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Role of the Serotonergic System in Alcohol Dependence: From Animal Models to Clinics

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Abstract

Alcohol dependence remains among the most common substance abuse problems worldwide, and compulsive alcohol consumption is a significant public health concern. Alcohol is an addictive drug that alters brain function through interactions with multiple neurotransmitter systems. These neurotransmitter systems mediate the reinforcing effects of alcohol. Specifically, the serotonergic system is important in mediating alcohol reward, preference, dependence, and craving. In this review chapter, we first discuss the serotonin system as it relates to alcoholism, and then outline interactions between this system and other neurotransmitter systems. We emphasize the serotonin transporter and its possible role in alcoholism, then present several serotonergic receptors and discuss their contribution to alcoholism, and finally assess the serotonin system as a target for pharmacotherapy, with an emphasis on current and potential treatments.

I. Introduction

Alcohol dependence is among the most common substance abuse problems worldwide, and compulsive alcohol intake is a significant public health concern (cf. Refs. 1-6). Alcohol interacts with multiple neurotransmitter systems to alter brain function and produces an imbalance between inhibitory and excitatory neurotransmitter regulation. Altered neurotransmission is associated with the reinforcing effects of alcohol consumption, as well as the abnormal behaviors exhibited following acute alcohol intoxication. Chronic alcohol exposure induces adaptive changes in normal neurocircuitry that lead to dependence.[7,8] A better understanding of the neurobiological impact of alcohol consumption will facilitate the development of novel intervention strategies that target both the prevention and treatment of alcohol dependence.

The serotonergic system plays a key role in the regulation of alcohol intake, reward, preference, and dependence.[9-15] Deficient serotonin (5-hydroxytryptamine, 5-HT) neurotransmission has been associated with increased alcohol consumption and vulnerability to alcohol dependence.[9,16-18] Acute alcohol exposure produces an increase in extracellular 5-HT levels, while chronic exposure causes an overall decrease in 5-HT neurotransmission as evidenced by lower levels of 5-hydroxyindoleacetic acid (5-HIAA), the primary metabolite of 5-HT, in cerebrospinal fluid of alcoholics (for review see Ref. 8). This reduction in extracellular 5-HT in a chronic alcohol exposure paradigm could be caused by accelerated 5-HT reuptake from the extracellular space through the serotonin transporter (5-HTT), or by dysfunctional 5-HT release from the raphe nuclei (for review see Ref. 8).

Alcohol was characterized in the past as a nonspecific drug; however, recent molecular and pharmacological studies have successfully defined specific protein targets. Several of these proteins belong to the serotonergic system, including 5-HT3, 5-HT1B, 5-HT1A receptors,

and 5-HTT. Serotonergic projections originating in the raphe nuclei innervate many of the brain regions involved in the rewarding effects of alcohol and other drugs.[19,20] Studies have shown that alcohol consumption affects the functionality and expression of 5-HTT[21-23] and, thus, alters the removal of 5-HT from the postsynaptic cleft in these areas following intake. Furthermore, 5-HT autoreceptors and heterore-ceptors have been linked to the regulation of alcohol intake (for review see Ref. 24). For example, alcohol directly targets the 5-HT3 receptor,[25] an excitatory ionotropic heteroreceptor often found on inhibitory GABA interneurons.[26] It has been hypothesized that direct activation of the 5-HT3 receptor on GABA interneurons is at least partly responsible for acute intoxication, producing both excitatory and inhibitory effects which vary according to the neurocircuitry involved.[26,27]

Dopamine release in mesolimbic reward pathways is an established mechanism of the rewarding effects of alcohol.[27] 5-HT neurons originating in the raphe nuclei can mediate dopamine release in the ventral tegmental area (VTA) and the nucleus accumbens (NAc).[7] Serotonergic projections also innervate other brain regions including the amygdala and the prefrontal cortex (PFC) (Fig. 1). Dysfunctional 5-HT1B heteroreceptors at the terminal of the NAc–VTA pathway may increase alcohol consumption by decreasing GABA release, and consequently increasing dopamine activation.[19,24,28-32] In addition, the dorsal striatum is under the control of serotonergic neurotransmission and has been associated with obsessive tendencies related to addiction.[8]

Pharmacological treatments for alcohol dependence have advanced over the years. However, there are still relatively few therapeutic drugs intended for the treatment of alcoholism. Currently, drugs that have been shown to effectively reduce alcohol intake include naltrexone (an opioid antagonist), acamprosate (glutamate-N-methyl D-aspartate (NMDA) and calcium channel dependent activity; the precise mechanism is unknown), and topiramate (γ-aminobutyric acid facilitator and glutamate function inhibitor).[33-38] Drugs that target the serotonergic system in the context of alcohol dependence include selective serotonin reuptake inhibitors (SSRIs) that block 5-HTT, partial 5-HT1A receptor agonists, and 5-HT3 receptor antagonists.[39,40]

Treating alcohol addiction is difficult because of the highly heterogeneous nature of alcoholic populations. In attempts to remedy the tendency to group addicts as a whole, various subtypes of alcoholism have been defined. These include Babor's type A and type B[41] and Cloninger's type I and type II.[42] Type A alcoholics have less severe substance dependence, a later onset of addiction, and a lesser degree of comorbid psychological dysfunction,[41] while type B alcoholics have earlier onset, a greater amount of stress, more childhood environmental risk factors, history of polydrug abuse, a greater potential for comorbid psychological dysfunction, and greater severity of dependence.[43] Type I alcoholics are characterized by late-onset drinking and the presence of genetic and environmental risk factors.[42] However, type II alcoholics are characterized by earlier onset, weak environmental influence, and a high frequency of antisocial and impulsive traits.[42] Studies have suggested an association between type I or type A alcoholism and dopaminergic dysfunction, where an alcoholic user seeks the anxiety relieving effects of alcohol.[44] Type B or type II alcoholism has been linked to deficient serotonergic neurotransmission and inherited biological risk factors.[45]

In this review chapter, we have discussed the role of the serotonergic system in alcoholism. The influence of genetic differences in 5-HTT and 5-HT receptor genotypes has been addressed to understand their involvement in alcohol craving. We discuss also the interactions between the serotonergic system and other neurotransmitters in the regulation of alcohol intake in animal models and clinics. Finally, we discuss the pharmacological

implications of drugs that target the 5-HTT and the 5-HT receptors, which have been shown to be potential treatments for alcohol dependence.

II. The Role of 5-HTT in Alcohol-Directed Neuroadaptation, Intoxication Response, and Potential for Abuse and Dependence

5-HTT is a member of the SLC6 family of transporters.[46] It is a transmembrane monoamine neurotransmitter sodium symporter that is sodium- and chloride-dependent and controls the concentration of 5-HT at both central and peripheral sites.[47] The functionality of 5-HTT is dependent on the concentration of transporters, the relative affinity for 5-HT, and the rate at which the transporters remove 5-HT. 5-HTT has been examined as a potential mechanism by which chronic alcohol exposure decreases 5-HT neurotransmission in alcohol-dependent individuals.

