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The Role of 5-HT₃ Receptors in Drug Abuse and as a Target for Pharmacotherapy

E.A. Engleman^{*}, Z.A. Rodd, R.L. Bell, and J.M. Murphy

Indiana University School of Medicine, Department of Psychiatry, Institute of Psychiatric Research, 791 Union Drive, and IUPUI School of Science, Department of Psychology, Indianapolis, IN 46202, USA

Abstract

Alcohol and drug abuse continue to be a major public health problem in the United States and other industrialized nations. Extensive preclinical research indicates the mesolimbic dopamine (DA) pathway and associated regions mediate the rewarding and reinforcing effects of drugs of abuse and natural rewards, such as food and sex. The serotonergic (5-HT) system, in concert with others neurotransmitter systems, plays a key role in modulating neuronal systems within the mesolimbic pathway. A substantial portion of this modulation is mediated by activity at the 5-HT₃ receptor. The 5-HT₃ receptor is unique among the 5-HT receptors in that it directly gates an ion channel inducing rapid depolarization that, in turn, causes the release of neurotransmitters and/or peptides. Preclinical findings indicate that antagonism of the 5-HT₃ receptor in the ventral tegmental area, nucleus accumbens or amygdala reduces alcohol self-administration and/or alcohol-associated effects. Less is known about the effects of 5-HT₃ receptor activity on the self-administration of other drugs of abuse or their associated effects. Clinical findings parallel the preclinical findings such that antagonism of the 5-HT₃ receptor reduces alcohol consumption and some of its subjective effects. This review provides an overview of the structure, function, and pharmacology of 5-HT₃ receptors, the role of these receptors in regulating DA neurotransmission in mesolimbic brain areas, and discusses data from animal and human studies implicating 5-HT₃ receptors as targets for the development of new pharmacological agents to treat addictions.

Keywords

Serotonin; dopamine; ethanol; cocaine; nicotine; amphetamine; opiates; addictions

1. Introduction

Addictions to alcohol, nicotine, and other drugs are a pervasive problem in the United States and worldwide. The impact on society is substantial when the total costs of lost productivity, hospitalizations for secondary effects, such as accidents or cancer, crimes committed under the influence, as well as violence toward others or oneself are considered. While significant inroads have been made into the effects of different drugs of abuse on neuronal circuitry within the brain, the translation of this knowledge into effective treatments for alcoholism and drug addiction has been much slower.

A major portion of the research on the neurobiological mechanisms of addiction has focused on the mesolimbic dopamine (DA) pathway. This system is comprised of DA neurons with

^{*}Address correspondence to this author at the Department of Psychiatry, Indiana University School of Medicine, Institute of Psychiatric Research (M114), 791 Union Drive Indianapolis, IN 46220, USA; Tel: 317-278-4988; Fax: 317-274-1365; eenglema@iupui.edu.

cell bodies in the ventral tegmental area (VTA) of the brain stem (also known as the A10 region of the tegmentum), which project to forebrain areas including limbic structures such as the nucleus accumbens and the amygdala as well as cortical areas including the prefrontal cortex (PFC). The latter projection forms the mesocorticolimbic pathway. Evidence indicates that the mesolimbic DA system appears to mediate the rewarding, reinforcing, and seeking or expectancy properties of drugs of abuse. Disruption of this pathway can reduce drug self-administration in animal models, and several neurotransmitter systems are known to regulate DA activity in this system including serotonin (5-HT), glutamate, gamma aminobutyric acid (GABA), endorphins, among others [1,2].

This review summarizes evidence indicating that the mesolimbic DA system is involved in the addictive properties of drugs of abuse and evaluates how this system is regulated by the serotonin (5-hydroxytryptamine) 5-HT₃ receptor. The aim is to provide an overview of the structure, function, and pharmacology of 5-HT₃ receptors and to discuss data from animal and human studies that suggest that this receptor is a promising target for the development of new pharmacological treatments for addiction.

