J Comp Neurol*. 1993; 334:603–617. [PubMed: 8408768]
- Volkow ND, Li TK. Drugs and alcohol: treating and preventing abuse, addiction and their medical consequences. *Pharmacol Ther*. 2005; 108:3–17. [PubMed: 16098597]
- Weiss F, Lorang MT, Bloom FE, et al. Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants. *J Pharmacol Exp Ther*. 1993; 267:250–258. [PubMed: 8229752]
- Weiss F, Mitchiner M, Bloom FE, et al. Free-choice responding for ethanol versus water in alcohol preferring (P) and unselected Wistar rats is differentially modified by naloxone, bromocriptine, and methysergide. *Psychopharmacology (Berl)*. 1990; 101:178–186. [PubMed: 2349359]
- Wise RA, Rompre PP. Brain dopamine and reward. *Annu Rev Psychol*. 1989; 40:191–225. [PubMed: 2648975]
- Wrase J, Reimold M, Puls I, et al. Serotonergic dysfunction: brain imaging and behavioral correlates. *Cogn Affect Behav Neurosci*. 2006; 6:53–61. [PubMed: 16869229]
- Yan QS. Extracellular dopamine and serotonin after ethanol monitored with 5-minute microdialysis. *Alcohol*. 1999; 19:1–7. [PubMed: 10487381]
- Yan QS, Yan SE. Activation of 5-HT(1B/1D) receptors in the mesolimbic dopamine system increases dopamine release from the nucleus accumbens: a microdialysis study. *Eur J Pharmacol*. 2001; 418:55–64. [PubMed: 11334865]
- Yan QS, Zheng SZ, Feng MJ, et al. Involvement of 5-HT1B receptors within the ventral tegmental area in ethanol-induced increases in mesolimbic dopaminergic transmission. *Brain Res*. 2005; 1060:126–137. [PubMed: 16212943]
- Yan QS, Zheng SZ, Yan SE. Involvement of 5-HT1B receptors within the ventral tegmental area in regulation of mesolimbic dopaminergic neuronal activity via GABA mechanisms: a study with dual-probe microdialysis. *Brain Res*. 2004; 1021:82–91. [PubMed: 15328035]
- Yoshimoto K, McBride WJ. Regulation of nucleus accumbens dopamine release by the dorsal raphe nucleus in the rat. *Neurochem Res*. 1992; 17:401–407. [PubMed: 1356241]
- Yoshimoto K, Ueda S, Nishi M, et al. Changes in dopamine transporter and c-Fos expression in the nucleus accumbens of alcohol-tolerant rats. *Alcohol Clin Exp Res*. 2000; 24:361–365. [PubMed: 10776677]

Figure 1. Schematic representation of the neurocircuitry of 5-hydroxytryptamine 1B (5-HT_{1B}) receptors involving releases of neurotransmitters in the central reward brain regions and dorsal raphe (DR) nuclei

The 5-HT_{1B} receptors located at the terminal of the NAc-VTA pathway (GABAergic projections, black dashed arrow) control the release of GABA and indirectly regulate dopamine release through the dopaminergic projections (VTA-NAc pathway, gray dashed arrow) (O'Dell and Parsons, 2004; Parsons and Justice, 1993a; Yan and Yan, 2001; Yan et al., 2004; Yan et al., 2005). Moreover, 5-HT_{1B} receptors located at the terminals of the serotonergic projections from the dorsal raphe innervating NAc, VTA and PFC regulate 5-HT release in these regions (black arrows) (Van Bockstaele et al., 1996; Van Bockstaele and Pickel, 1993; Yoshimoto and McBride, 1992). There are cortical glutamatergic projections bearing 5-HT_{1B} receptors at the terminals in the NAc and VTA (gray arrows) (Muramatsu et al., 1998); the 5-HT_{1B} receptors control glutamate release in these brain regions. GABA: gamma-aminobutyric acid; NAc: nucleus accumbens; VTA: ventral tegmental area; DR: dorsal raphe nuclei; PFC: prefrontal cortex.

Table 1

Summary of findings investigated the effects of intraperitoneal (i.p.) injections of drugs targeting 5-hydroxytryptamine 1B (5-HT1B) receptors in the regulation of alcohol consumption.

Strain	Drug treatments	Alcohol-drinking behavior and others	Selectivity	References
Wistar rats	5-HT1B agonist, CP-94,253	Decrease alcohol intake	Highly selective	(Maurel et al., 1999b)
Wistar rats	5-HT1B agonist, RU-24969	Decrease alcohol intake	Highly selective	(Tomkins and O'Neill, 2000)
	5-HT1B antagonist, GR-127935	Blocked the agonistic effect of alcohol	Highly selective	
Swiss Carworth farm Webster (CFW) mice	5-HT1B agonist, anpirtoline	Decrease alcohol intake	Moderate selectivity	(Miczek and De Almeida, 2001)
Cologne Alcohol-Addicted (cAA) rats	5-HT1B agonist, m-chlorophenylpiperazine	Decrease alcohol intake	Very low selectivity	(Maurel et al., 1999a; Miczek and De Almeida, 2001)
Wistar rats	5-HT1B agonist, CGS12066B	Decrease alcohol intake	Low selectivity	(Tomkins and O'Neill, 2000)

Table 2

Summary of findings investigated the effects of intracerebro-injections of viral vector and agonist of 5-hydroxytryptamine 1B (5-HT1B) receptors in the regulation of alcohol-drinking behavior.

Strain	Drug treatments	Injection sites	Drinking behavior	References
Long-Evans rats	Viral vector expressed 5-HT1B receptors, herpes simplex virus	NAc shell	Increase alcohol consumption	(Hoplight et al., 2006)
Long-Evans rats	5-HT1B agonist, CGS-12066B	NAc core	Decrease alcohol consumption	(Czachowski, 2005)

NAc: nucleus accumbens.