A. Alcohol's Influence on 5-HTT Expression, Function, and Region-Specific Neuroadaptations

Alcohol's influence on 5-HTT mRNA and protein levels has been shown in numerous models of alcohol intake and dependence. In animal models, alcohol exposure induced increases in 5-HTT mRNA concentrations in central serotonergic brain regions, as well as in reward circuitry and information processing regions.[48,49] A series of human postmortem autoradiography studies determined that chronic alcohol exposure decreases 5-HTT binding potential for ligands that mimic 5-HT.[21-23] However, some positron-emission tomography (PET) scan findings have indicated that there is no difference in 5-HTT density in the brains of alcoholics.[45,50]

Chronic voluntary alcohol consumption increased 5-HTT mRNA levels in the dorsal and median raphe nuclei where 5-HT cell bodies are located in Wistar rats.[49] However, when high alcohol-consuming rats were treated with the noncompetitive opioid antagonist naltrexone, 5-HTT gene expression in the aforementioned areas was significantly reduced, and voluntary alcohol consumption significantly decreased.[49] This effect indicates that alcohol consumption did not alter 5-HTT expression exclusively in a direct way, and suggests that interactions between alcohol and neurotransmitter systems cause complex changes in adjacent pathways. Chronic voluntary alcohol consumption also increased 5-HTT protein levels in the raphe nuclei of living nonhuman primates.[48] A single-photon emission computed tomography (SPECT) study, using the radioligand [^{123}I]2β-carbomethoxy-3B-(4-iodophenyl)tropane ([^{123}I]β-CIT), concluded that rhesus monkeys showing higher 5-HTT protein levels consumed greater amounts of alcohol. Interestingly, [^{123}I]β-CIT binding was not found to be significantly increased in other brain regions. However, extracellular 5-HT in the raphe nuclei activates autoreceptors on serotonergic cell bodies and this region-specific change in 5-HT binding may indeed be indicative of 5-HT release from serotonergic projections in other brain regions.[48,51]

Postmortem autoradiography study has been used to examine the activity of 5-HTT in specific regions of the human brain. A study using [^{3}H]citalopram reported lower 5-HTT binding in the anterior cingulate cortex of nonabstinent types I and II alcoholics.[21] However, no significant change in 5-HTT density was observed in the superior frontal gyrus. Collectively, the frontal cortex plays an important role in motivation and learning, and low 5-HTT density in this area has been associated with depression and other psychiatric illnesses.[21] A decrease in 5-HTT [^{3}H]citalopram binding sites was also reported in the dorsal amygdala and the caudate body of the same postmortem brains as compared to the control group.[22,23] No significant differences were seen, however, in the ventral amygdala, the rostral caudate, or the putamen of alcoholics. [^{3}H]citalopram binding in the caudate

putamen was decreased in type I alcoholics as compared to type II; however, no significant difference was found between the two groups in the dorsal amygdala.[22] Alcohol was detected via blood sample analysis in the majority of the alcoholic subjects included in the above postmortem studies when the tissue was collected.[21,22] Importantly, these findings indicate that brain areas are selectively affected in alcohol-dependent individuals, and that alcohol does not cause global decreases in brain 5-HTT.[21]

In vivo SPECT and the radioactive ligand [^{123}I] β-CIT have also been tested in humans to measure 5-HTT availability based on binding potential. 5-HTT β-CIT binding was found to be lower in the dorsal brainstem, where high density of serotonergic neurons are located, of male alcoholics following 3–5 weeks of abstinence.[52] The severity of this decrease was negatively correlated to longer lengths of lifetime drinking. An *in vivo* PET imaging study using the PET tracer [^{11}C](+)McN5652 found corresponding decreases in 5-HTT distribution volumes in recovering and abstinent alcoholics.[53] However, a different PET analysis employing the novel tracer, [^{11}C]-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile ([^{11}C]DASB), disagreed with the previous postmortem, SPECT, and PET results.[21-23,48,52] It is suggested that [^{11}C]DASB targets 5-HTT with higher specificity, possesses a faster washout time, and enters the brain more readily than the SPECT ligand β-CIT or PET ligand [^{11}C](+)McN5652, and therefore produced different results than those from past studies.[50] Using [^{11}C]DASB, no significant differences in 5-HTT binding potential were measured in the occipital cortex, thalamus, frontal cortex, amygdala, hippocampus, raphe nuclei, anterior cingulate, or caudate putamen in alcoholics compared to control subjects.[50] These findings suggest that decreased 5-HT neurotransmission is not a direct result of lower 5-HTT density in alcohol-dependent individuals, as was previously hypothesized. These findings were confirmed in type II alcoholics using [^{11}C]DASB.[45]

Moreover, it has been reported that alcohol exposure increases the expression, as well as the function, of 5-HTT *in vivo* in human dendritic cells.[46] This pharmacological effect of alcohol may be responsible for a certain degree of the neuroimmune degeneration seen in alcoholic individuals who present weakened immune responses. Dendritic cells that were treated with alcohol had higher levels of cyclic AMP (cAMP) mRNA indicating that the cAMP signaling pathway mediates alcohol directed upregulation of 5-HTT expression. cAMP has also been shown to increase 5-HTT mRNA levels in human placental choriocarcinoma cells.[54] In addition, 5-HTT transcription has been shown to be protein kinase-c dependent. 5-HTT expression increases in a dose-dependent manner as protein kinase-c is added to the cell culture medium.[55]

One explanation for contrasting findings across studies is sexual differences. Incongruence between male and female subjects is not uncommon. Studies demonstrated that male subjects showed a 30% decrease in [^{123}I]β-CIT-5-HTT binding in the midbrain, but no significant change was seen in female subjects.[52,56] Gender-specific differences in 5-HTT expression have also been reported in lymphoblast cell lines, with 5-HTT mRNA levels being lower in females as compared to males. Gender-specific epigenetic differences affect 5-HTT expression. Site-specific DNA modification affects gene expression in all mammalian cells. DNA methylation at the 5′ position of cytosine residues present in CpG islands—stretches of DNA that contain cytosine positioned directly next to guanine—has been consistently shown to alter gene expression.[57] Higher levels of CpG island methylation at specific residues have been shown to decrease 5-HTT transcription. This is especially true for residues that are located close to the start site. In general, CpG island methylation is higher in males than in females[58]; this may explain some gender-based differences in 5-HTT expression results. Exposure to other types of drugs, variant endogenous 5-HT concentrations, and genotype also affect the outcome of binding experiments.[50]

B. Relationship Between Functional Polymorphisms in the 5-HTT Gene Promoter and Alcohol Dependence

The 5-HTT gene is located on chromosome 17q11.1–q12 at the SLC6A4 locus.[59] A functional 5-HTT linked polymorphic region (5-HTTLPR) at the 5′ end alters 5-HTT transcription[60] and has been examined in humans to help define a hereditary basis for the development of alcohol dependence. Two functional 5-HTTLPR polymorphisms are produced by an insertion/deletion mutation of 44 base pairs, and are denoted as the long (L) and short (S) alleles. Healthy individuals that possess two copies of the L version of the allele (LL) exhibit greater 5-HTT activity at the synaptic cleft and higher mRNA density in the raphe nuclei than those that possess one or more copies of the S allele (SS/LS).[59,61] 5-HTTLPR genotype affects an individual's response to alcohol craving,[62] strength of withdrawal symptoms,[63,64] reaction upon first exposure,[65,66] and alcohol neurotoxicity.[59,67] The 5-HTTLPR has also been linked to antisocial behavior and impulsivity.[59]

The development of alcohol dependence may be partially due to a predisposing genetic influence. Numerous studies have searched for a concrete genetic relationship between the 5-HTT gene and alcohol dependence; however, because of the complex nature of alcohol-influenced neurotransmission, it has been difficult to reach a consensus. In addition to differences in pharmacological response to alcohol, alcoholics frequently present comorbidities with depression and anxiety, and there are physiological differences between women and men, as well as between different ethnic groups.