2. The Mesolimbic Dopamine System and Addiction

2.1. Neurobiological Mechanisms of Drug Abuse

Although clearly not the only system involved in reward [3], activation of the mesolimbic DA system is often considered to be a common denominator in the action of many drugs of abuse, with cocaine, ethanol, amphetamine, opiates, and nicotine activating this system [4]. By doing so, these drugs are thought to be tapping into an organism's natural "pleasure" pathway, because the mesolimbic DA circuit is also activated during behaviors such as food consumption and mating, which are necessary for survival of the individual and the species. Thus, activation of this system by exposure to addictive drugs may perpetuate drug self-administration and possibly lead to addiction [5]. However, rather than acting through the natural integrated neuronal systems subserving behaviors that mediate survival, many addictive drugs act directly or indirectly on DA neurons. This activation of the mesolimbic DA system can occur either through direct activation of receptors, as seen with nicotine and opiates, or through modulation of neurotransmitter transporter activity or neurotransmitter release, as seen with cocaine or amphetamine.

2.2. Overview of Animals Models of Drug Abuse

Animal models have been successfully used in developing treatments for a number of medical and psychiatric disorders [6,7]. An animal model has the advantage of allowing the experimenter to control factors such as genetic background, environmental factors and prior drug exposure. In addition, an animal model allows for the examination of neurobehavioral, neurochemical and neurophysiological correlates with the behavioral, physiological or neurological state that is modeled. These correlates in turn facilitate the development of pharmacological and/or behavioral treatments for the disorder in question.

The observation that people with very similar environmental backgrounds often differ considerably in ethanol consumption and the well-documented familial incidence of alcoholism strongly suggest that heredity contributes to excessive ethanol consumption in some individuals [8-10]. Similarly, it is clear that outbred rats exhibit a wide-range of ethanol-consumption levels [11], and, as in humans, the propensity to ingest ethanol is genetically influenced. In the late 1940's, Williams and associates [12] and Mardones and colleagues [13] proposed a genetic influence on ethanol self-administration in rodents. This was followed by reports that C-57 substrains of inbred mice display high ethanol-preference, while DBA inbred mice display low ethanol-preference (aversion) [14-16]. However, inbred strains may

not be the best models to examine “correlated traits and responses” [17-19]. This is because inbreeding results in fortuitous (chance) fixation of genes associated with the phenotype being examined. Therefore, selective bi-directional breeding, for ethanol preference versus nonpreference [1,13,18,20-25], has provided powerful research tools for examining genetic and environmental factors affecting excessive ethanol intake.

A genetic component to human drug addiction has been shown as well [26-34]. Testing for sensitivity to, and/or self-administration of, amphetamine [35-37], cocaine [35-41], nicotine [42,43], methamphetamine [41] and opiates [35,44] in selectively bred rodent lines has provided additional support for a genetic influence on drug abuse and dependence [45].

In addition to consuming addictive drugs, (for example, selective breeding has resulted in a rat line which consumes opiates in its drinking water [38,44]) animals can also be trained to self-administer drugs intravenously. Ethanol, cocaine, amphetamine, nicotine, and opiates are all self-administered IV in rodents and/or monkeys (e.g. [46]). This eliminates the contribution of orosensory factors affecting the self-administration of drugs of abuse, which suggests a pharmacological explanation for the self-administration behavior. Therefore, self-administration of drugs of abuse is an important criterion in establishing an animal model of addiction, which, as indicated above, provides an important tool for the development of effective treatments.