Because of the intricacy of genotypic, phenotypic, and environmental influences, individual studies of genotype-related to alcohol dependence demonstrate disparate findings. Some studies have linked the short version of the 5-hydroxytryptamine-transporter-linked promoter region (HTTLRP) to alcohol addiction.[68-72] Other studies have determined a significant relationship between the presence of the long allele and alcohol dependence.[59,73-75] It is noteworthy, however, that other groups have demonstrated that there is no relationship between allelic make-up and alcohol dependence.[63,71,76-82] To encompass a heterogeneous population and determine an overall consensus between studies, meta-analytic reviews have been performed. Two separate meta-analyses have determined that alcoholics are 15–18% more likely to possess an S allele.[68,83] A survey of data from one meta-analysis of 2325 control subjects and 3489 subjects diagnosed with alcohol dependence[68] demonstrated that S-allele carriers were 18% more likely to develop alcohol dependence. This amplified S frequency was stronger in alcohol-dependent individuals who reported an early onset of the problem of alcohol consumption and more severe alcohol dependence, and highest in those who also suffered from a co-occurring psychiatric disorder.[68] These findings are especially applicable for type II or type B alcoholics. A second meta-analysis concerning the link between the 5-HTTLPR polymorphism and alcohol dependence included a total of 8050 subjects and concluded that individuals who had been clinically diagnosed with alcohol dependence were 15% more likely to possess one or more short alleles,[83] and homozygous SS individuals were more likely to develop alcohol dependence than heterozygous individuals. The authors of this study suggested that due to the weakness of this association, it is important to interpret the results carefully and consider that 5-HTTLPR expression and the development of alcohol dependence may not be the result of a direct causal relationship. 5-HTTLRP genotypes are also related to behaviors such as reaction to stress, impulsivity, and low emotional regulation that influence the development of alcohol dependence.[83]

C. Relationship Between Functional Polymorphisms in the 5-HTT Gene Promoter and Alcohol Response, Alcohol-Directed Neuroadaptation

Studies have searched for specific genotype-centric differences in alcohol response to understand the etiology of alcohol abuse. It has been shown that L-allele carriers experience fewer negative side effects upon first exposure to alcohol[65] and stronger cravings,[62] which may increase susceptibility to alcohol abuse. S-allele carriers are also vulnerable to alcohol dependence as they build tolerance more efficiently,[84,85] are more likely to binge drink,[86] experience heightened withdrawal symptoms,[63] and are statistically more likely to relapse.[87]

Lower intoxication upon first exposure to alcohol has been linked to increased availability of 5-HTT in nonhuman primates.[88] This finding was also confirmed in young male, LL alcoholics, who self-reported lower intoxicative response upon first exposure.[66] The long version of 5-HTTLPR has also been shown to affect alcohol craving in L-carriers who have lower synaptic 5-HT on the basis of self-reported assessments in the presence of cues.[62] Craving measurements were higher in LL/LS alcoholics than in SS alcoholics, especially in those who reported a longer length of lifetime consumption.[62] To further test this effect, craving level was assessed following tryptophan depletion, which mimics a transient 5-HT decrease. Acute tryptophan depletion caused a reduction in “urge to drink” in LL/LS compared to SS subjects. This effect is likely due to a brief reduction in extracellular 5-HT and a decrease in auto-receptor activation that transiently increases 5-HT neurotransmission and alleviates the severity of craving.

The expected availability of 5-HTT is dependent on genotype-related changes following chronic alcohol exposure. It has been suggested that LL alcoholics are more susceptible to alcohol neurotoxicity following chronic consumption than SS alcoholics.[74] As predicted, LL control subjects have shown higher effective binding potential for [^{123}I]β-CIT than SS subjects in the raphe nuclei, which is interpreted to indicate higher 5-HTT levels in this region. Furthermore, when compared to healthy LL controls, LL alcoholics presented a significant decrease in 5-HTT binding potential.[74] This was not the case for SS alcoholics versus SS controls that had essentially equal 5-HTT binding. These data indicate that chronic alcohol consumption causes the availability of 5-HTT in the raphe nuclei to decrease substantially only in LL alcoholics.

Another factor concerning genotype-related response to alcohol is complex intersystem neural communication. Serotonergic neurotransmission directly influences mesolimbic dopamine activity via the 5-HT3 receptor.[89-92] This interaction is of interest in alcoholics who carry the LL genotype and have greater 5-HTT synaptic activity than SS carriers. To determine whether genotype affects dopaminergic activation, growth hormone secretion was measured in LL, LS, and SS alcoholic subjects following apomorphine injections. LL individuals had a lower response to apomorphine administration than SS and LS individuals. The reduction in dopamine response suggests that 5-HT3 receptors located on dopamine neurons are less sensitive following chronic alcohol exposure.[60]

The alcohol-intoxication effect discussed above necessitates a different hypothesis as to why, statistically, chronically alcohol-dependent humans and animal models show deficient 5-HT neurotransmission overall. Prior to chronic alcohol exposure, LL subjects possess increased 5-HTT activity and, therefore, reduced synaptic 5-HT. However, in chronic alcohol consumption paradigms, LL alcoholics may actually possess reduced 5-HTT activity. It is probable that a decrease in presynaptic 5-HTT clearance may increase synaptic 5-HT activation of inhibitory autoreceptors. This feedback mechanism may cause an overall decrease in 5-HT release and an associated deficit in serotonergic neurotransmission.[61,62]

Following repeated alcohol exposure, S-carriers report lesser degrees of intoxication than L-carriers at equivalent blood alcohol concentrations.[84,85] This may indicate that S-carriers develop alcohol tolerance more efficiently than L-carriers, as previous findings correlate persistently increased extracellular 5-HT with faster development of alcohol tolerance.[84] Although SS individuals may experience lower alcohol craving than L-carriers, it has been shown that SS alcoholics are more likely to binge drink. This assertion was first made on the basis of an analysis of the drinking behavior and associated polymerase chain reaction (PCR) genotyping of female college students.[86] SS female alcoholics who also possess the efficiently expressed version of the monoamine oxidase type A (MAO-A) promoter region reported even higher frequencies of binge drinking behavior. These 5-HTTLPR data were confirmed via platelet analyses of 5-HTT availability in a population that included both men and women. The corroborating study found that SS alcoholics consumed more alcohol and were, generally, younger than LL alcoholics.[59] Whether genotype has an effect on withdrawal symptoms is somewhat unclear. Studies reported that there were no significant withdrawal-associated 5-HTTLPR genotypes in alcoholics.[64] However, a subgroup of alcoholics who presented severe symptoms of withdrawal had a higher frequency of the S allele.[63] Moreover, 5-HTT genotype has been examined in the context of relapse. Variant 5-HT neurotransmission has been associated with impulsivity and the ability to avoid instant-gratification patterns, which may impart difficulties in alcohol abstinence.[87]

Determining genetically linked differences in alcohol response is important when considering treatment. Studies that examined the therapeutic effects of ondansetron, a 5-HT3 receptor antagonist, hypothesized that the rewarding effects of alcohol are amplified in LL alcoholics treated with SSRIs as compared to SS alcoholics.[93,94] Low synaptic 5-HT availability prior to alcohol consumption as a result of the LL genotype has been found to cause increased densities of 5-HT3 receptors on dopaminergic neurons. Thus, alcohol consumption is considered rewarding because it causes a greater increase in dopamine activity in LL alcoholics. SSRI treatment may potentiate this effect by causing an additional neuroadaptative increase in transporters. However, ondansetron would attenuate this effect by antagonizing 5-HT3 receptors. This theory was strengthened by a simulation of the rewarding properties of alcohol, which found that acute and chronic consumption caused increased dopamine responses that were accelerated in LL alcoholics treated with SSRIs and, conversely, in SS alcoholics treated with ondansetron.[95]

There are other contributing genetic factors that mediate 5-HTT expression apart from 5-HTTLPR long/short genotype and that warrant mention. One important genotypic variation is the existence of a second type of functional polymorphism present in the 5-HTT promoter region of the L allele, a single nucleotide A to G substitution at rs25531. An *in vitro* analysis in human cell lines showed that L alleles that contain this substitution (L_G) cause 5-HTT mRNA to be expressed at levels similar to that in the S allele. Carriers of two L alleles that do not have this mutation (L_A) transcribed 5-HTT mRNA at the highest levels.[96] In addition, the *in vivo* binding potential of 5-HTT is greater in the putamen of healthy L_A/L_A individuals than in healthy L_G/L_G individuals according to a [^{11}C]DASB PET scan study.[97] This genotypic effect was strongest in subjects with European ancestry. Because this single nucleotide substitution is not considered in many previous genetic studies of alcohol dependence, some results may be less conclusive than predicted.

The 5-HTT promoter polymorphism is not the only genetic factor that affects 5-HTT protein expression. The promoter region contains a TATA-like domain and a series of transcription factor binding sites, including one for the transcription factor AP2 (TFAP2B).[55,96] The transcription factor TFAP2B affects gene expression of 5-HTT as well, as MAO-A has been linked to severe alcoholism in females.[98] A functional polymorphism alters the degree of

TFAP2B expression. The presence of the higher functioning version of the TFAP2B allele has been linked to severe alcoholism in females.[98]

III. Serotonergic Receptors: Molecular, Pharmacological, and Physiological Aspects and Their Role in Alcohol Dependence

A series of 5-HT receptor subtypes have been shown to play a role in alcohol dependence, including the 5-HT3, the 5-HT1B, and the 5-HT1A receptors. These receptors are distributed throughout the nervous system and possess different molecular and pharmacological characteristics. Each of these receptors has been implicated in both alcohol intake and craving.