Intracranial self-administration (ICSA) is a technique used to examine whether a specific brain region mediates ethanol or drug reinforcement. Many addictive drugs are self-administered directly into the VTA, nucleus accumbens (NAcb), PFC and other areas of the mesocorticolimbic DA system [47]. Intracranial self-stimulation (ICSS) is another technique used to examine the role of specific brain regions in mediating ethanol or drug reinforcement. The ICSS technique involves implanting electrodes directly into specific brain regions to determine if the animal can be trained to press a lever for the delivery of an electrical stimulus directly into the brain region. If the electrical stimulation is reinforcing, and presumably rewarding, the animal will continue to press the lever to receive the stimulation. Similar to ICSA, several areas within the mesocorticolimbic DA system support ICSS including the VTA, NAcb, PFC and medial forebrain bundle (MFB) [48]. With ICSA, and to some extent ICSS, the neuroanatomical site of action for a pharmacological reduction, or enhancement, of ethanol or drug reinforcement can be determined.

Conditioned place preference (CPP) is another method used to assess the rewarding properties of a drug [2,48-51]. Moreover, the efficacy of putative treatments for addiction can be evaluated within this paradigm. CPP involves multiple training sessions in which animals are placed in an apparatus with two distinctive environments, one consistently paired with drug administration and the other paired with vehicle administration. After several pairings with the respective environments, the animal is placed in the apparatus for a “test” session in which it may freely move between the two environmentally distinct chambers. If the animals spend significantly more time in the environment associated with the drug treatment, compared with the environment associated with the control/vehicle treatment, or more time in the drug-paired compartment than was apparent in a baseline session prior to the training sessions, the drug is considered rewarding. Most drugs of abuse, including cocaine, amphetamine, opioids, THC and, under certain conditions, ethanol, produce a CPP in this paradigm [52] and alterations of neurotransmission in mesocorticolimbic pathway reduce the time spent in the drug-paired environment and, thus, the drug's rewarding properties.

3. The 5-HT₃ Receptor

3.1. Structure and Function

5-hydroxytryptamine (5-HT; serotonin) was identified as a neurotransmitter in the mid 20th century. Since that time, seven different classes of 5-HT receptors (5-HT₁ through 5-HT₇) have been identified and these have been further subdivided into at least 14 different receptor subtypes. Most 5-HT receptors are metabotropic receptors that are coupled to G-proteins. However, the 5-HT₃ receptor is unique among serotonin receptors in that it is an ionotropic, or ligand gated ion channel. Originally described as the M-type receptor due to its effects on mesenteric or gut contraction, the 5-HT₃ receptor was cloned in 1991 and later found to be a member of the Cys-loop family of ligand-gated ion channels, which include the nicotinic acetylcholine (nACh) receptor and the GABAA receptor [53]. Members of this family of receptors all have an N-terminal binding domain containing a conserved cysteine loop and four transmembrane domains. The second transmembrane domain forms the internal lining of the ion channel [54]. The 5-HT₃ receptor is a pentameric structure made up of 5 receptor subunits that, when assembled, form a pore that gates cations (specifically Na⁺ and K⁺). Thus, activation of the receptor is generally excitatory to the neurons on which it resides, with the influx of cations depolarizing the neuron which releases one of a number of neurotransmitters and/or neuropeptides (see discussion below). In the brain, the 5-HT₃ receptor is generally thought to be a homomeric receptor made up of five 5-HT_{3A} receptor subunits [55]. A 5-HT_{3B} subunit has also been identified and is found mainly outside the central nervous system and combines with 5-HT_{3A} subunits to form hetero-pentamers [56]. A more detailed review of the structure, function, and pharmacology of the 5-HT₃ receptor has been recently published [57].