A. 5-HT3 Receptors

The 5-HT3 receptor is the only ligand-gated ion channel associated with 5-HT.[99] Five subunits, each composed of four transmembrane domains, form a channel which is permeable to Na^+, K^+, and Ca^{2+} when the receptor is activated by 5-HT binding.[99,100] This activation induces rapid depolarization that may increase the concentration of cytosolic Ca^{2+}.[99] Other agonists that activate 5-HT3 receptors are 2-methyl-5-HT, phenylbiguanide, and m-chlorophenylbiguanide.[101,102] The 5-HT3 antagonists most studied include zacopride, MDL72222, tropisetron, ondansetron, and granisetron.

Alcohol administration has been shown to potentiate the 5-HT3 receptor,[103-105] and this potentiation varies inversely with agonist concentration.[104] Studies focusing on residue 294 of the 5-HT3 receptor revealed that mutation of this residue to threonine in the 5-HT3 subunit eliminates the alcohol potentiation function of this receptor.[106] These studies suggest that 5-HT3 receptor in the central nervous system is a site of alcohol action.

The 5-HT3 receptor is localized in cortical and subcortical brain regions.[107,108] Although there is very low 5-HT3 receptor density in the VTA and NAc, electrophysiology and microdialysis studies indicate that 5-HT3 receptors play a role in regulating the activity of VTA dopaminergic neurons and their projections to the NAc.[89-92] Systemic administration of 5-HT3 receptor antagonists has been shown to effectively reduce alcohol intake in rats in free-choice conditions.[109,110]

B. 5-HT1B Receptors

The 5-HT1B receptor (human analog 5-HT1Dβ) is coupled to a G protein and contains seven transmembrane domains, one of which is composed of eight amino acids and acts as the ligand binding site.[111-113] Studies investigating 5-HT1B receptor signal transduction indicate that these receptors are coupled to an intermediate inhibitory G protein. When activated, this G protein acts as a second messenger, inducing a decrease in the activity of adenylyl cyclase.[114-118]

The 5-HT1B receptor has been implicated in several physiological functions, including locomotor activity, drug abuse reinforcement, migraine, aggressive behavior, depression, and anxiety states (for review see Ref. 24). 5-HT1B receptors are serotonergic autoreceptors located at the terminal (for review see Ref. 24); their activation inhibits the presynaptic release of 5-HT.[119-122] Studies investigating the distribution of 5-HT1B receptors in the central nervous system have demonstrated that high densities of these receptors are located in the globus pallidus, ventral striatum, substantia nigra, and dorsal subiculum.[24,28,123-126] Moderate expression of the 5-HT1B receptor has been found in the caudate putamen, hippocampus, entopeduncular nucleus, periaqueductal gray, superior colliculus, and some regions of the cerebellum. 5-HT1B receptors are located on the terminals of VTA neurons

that project to the NAc, amygdala complex, and frontal cortex.[127] The VTA sends dopaminergic projections to the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and to the NAc.[128,129] Collectively, these regions form a reward circuit for drugs of abuse, including alcohol, and are central in the development of addiction/dependence.[130-132] This complex is called "the extended amygdala," and is connected to the raphe nuclei, the locus coeruleus, the hippocampus, and the ventral pallidum.[133-137] A large number of studies using pharmacological, molecular, and genetic manipulations have suggested that 5-HT1B receptors modulate the reinforcement and intoxication effects of alcohol and that these receptors are key players in regulating alcohol intake.[24,138-145]

The alcohol intake phenotype has been shown to be linked in mice to chromosome 9 where the 5-HT1B receptor gene is located, and knockout mice lacking 5-HT1B receptors tend to have increased alcohol intake versus controls.[139,146] Moreover, the role of 5-HT1B receptors in alcohol dependence has been investigated in studies using gene manipulation. Microinjections of the viral vector-herpes simplex virus (HSV) carrying 5-HT1B receptors in the NAc shell increased alcohol intake in Long–Evans rats.[138] Manipulation of 5-HT1B receptors in brain assists in determining the neurocircuitry involving this receptor in alcohol intake. Importantly, a clinical study demonstrated that alcohol dependence is associated with upregulation of 5-HT1B receptor levels in the ventral striatum.[147]

Numerous single nucleotide mutations have been identified in the 5′ untranslated region, the 3′ untranslated region, and the coding region of the 5-HT1B receptor gene.[148] To date, 16 polymorphisms in the 5-HT1B receptor gene have been reported.[64] Many of these polymorphisms are functional, and some have been shown to alter the expression of 5-HT1B receptor. Two specific mutations examined in the context of alcohol dependence are the G861C polymorphism and the A-161T polymorphism. The resultant associations between these genotypic changes and alcohol dependence have been inconsistent, and no clear relationship between these polymorphisms and the propensity for alcoholism has been established. Studies have revealed that the 861 G > C polymorphism of the 5-HT1B receptor gene (human analog 5-HT1Dβ) was found to be associated with antisocial alcoholism.[149-151] The A-161T polymorphism has been shown to be more associated with alcoholism in individuals who have concurrent anxiety or depression versus those that are antisocial.[152] It is noteworthy that Han Chinese alcoholics classified as antisocial were more likely to possess the A allele, while alcoholics that were classified as depressed or anxious were more likely to possess the T allele.[152] However, the same study reported that no significant A-161T genotypic differences exist between control group and the collective of alcohol-dependent individuals.[152]

Understanding the pharmacology of 5-HT1B receptors is an important step in determining the physiological role of these receptors. Pharmacological studies have demonstrated that RU 24969 and trifluoromethyl-phenylpiperazine possess high affinity for 5-HT1B receptor binding sites in rodents, and that serotonergic agonist 5-CT has high affinity for both 5-HT1D and 5-HT1B receptor binding sites.[153-155] Another agonist, CP 93129, demonstrates stronger affinity for 5-HT1B receptor binding sites over 5-HT1D receptors,[156] whereas sumatriptan has a higher affinity for 5-HT1D receptor binding than for 5-HT1B receptors.[28,157] Although the compounds tested are not highly selective to 5-HT1B receptors, it is important to note that the pharmacological manipulations of these receptors in animal models have contributed largely to understanding the role of 5-HT1B receptors in the regulation of alcohol intake. Studies that tested partial and selective 5-HT1B agonists have shown that these compounds when administered i.p. reduced alcohol intake in animals.[143-145,158] Some of these agonists are discussed in the Section V.B.2.

C. 5-HT1A Receptors

Like the 5-HT1B receptor, the 5-HT1A receptor is a G-coupled transmem-brane protein with seven domains.[159] Activation of 5-HT1A receptors inhibits adenylyl cyclase in rodents.[160-162] Studies using radioligand binding sites demonstrated a high density of 5-HT1A receptors present in the limbic system including the hippocampus, lateral septum, entorhinal cortex, amygdala, and raphe nuclei.[163,164] 5-HT1A receptors are located on the dendrites of serotonergic neurons (autoreceptors), as well as on postsynaptic membranes of nonserotonergic neurons (heteroreceptors).[165-167] As such, 5-HT1A receptors play a role in the regulation of 5-HT release,[168,169] as well as in the regulation of the release of other neurotransmitters including noradrenaline and dopamine.[170,171] 5-HT1A receptors are involved in several physiological functions including sexual behavior, sleep, regulation of body temperature, and pain.[172-175] Moreover, 5-HT1A receptors are involved in psychiatric disorders including anxiety[164,176] and depression.[177,178] Importantly, studies conducted in animals and humans have demonstrated a role of 5-HT1A receptors in alcohol-drinking behavior.[179-182]

Pharmacological studies suggest that there are several selective agonists for 5-HT1A receptors. Among these are 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), ipsapirone, gepirone, buspirone, and tandospirone.[183] 5-HT1A receptor antagonists include spiperone,[184] (–)pindolol, (–)propranolol,[160,185] and (–)tertatolol.[186,187] Studies of alcohol-preferring rats demonstrated deficits in 5-HT transmission and a compensatory upregulation of 5-HT1A receptors.[188] Moreover, 5-HT1A receptors have been linked to alcohol consumption and alcohol withdrawal symptoms.[189,190] A large body of evidence using pharmacological investigations has demonstrated the involvement of 5-HT1A receptors in alcohol dependence.[179,181,182,191,192] The role of 5-HT1A receptor agonists in alcohol intake is discussed further in the Section V.B.3.