3.2. Anatomical Distribution

The 5-HT₃ receptor is found throughout the brain and central nervous system and is in relatively high concentrations in brainstem areas, such as the area postrema and nucleus of the solitary tract [58]. Within the forebrain, 5-HT₃ receptors have been found in the entorhinal, frontal and cingulate cortices, hippocampus, and amygdala [58]. Interestingly, 5-HT₃ receptors are found in very low levels in areas such as the VTA, NAc, striatum, substantia nigra, thalamus, or dorsal raphe nucleus (DRN) [59,60] despite clear pharmacological and physiological evidence that they affect DA neurotransmission in these areas. Immunohistochemical and in situ hybridization data suggest that 5-HT₃ receptors are expressed in certain subpopulations of GABAergic neurons in the rat hippocampus and neocortex [61] and are expressed in a very high proportion of GABAergic neurons that also contain cholecystokinin [62,63]. In most brain areas 5-HT₃ receptors appear to be associated with axons and axon terminals, except for the CA1 region of the hippocampus where the majority of 5-HT₃ receptors have a dendritic location [64]. In comparison with other 5-HT receptors, the density of 5-HT₃ receptors is lower throughout the brain. Nevertheless, 5-HT₃ receptors play an important role in the regulation of mesocorticolimbic neurotransmission, the effects of drugs on mesocorticolimbic neurotransmission, and in the self-administration of at least some drugs of abuse.

3.3. 5-HT₃ Pharmacology

Many selective and nonselective agonists and antagonists of the 5-HT₃ receptor have been characterized pharmacologically. Some of the selective agonists include 2-methyl-5-HT, quipazine, phenylbiguanide (PBG), and methyl-cyanophenylbiguanide (m-CPBG). Some arylbiguanide and arylguanide derivative agonists show increased lipophilicity [65], and may lead to the development of new compounds that cross the blood brain barrier [66]. All of these compounds show some partial agonist characteristics and have different affinity and selectivity for the 5-HT₃ receptor. The most potent and selective of these compounds is m-CPBG [57]. However, m-CPBG does not readily cross the blood brain barrier, thus its use is limited when given systemically to examine effects on brain function. In contrast, many potent and highly

selective 5-HT₃ antagonists have been developed that are rapidly absorbed, readily cross the blood brain barrier and are metabolized by the cytochrome P450 system [67]. These characteristics have led to their relatively wide use clinically (e.g., Tropisetron, Granisetron, Ondansetron, Itasetron, and Alosetron). These drugs are widely used to treat nausea and emesis associated with cancer treatment [68]. Several of these compounds were derived as 5-HT analogs and their biochemistry and pharmacology have been well characterized [57].

5-HT₃ receptor agents have also been shown to affect neurotransmitter and drug levels through other mechanisms. For instance, in addition to increasing neurotransmitter release by its interaction with the 5-HT₃ receptor, m-CPBG has also been shown to inhibit both binding to the dopamine transporter (DAT) and dopamine uptake into synaptosomes prepared from both NAcB and caudate putamen (CP) in the rat with IC₅₀ values in the micromolar range [69-71]. Also, MDL-72222 has been shown to reduce ethanol absorption from the gut in rats [72], but not in pigeons [73]. With regard to early work with 5-HT₃ antagonists, ICS 205-930 inhibits benzodiazepine (BDZ) binding to the GABA-BDZ complex, a characteristic seen with other 5-HT₃ antagonists of the time [74]. These authors suggested this effect resulted from a direct action at the GABA-BDZ complex. Such interactions may play an important role in the outcome of certain experiments depending upon the dosages and species of the subject employed.

3.4. Direct Actions of Drugs of Abuse on the 5-HT₃ Receptor

Ethanol interacts with the 5-HT₃ receptor in some unique ways, which are still being delineated. This interaction has important implications for the effect of ethanol on neurotransmission and the role of 5-HT₃ receptors in alcoholism [54,75-78], and along with preclinical and clinical results, has increased interest in the 5-HT₃ receptor as a potential site for pharmacological treatment of alcohol and drug abuse [79,80]. Ethanol also binds to, and potentiates the function of, other structurally related ligand gated ion channels, such as nACh receptors [78,81]. Recent evidence indicates that ethanol (and other short-chain alcohols) can bind to the 5-HT₃ ion channel directly [82] and enhance their ion current flow [76,83,84]. The potentiating effect of ethanol on the ion channel occurs within milliseconds. This effect is rapidly reversed upon removal of ethanol and is thought to occur because ethanol, and some other alcohols, promotes a stable configuration of the channel in an open state [85]. Additionally, alcohols increase the rates of channel activation while decreasing the rates of deactivation and desensitization [85]. Kinetic studies indicate that these changes are the products of channel gating that is independent of agonist affinity [86,87]. More recent work using recombinant molecular techniques suggests that there may be two distinct sites for allosteric modulation and direct activation in the second transmembrane domain of the 5-HT₃ receptor [88]. Importantly, the concentrations of ethanol which potentiate ion flow through the channel are within the range inducing intoxication in humans, suggesting that the 5-HT₃ receptor plays a role in the acute intoxicating effects of ethanol and possibly other drugs of abuse [54].

In dissociated frontal cortex neurons from mice overexpressing the 5-HT₃ receptor, a current induced by 5-HT or 2-methyl-5-HT was blocked by zacopride, a 5-HT₃ antagonist, and enhanced by ethanol and trichloroethanol, where little or no 5-HT₃ mediated current was observed in neurons from the wild-type mice [89]. In addition, ethanol increases the amplitude currents evoked by 5-HT at the 5-HT₃ receptor [90]. Similar effects have been observed with certain abused inhalants, such as 1, 1, 1-trichloroethane, as well [91]. The direct activation of 5-HT₃ receptors is thought to be one mechanism by which ethanol, and some other drugs of abuse, increases the release of DA in the mesolimbic system. If true, ethanol's site of interaction with the 5-HT₃ receptor would provide an important target for therapeutic agents targeting alcohol abuse and certain other drug addictions.

4. 5-HT₃ Receptors, Dopamine, and Drugs of Abuse

4.1 5-HT₃ Receptors Regulation of DA Neurotransmission

5-HT₃ receptors are known to regulate DA neurotransmission in many brain areas including mesolimbic, mesocortical, and nigrostriatal DA pathways [92]. The VTA and the NAc receive 5-HT inputs from the DRN [93] and activation of these 5-HT projections increases extracellular levels of both 5-HT and DA in the NAc [94]. Despite low densities of 5-HT₃ receptors in mesolimbic areas [95], electrophysiological and microdialysis studies indicate that 5-HT₃ receptors play an important role in regulating mesolimbic DA neuronal activity and release. Administration of 5-HT₃ antagonists reduces spontaneous activity of DA neurons in the VTA [96,97] suggesting that 5-HT exerts tonic control of DA neuronal activity in the mesolimbic system *via* 5-HT₃ receptors in the VTA. However, the opposite effect was found with another 5-HT₃ antagonist, itasetron [98]. Other studies show no effect of 5-HT₃ receptor antagonist administration on extracellular DA levels in the NAc [99-101] or DA release from NAc slices [102]. Additionally, reverse microdialysis application of 0.1 to 0.4 μ M 5-HT into the NAc, elevated local extracellular DA levels, and co-perfusion of the 5-HT₃ antagonist MDL-72222 attenuated this effect [103]. Also, local application of the 5-HT₃ agonist m-CPBG, *via* reverse microdialysis, increased somatodendritic release of DA in the VTA, which was blocked by the co-perfusion of ICS 205-930, a 5-HT₃ antagonist, with ICS 205-930 significantly reducing somatodendritic DA release by itself [104]. Systemic administration of the 5-HT₃ agonist 2-methyl-5-HT increased DA release in the NAc, which was dependent on DA impulse flow [105]. Stimulation of DRN 5-HT neurons results in increased DA release in the NAc, which is blocked by ondansetron or zacopride administration [106]. Reverse microdialysis of 5-HT₃ agonists into the NAc also increases extracellular levels of DA [101,107]. In addition, superfusion of slice preparations of striatum with a 5-HT₃ agonist increased release, or potentiated K⁺-induced release, of DA measured in superfusate [108-110], with similar effects being seen with NAc slice preparations [111].