IV. Interactions Between the Serotonergic System and Other Neurotransmitter Systems in the Modulation of Alcohol Consumption

Alcohol abuse is a disorder characterized by a disruption of several neurotransmitter systems, including 5-HT. 5-HT interacts with and modulates other neurotransmitter systems (Fig. 1) to reinforce the hedonic effects of alcohol, some of which are discussed below.

A. Dopaminergic System

It is well established that enhanced dopaminergic neurotransmission arising from the VTA and terminating in the NAc is involved in reward[130] and that acute alcohol exposure increases dopaminergic neurotransmission.[193,194] A large portion of the VTA consists of dopaminergic projection neurons that are under the inhibitory control of GABAergic interneurons.[195] The VTA and the NAc receive substantial innervations from the dorsal raphe serotonergic neurons[32] (Fig. 1) and 5-HT is believed to modulate neurons in the VTA through several receptors including 5-HT1B, 5-HT2, and 5-HT3 receptors.

The 5-HT1B receptor is known to function both as an autoreceptor and as a heteroreceptor to inhibit presynaptic neurotransmitter release.[196] An increase in 5-HT1B activation via the selective 5-HT1B agonist, CP93129, within the VTA has been shown to disinhibit dopamine neurons by inhibiting GABA release, thereby increasing extracellular dopamine and decreasing extracellular GABA in both the NAc and the VTA.[197] Systemic alcohol-induced enhancements of dopamine in the VTA and the NAc were significantly reduced by local administration (into the VTA) of the selective high affinity 5-HT1B receptor antagonist SB216641 but not the 5-HT1D/1A receptor antagonist BRL 15572.[198] Furthermore, the 5-HT1B receptor agonists, *m*-chlorophenylpiperazine (mCPP) and Trifluoromethylphenyl

piperazine (TFMPP), dose-dependently suppressed alcohol intake[39,144,199] presumably because activation of this receptor increased dopamine neurotransmission in the VTA and the NAc.

Although we did not emphasize the role of 5-HT2 receptors in alcohol dependence in the review chapter, we briefly cover the interaction between 5-HT2 and the dopaminergic system as it relates to alcohol-drinking behavior. 5-HT2 receptor modulation has been shown to affect several aspects of dopaminergic neurotransmission, although with less consistency than the 5-HT1B receptor modulation. *In vitro* applications of the 5-HT2 receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) potentiated the inhibitory effects of dopamine acting at D2 receptors on dopaminergic cell bodies in the VTA, and this effect was reversed by the selective 5-HT2 antagonist ketanserin.[200] In agreement with these results, local infusion of the 5-HT2 antagonist ritanserin into the medial PFC of rats increased extracellular dopamine in this area.[201] However, infusion of DOI directly into the NAc increased extracellular dopamine only in the posterior NAc whereas coperfusion with a 5-HT2 antagonist completely blocked the DOI-stimulated dopamine release.[202] These differential effects could be due to the nonselectivity of the 5-HT2 agonists/antagonist. For instance, it has been demonstrated that 5-HT2A and 5-HT2B/2C receptors exert different functions in the modulation of dopamine release.[203] *In vivo* electrical stimulation of the dorsal raphe nuclei followed by the selective blockade of the 5-HT2A receptor subtype by SR 46349B significantly reduced dopamine release into the NAc whereas application of the 5-HT2B/C receptor antagonist SB 206553 significantly enhanced dopamine release in the NAc.[203] Furthermore, administration of the selective 5-HT2C antagonist SB242084 into the medial PFC decreased dopamine outflow into the NAc following morphine administration.[204] These studies suggest that there are complex interactions between 5-HT and other neurotransmitter systems that differ depending on which brain region is examined.

Several lines of evidence have demonstrated that 5-HT2 receptor antagonists reduce alcohol consumption. For example, the 5-HT2 antagonist ritanserin was shown to be effective in reducing alcohol intake in Wistar rats under free choice conditions.[205] Additionally, in several alcohol-preferring rat lines, the 5-HT2A antagonist amperozide was shown to be effective in reducing alcohol intake although it also reduced total fluid intake.[206,207] Moreover, it has been shown that direct self-coadministration of the selective 5-HT2A antagonist R-96544 and alcohol directly into the posterior VTA significantly reduced operant responding to alcohol alone in this area.[208] 5-HT could, therefore, be acting on different subtypes of 5-HT2 receptors within reward areas to modulate dopamine release and thereby alcohol consumption.

The 5-HT3 receptor has also been reported to alter dopaminergic neuro-transmission in central reward regions. *In vivo* application of the 5-HT3 agonist CPBG has been shown to increase extracellular dopamine in the NAc[90] and the VTA,[89,209] suggesting an action of the 5-HT3 receptor activation on both terminal and somatodendritic dopamine release. Local perfusion of the 5-HT3 antagonist ICS 205-930 in both VTA and NAc in combination with an i.p. injection of alcohol prevented the alcohol-induced increase in extracellular dopamine in these regions.[89,90] Consistent with the fact that increased dopamine mediates the reinforcing properties of alcohol, 5-HT3 antagonists have been shown to decrease voluntary alcohol consumption in rats under 24 h free-choice conditions.[110,210] Furthermore, in Wistar rats that readily self-administer alcohol directly into the posterior VTA, self-coadministration of ICS 205-930 and alcohol abolishes this operant response, which suggests that 5-HT3 receptors within the posterior VTA are necessary for alcohol self-administration.[211]

B. Glutamatergic/GABA Systems

It is well established that alcohol has a direct effect on NMDA receptors and that it prevents NMDA-mediated calcium influx in a noncompetitive manner (for review, see Ref. 212). These effects have been observed in several brain regions, including the cerebral cortex, NAc, amygdala, hippocampus, and VTA.[212] *In vivo* microdialysis studies have shown that acute alcohol exposure significantly reduces basal glutamate levels in the NAc whereas chronic exposure increases extracellular glutamate in the NAc and NMDA sensitivity in the striatum.[213-215] Activation of the NAc via glutamatergic mechanisms is implicated in the reinforcing effects of alcohol. For instance, direct infusion of the mGLUR5 antagonist MPEP, or the mGLUR2/3 agonist LY379268, into the NAc reduced alcohol self-administration in alcohol-preferring rats.[216] These results suggest that decreased glutamatergic activity in the NAc reduces alcohol-drinking behavior.

Excitatory glutamatergic efferents from the PFC to the NAc are strongly believed to contribute to drug addiction (for review see Ref. 217). The PFC is composed primarily of glutamatergic pyramidal neurons which are under the control of local GABAergic interneurons (for review see Ref. 218). 5-HT has been strongly implicated in modulating glutamatergic neurotransmission within the PFC and the NAc. For instance, studies have demonstrated that activation of presynaptic 5-HT1B receptors on glutamatergic terminals located in the NAc blocks glutamate mediated EPSPs on medium spiny neurons in the NAc.[219] The PFC is highly enriched in 5-HT1A receptors,[220] and 5-HT primarily down-regulates fast spiking interneuronal activity via 5-HT1A receptors in this region, disinhibiting glutamatergic pyramidal neurons.[221] Furthermore, 5-HT has been shown to excite striatal cholinergic and fast spiking GABAergic interneurons, which in turn inhibit glutamatergic input to projecting medium spiny neurons.[222-224] Thus, 5-HT has various effects in different regions by potentiating pyramidal neurons in the PFC and inhibiting medium spiny neurons in the NAc. Interestingly, it has been shown that Sardinian alcohol-preferring rats displayed lower 5-HT and 5-HIAA in the frontal cortex than their nonpreferring counterparts but no changes in 5-HT or metabolites were found in the NAc.[225] This 5-HT imbalance could act as a mechanism by which alcohol is reinforcing to some animals and not to others. Although these findings are not consistent across high alcohol preferring rat strains,[226,227] they do share similarities in that the overall consensus is a reduction in 5-HT in high-alcohol-preferring models compared to their nonpreferring counterparts.

C. Endocannabinoid System

Endocannabinoids act as retrograde messengers in the central nervous system and have been implicated in the reinforcing effects of drugs of abuse and feeding behavior. 2-Arachidonoylglycerol (2-AG) and anandamide (AEA) are the predominant endocannabinoids within the central nervous system and have their neurological effects by acting on presynaptic cannabinoid 1 (CB1) receptors (for review see Ref. 228). For instance, studies have demonstrated that CB1−/− C57BL/6J knockout mice consumed significantly less alcohol than their CB1+/+ counterparts in a free choice paradigm whereas food and water intake remained relatively unchanged.[229] Endogenous cannabinoids are thought to be synthesized on demand in the postsynaptic neuron and mediated by postsynaptic calcium influx. They are then released in a retrograde fashion and bind to presynaptic CB1 receptors.[230] CB1 receptors in the NAc are primarily located on excitatory presynaptic terminals where their activation results in the inactivation of presynaptic voltage gated calcium channels and subsequent neurotransmitter release.[231,232] Thus, an increase in 2-AG or AEA within this region may significantly decrease the excitatory input the NAc receives from key reward regions such as the PFC, amygdala, and hippocampus.

Moreover, acute systemic administration of alcohol dose-dependently was found to increase 2-AG levels in the NAc of alcohol-naïve rats and this effect was potentiated and prolonged in rats with a history of alcohol consumption.[233] As a consequence of chronic alcohol use, prolonged elevations in brain endo-cannabinoid levels decrease CB1 receptor binding.[234] Since both systemic alcohol administration and voluntary consumption are associated with increases in 2-AG and AEA in key reward regions,[233,235,236] and CB1 knockout mice display reduced alcohol-drinking behavior,[229] activation of CB1 receptors may be important for mediating alcohol-seeking behavior. Indeed, several reports have shown that administration of the selective CB1 receptor antagonist SR141716A reduces alcohol consumption in both rat[235,237] and mouse[238] models whereas intra-NAc administration of CB1 receptor agonists increased alcohol consumption.[239]

The endocannabinoid system has been shown to interact with other neurotransmitter systems involved in alcohol consumption both *in vitro* and *in vivo*. It has been shown that male Wistar rats treated i.p. with SR141716A display increased 5-HT and 5HIAA both in the medial PFC and NAc as measured by microdialysis.[240] Furthermore, studies have demonstrated that stimulation of CB1 receptors in mouse brain cortical slices inhibited subsequent 5-HT release,[241] whereas other researchers have shown that administration of SR141716A dose-dependently increased 5-HT, dopamine, and their respective metabolites in the forebrain of shrews.[242] Additionally, acute alcohol-induced increases in dopamine in the NAc of wild type mice were abolished by pretreatment with SR141716A whereas no effect on extracellular dopamine was found in CB1−/− mice, implicating that the alcohol-induced increase in dopamine was mediated by activation of CB1 receptors.[229]

5-HT has been shown to interact with the endogenous cannabinoid system in a reciprocal fashion. For example, activation of CB1 receptors by AEA inhibits glutamate release in the dorsal raphe, whereas depolarization of dorsal raphe 5-HT neurons triggers endocannabinoid release which further mediates the depolarization-induced suppression of excitation.[243] In agreement, activation of 5-HT2 receptors by 5-HT in the inferior olive induced endocannabinoid release which decreased the probability of glutamate release from the presynaptic terminal.[244] Furthermore, it was demonstrated *in vitro* that 5-HT2A receptor activation triggered an increase in 2-AG release through the activation of phosphatidylinositol-specific phospholipase C.[245] Thus, 5-HT may, in part, modulate other neurotransmitter systems by acting to stimulate endocannabinoid release.

V. Serotonergic System as a Potential Therapeutic Target in Alcohol Dependence/Addiction

Treating alcohol dependence is challenging because of its complexity. Investigations testing naltrexone (a noncompetitive opioid antagonist) to treat alcohol dependence have shown that in heavy-drinking subjects, naltrexone administration attenuated relapse during the treatment period. However, a study investigating the long-term effects of naltrexone showed that individuals doubled their drinking over the 6 months following termination of naltrexone treatment.[246] This suggests that the therapeutic effect of naltrexone is abolished once the treatment is completed. Although, naltrexone demonstrated significantly greater efficacy compared to placebo during the drug administration period, once the treatment was discontinued, the frequency of heavy drinking days gradually increased in patients suffering from alcoholism.[247]

Studies have shown that SSRIs effectively maintain the attenuation of alcohol intake achieved during treatment for at least 6 months after pharmacotherapy in type A alcoholics.[248] As suggested above, subgroups of alcoholics may respond differently to treatment with serotonergic medication. Although SSRIs-treatment may be associated with a

specific subtype of alcoholism, experimental studies have reported that SSRIs reduce alcohol intake in some alcoholics[249-253]; see also Table I. Several types of 5-HT receptors have been shown to play a role in alcohol-drinking behavior and are potential treatment targets, including 5-HT3, 5-HT1B, and 5-HT1A receptors[143,144,151,181,192,254]; see also Table II. We discussed here the possible outcomes of the pharmacotherapy for the treatment of alcohol dependence with regard to drugs that target the 5-HTT and the 5-HT receptors (Tables I and II).

A. Serotonin Transporter as Potential Pharmacological Therapeutic Target for the Treatment of Alcohol Dependence

Dysfunction of the serotonergic system has been considered for many years to be the cause of mood disorders including anxiety and depression.[255-257] Studies have shown that some alcoholic patients show symptoms of depression.[258,259] Low 5-HT turnover may lead to behavioral impulsivity and aggression, as well as early onset of alcohol intake.[16,260-263] Genetic and imaging studies have demonstrated that reduced 5-HTT availability is associated with anxiety disorder and depressive state in alcoholic patients suffering from major depression.[52,264-267] In accordance, studies in animal models have shown a link between 5-HT deficit and aggression that together are associated with excessive alcohol intake,[139,268] alcohol consumption, and measurable behavioral depression in selected alcohol-preferring AA rats[269] and in fawn-hooded rats.[270] Increase in alcohol intake is due to the fact that these animals develop tolerance to the depressant effects of alcohol and possess faster alcohol metabolism.

In clinical studies, individuals that consume alcohol heavily present dysfunctional serotonergic neurotransmission.[18] Lower cerebrospinal fluid concentrations of the 5-HT metabolite 5-HIAA have been found in abstinent alcoholics.[271-273] Interestingly, low concentrations of 5-HIAA in cerebrospinal fluid were found to be associated with type II alcoholism.[263,274] SSRIs have been used to treat alcohol addiction in subgroups of alcoholics.[52,275] Moreover, studies have suggested that there might be an association between alcohol consumption and hyposerotonergic activity in humans.[9,18,276] Decreased 5-HT turnover rate has been associated with reduced response to excessive alcohol consumption.[277] Moderate reductions in alcohol consumption were found in alcoholics treated with SSRIs.[278] It is noteworthy that findings related to SSRIs have been variable between alcoholics.[279] We discussed here the variability in SSRIs efficacy in type A and B alcoholics.

1. Effects of Fluoxetine on Alcohol Consumption—Fluoxetine is an SSRI that was found to decrease the quantity of daily alcoholic drinks and decrease total drinks over a period of 14 days, with no significant effect on days of abstinence, in some alcoholics.[249] However, fluoxetine was not found to be effective for the treatment of a heterogeneous group of alcohol-dependent individuals.[280] In addition, fluoxetine was effective only in improving depressive symptoms in alcoholics with comorbid depression.[281] Importantly, in the absence of a comorbid mood or anxiety disorder, fluoxetine is not to be used to maintain abstinence or reduce drinking in high-risk/severity alcoholics (type B).[279]

Moreover, studies have suggested that fluoxetine is effective in relieving alcohol withdrawal symptoms. Fluoxetine reduces anxiety and alleviates depressive state during alcohol withdrawal.[282] In addition, independently from craving, fluoxetine at antidepressant doses is able to prevent short-term relapses in alcoholics.[283] In animal models, fluoxetine inhibited locomotor hyperactivity, agitation, increased stereotyped behavior, and tremors associated with withdrawal.[284] This later study suggests that the inhibitory effects of fluoxetine on the

signs of alcohol withdrawal were specific and may not be related to other effects including sedation and muscle relaxation.

2. Effects of Sertraline on Alcohol Consumption—Sertraline is another SSRI that has been clinically shown to reduce alcohol consumption. Studies have investigated the effects of sertraline in alcohol-dependent patients with and without lifetime histories of depression. The findings revealed that there was no antidepressive effect of sertraline; however, sertraline was effective in reducing alcohol intake in subjects without a lifetime history of depression.[275] It has also been revealed that sertraline treatment reduced alcohol intake in type A alcoholics but not in type B.[285] Further studies indicate that type A alcoholics demonstrated a consistent benefit from sertraline that lasted for at least 6 months after the completion of pharmacotherapy.[248] In contrast, sertraline has not been found to be efficacious in type B alcoholics during treatment or after. Sertraline was actually shown to increase alcohol intake in type B alcoholics 6 months after withdrawal from the medication. It is suggested that there might be a deficit in 5-HT synthesis in the brains of type B alcoholics,[248] resulting in a neuroadaptative upregulation of some 5-HT receptors. Thus, treating type B alcoholics with SSRIs may induce neuronal overstimulation because of increased 5-HT at the synaptic cleft and resulting in increased alcohol intake.[93,286]

3. Effects of Escitalopram on Alcohol Consumption—Escitalopram, an active analog of citalopram, is another SSRI. Studies in rat models revealed that escitalopram was less effective than fluoxetine in reducing withdrawal symptoms.[287] Unlike fluoxetine, escitalopram did not prevent withdrawal effects including locomotor hyperactivity, agitation, and audiogenic seizures.[284] These results show that escitalopram has a limited ability to ameliorate alcohol dependence and alcohol withdrawal in rat models.[287]

4. Effects of Zimelidine on Alcohol Consumption—The effect of zimelidine, another SSRI, on alcohol consumption was tested in nondepressed healthy heavy drinkers without regard for subtype. Zimelidine treatment was associated with increased length of abstinence and decreased the number of drinks consumed daily.[251] In a follow-up study, the authors demonstrated that ~ 50% of the subjects responded to the treatment, 35% partially responded, and 10–15% were nonresponsive to the treatment.[250] This suggests that this study may have individuals from various alcoholic subtypes, which may have led to differential findings.

5. Effects of Tianeptine on Alcohol Consumption—Tianeptine, a unique tricyclic antidepressant, in contrast to SSRIs, actually increases 5-HT reuptake.[288] In animal models, tianeptine decreases alcohol intake[289] and reverses the anxiogenic effects of alcohol withdrawal in rats.[290] Moreover, tianeptine was suggested to be a potent pharmacologically active drug in the ethanol withdrawal syndrome in rats (for review see Ref. 291). In clinics, patients treated with tianeptine have shown long-term improvement in depression and anxiety after alcohol withdrawal.[292] Moreover, tianeptine has been shown to be effective in preventing alcohol intake in alcoholics suffering from depression.[293] Together, these findings suggest that tianeptine might be used for the treatment of alcohol dependence associated with depression.

B. Serotonin Receptors as Potential Pharmacological Targets for the Treatment of Alcohol Dependence

1. Role of 5-HT3 Receptors in Pharmacotherapy of Alcohol Dependence—Rodents treated with 5-HT3 receptor antagonists have shown reduction in alcohol consumption.[182,294] Further, 5-HT3 receptor antagonists have been shown to block both alcohol- and morphine-induced dopamine releases in the mesolimbic system.[89,90,295] These

findings demonstrate the importance of the 5-HT3 receptor in alcohol-mediated activation of the dopamine reward pathways in the mesolimbic system, even though there are low densities of the receptor in this system.[296] 5-HT3 receptor antagonist administration in the NAc was found to be effective in reducing the initiation and in the maintenance of free-choice alcohol intake. However, this effect was abolished after a 2-week deprivation period.[297] Moreover, chronic alcohol consumption reduced 5-HT transmission in the NAc by reducing basal 5-HT release; however, a 2-week period of alcohol deprivation led to an elevation of 5-HT release compared to control groups.[298]

Ondansetron is the only 5-HT3 receptor antagonist that has been shown to be beneficial for the treatment of alcohol dependence, and has been clinically demonstrated to reduce alcohol preference and craving in some alcoholic subtypes. In a 6-week double-blind clinical trial study, ondansetron treatment was associated with the attenuation of alcohol consumption in male alcoholics in a dose-dependent manner.[299] Additionally, in a 12-week double-blind clinical trial, ondansetron was found to be effective at reducing alcohol intake only in early-onset alcoholism or type B.[93] Further study confirmed the efficacy of ondansetron in type B alcoholics showing severe psychological problems related to alcohol addiction.[300] The effectiveness of ondansetron treatment in type B but not type A alcoholics has been confirmed by other studies as well.[301] It is important to note that type B alcoholics with apparent serotonergic deficits respond best to drugs that block 5-HT3 receptors.[93,302] However, type A alcoholics who have a normal serotonergic system may respond best to drugs that effect the uptake of 5-HT.[301]

2. Role of 5-HT1B Receptors in Pharmacotherapy for Alcohol Dependence— There is a large body of evidence demonstrating the importance of 5-HT1B receptors in alcohol intake in animal models. Early studies suggested that 5-HT1B receptor knockout mice consumed alcohol at an increased rate,[139-141] while later studies suggested no difference from wild type.[303] The disparity between these findings might be due to the doses of alcohol tested, exposure paradigm, and environmental factors influencing alcohol intake. Differences in alcohol intake in 5-HT1B receptor knockout mice may suggest that phenotypical abnormalities attributed to the knockout mutation may exist.[304,305]

Pharmacological studies using rodents have investigated the role of 5-HT1B receptors in alcohol intake. Administration of CP-94253 (i.p.), a partial 5-HT1B receptor agonist, reduced alcohol self-administration[142] and its aggression-heightening effects.[145,158] It should be taken into consideration that CP-94253 is a nonselective 5-HT1B receptor agonist and thus the effects of this drug may involve other receptors. Other drugs targeting 5-HT1B receptors have been studied in animal models of alcoholism. For example, the 5-HT1B receptor agonist mCPP was shown to reduce alcohol intake in the cologne alcohol-addicted (cAA) rat model of alcoholism.[143] Moreover, administration of CGS12066B (i.p.), another partial 5-HT1B receptor agonist, reduced oral alcohol self-administration in Wistar rats.[144] Lastly, administration of the 5-HT1B receptor agonist, anpirtoline (i.p.), significantly decreased alcohol intake in Swiss Webster mice.[145] Together, data generated from pharmacological studies and mice lacking 5-HT1B receptors suggest an important role for these receptors in alcohol intake in animal models. Studies are warranted to develop new selective compounds targeting 5-HT1B receptors as therapeutic drugs for the treatment of alcohol dependence in humans.

3. Role of 5-HT1A Receptors in Pharmacotherapy of Alcohol Dependence— Several 5-HT1A receptor agonists have been tested in animal models to demonstrate the role of this receptor in alcohol dependence. For example, studies reported that the 5-HT1A receptor agonist buspirone reduces alcohol intake in rats and monkeys.[179,180] Treatment with another 5-HT1A receptor agonist, ipsapirone, induced a dose-dependent reduction in

alcohol preference and intake in rats.[181,182] A study using Wistar rats tested three 5-HT1A receptor agonists, 8-OH-DPAT, buspirone, and NDO-008 on alcohol preference.[191] Treatment with these agonists induced a significant reduction in alcohol consumption in the high preference group but not in the low preference group of rats. These preclinical studies suggest that 5-HT1A receptor agonists may be effective in reducing alcohol intake.

Postmortem studies of alcoholics have shown that blood alcohol concentration is correlated with a downregulation in 5-HT1A receptor binding sites in frontal-parietal cortical and hippocampal brain regions.[306,307] Moreover, the 5-HT1A receptor agonist, buspirone, has been shown to be effective in the treatment of comorbid anxiety and depressive features in alcoholics.[308-310] Studies have investigated 51 patients diagnosed with generalized anxiety disorder and depressive symptoms with concomitant alcohol abuse features.[310] These studies revealed that the buspirone metabolite 1-pyrimidinylpiperazine (1-PP) improved anxiety and depressive symptoms, and reduced the number of alcohol-seeking days. Buspirone was also found to reduce alcohol craving, and lead to reduced anxiety and improvement of depressive symptoms in another study.[308] Together, these studies suggest that targeting the 5-HT1A receptor with drugs such as buspirone may improve alcohol craving in patients suffering from alcohol dependence with features of anxiety disorder and depression.

VI. Conclusions

The serotonergic system plays an important role in the modulation of alcohol-drinking behavior, dependence, and withdrawal. Serotonergic dysregulation is associated with increased alcohol consumption and vulnerability to alcohol dependence. 5-HTT and 5-HT receptors, including 5-HT1A, 5-HT1B, and 5-HT3 receptors, are involved in alcohol-related changes in serotonergic neurotransmission.

Animal and clinical studies have demonstrated that chronic alcohol consumption alters 5-HTT function and expression. It is noteworthy that there is a possible genetic relationship between the 5-HTT gene and alcohol dependence. There are two functional polymorphic regions in this gene that appear to contribute to the hereditary basis for the development of alcohol dependence. The development of alcohol dependence may be due partly to a genetic predisposition involving 5-HTT polymorphisms. Targeting 5-HTT with SSRIs has been shown to be a promising pharmacotherapy in some alcoholics. It is noteworthy that SSRIs have been clinically shown to be effective only in type A alcoholics.

Pharmacological studies have demonstrated that several 5-HT receptors including 5-HT1A, 5-HT1B, and 5-HT3 receptors are involved in alcohol dependence. Interestingly, the 5-HT3 antagonist, ondansetron was found to be effective in type B alcoholics but not in type A. Moreover, the 5-HT1A receptor agonist, buspirone, is a potential therapeutic drug for the treatment of alcohol craving in patients suffering from anxiety disorder and depression. Finally, we suggest that clinical tests targeting the 5-HT1B receptor with new selective drugs should be considered as a potential therapy for the treatment of alcohol dependence associated with anxiety disorder and depressive state.

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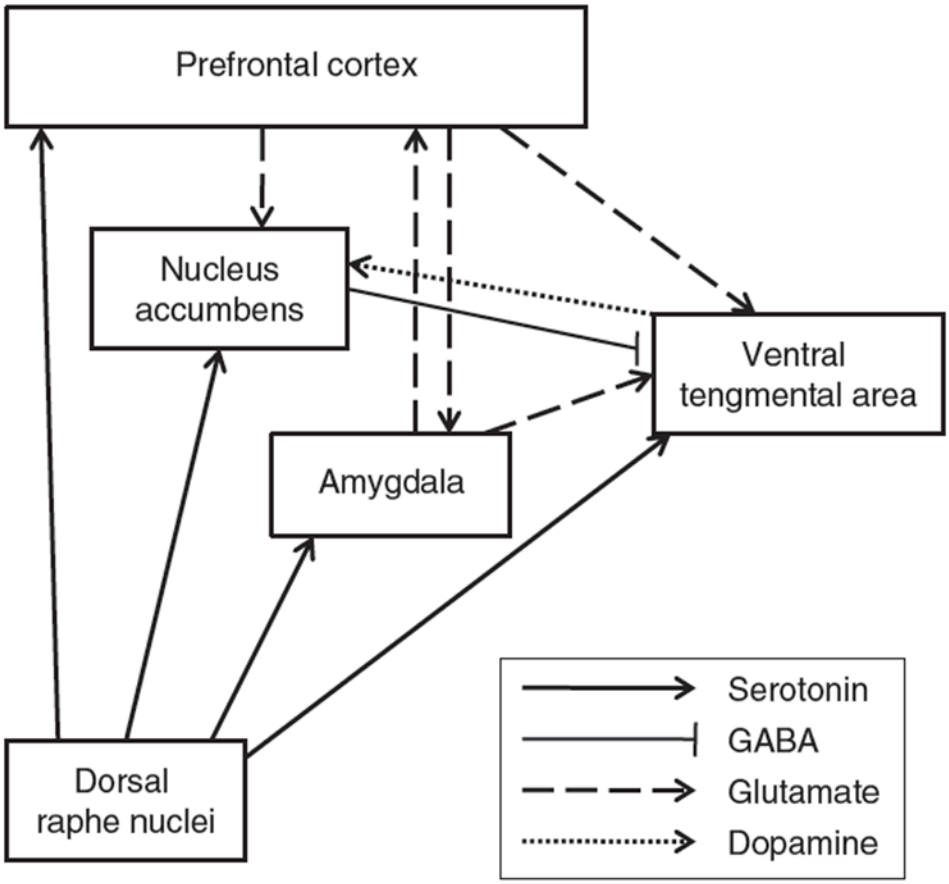

FIG. 1.

Schematic representation of the serotonergic neurocircuitry as it relates to the other neurotransmitter systems involved in alcohol dependence. Serotonergic neurons project to different reward brain regions such prefrontal cortex (PFC), nucleus accumbens (NAc), ventral tegmental area (VTA), and amygdala. The GABAergic NAc-VTA pathway contains 5-HT receptors at its terminal and controls the release of GABA, which in turn regulates the release of dopamine of the VTA-NAc pathway. The glutamatergic projections from the PFC targeting the NAc and VTA express 5-HT receptors at their terminals, which control the release of glutamate.

TABLE I

Involvement of SSRIs and Other Antidepressants in Alcohol Dependence or Craving

Type of SSRIs and other antidepressants	Effectiveness of SSRI or antidepressant in alcohol dependence or craving	Long-term effect after withdrawal of medication	References
Fluoxetine	Reduces alcohol consumption in type A but not type B alcoholics Reduces anxiety and alleviates depression state during alcohol withdrawal in alcoholics	Not determined	276,280,281,283
Sertraline	Reduces alcohol consumption in type A but not type B alcoholics	The effects of the drug can last for at least 6 months after the completion of the pharmacotherapy	248,285,311
Escitalopram	Reduces alcohol consumption in alcoholics but it is less effective than fluoxetine or sertraline	Not determined	284,287
Zimelidine	Induced increases in the days of abstinence and decreased the number of drinks consumed in alcoholics	Not determined	250,251
Tianeptine	Acute drug treatment was more effective than chronic treatment in the improvement of depression state and anxiety after alcohol withdrawal in alcoholics	Not determined	288,290,292,293

TABLE II

Role of 5-HT Receptors in the Attenuation of Alcohol Consumption

Type of 5-HT receptors	Effect of selective 5-HT receptor agonist or antagonist in animal model in alcohol intake	Effect of selective 5-HT receptor agonist or antagonist in clinics in alcohol consumption	References
5-HT1A receptors	Agonists, 8-OH-DPAT, buspirone, and NDO-008 reduced alcohol intake in Wistar rats	Partial agonist, buspirone, reduced depressive state and the number of days in desire to drink alcohol	179-181,308,310
5-HT1B receptors	Agonists, CP-94253, mCPP, and CGS-12066B reduced alcohol intake in Wistar rats	Not determined	142,145,158,294
5-HT3 receptors	Antagonists reduced alcohol intake in rats	Antagonist, ondansetron, reduced alcohol intake in type B but not type A alcoholics	94,182,294,297,300,301