With regard to 5-HT₃ regulation of DAergic levels in the PFC, reverse microdialysis of the 5-HT₃ antagonist ICS 205,930 increased extracellular DA levels in the PFC [112]. Co-perfusion of MDL-72222 also failed to block the elevation in extracellular DA levels induced with 5-HT in the PFC [113]. However, local perfusion of the selective 5-HT reuptake inhibitor fluoxetine into the PFC elevated DA levels, and this effect was blocked by co-perfusion of ICS 205-930 [114]. In a study using a 5-HT₃ agonist, reverse microdialysis of the 5-HT₃ agonist increased extracellular DA levels in the PFC [115]. Therefore, despite the relatively low density of 5-HT₃ receptors, data from various studies employing neuroanatomy, electrophysiology, neurochemistry, and pharmacology indicate that 5-HT₃ receptors are present and functional in areas of the mesolimbic and nigrostriatal DA systems. Although the effect of 5-HT₃ receptors on basal DA neurotransmission is still under investigation, experiments with selective 5-HT₃ receptor agonists and antagonists consistently show that activation of these receptors increases extracellular levels of DA in the NAc and VTA. Effects in the PFC have been less consistent and may reflect neuroanatomical heterogeneity of 5-HT₃ receptor regulation of DA levels.

4.2. 5-HT₃ Receptors, Drugs of Abuse, and Mesolimbic DA

Operant oral self-administration of ethanol increases extracellular levels of DA and 5-HT in the NAc of both outbred and selectively bred alcohol-preferring rats [116-118]. Co-administration of the 5-HT₃ agonist m-CPBG reduces the threshold dose at which ethanol increases extracellular DA levels in the NAc [101]. Consistent with these data, administration of 5-HT₃ antagonists block the release of mesolimbic DA induced by ethanol administration [101,104,119].

Reports are inconsistent with respect to the effect of 5-HT₃ receptor activity on the neurochemical responses to other drugs of abuse. 5-HT₃ antagonists have been found to attenuate cocaine- [120,121] or morphine- [122-124] induced increases in extracellular levels of DA in the NAc. Others have observed no effect of 5-HT₃ antagonist administration on cocaine- or amphetamine-induced increases in extracellular DA levels in the NAc [124]. On the other hand, overexpression of the 5-HT₃ receptor in mice results in enhanced cocaine-induced DA release in slice preparations [125]. As indicated above, a similar effect has been reported for ethanol [89]. Morphine effects on DA levels were also attenuated by local application of 5-HT₃ receptor antagonists into the VTA [122]. However, both ICS205-930, and another selective 5-HT₃ antagonist, BRL 46470A, failed to prevent morphine-induced increases in cell firing rates in the VTA of chloral hydrate anesthetized rats [126]. These studies indicate that ethanol and, to some extent, other drugs of abuse activate the mesolimbic DA system and these effects may be attenuated with administration of 5-HT₃ receptor antagonists.

4.3. Neuroadaptation: 5-HT₃ Receptors and Dopamine

In addition to acute effects, chronic administration of drugs of abuse and/or 5-HT₃ agents produces neuroadaptive changes at the 5-HT₃ receptor and its control of the mesolimbic DA system. In early work, it was shown that reverse microdialysis of the 5-HT₃ agonist 2-Me-5-HT increased NAc DA and that prior ethanol drinking experience, by selectively bred alcohol-preferring rats enhanced this effect [127]. Moreover, chronic ethanol intake reduced NAc 5-HT activity in these animals. In a more recent study, alcohol-preferring rats given continuous access to 10% ethanol for eight weeks (ND group) showed a significant reduction in the effectiveness of the 5-HT₃ agonist to increase extracellular levels of DA in the NAc compared with a water control group (WC) [128]. This effect was found to persist for at least 2 weeks after the last ethanol exposure in an alcohol deprivation group (AD) [128]. Concurrent with the changes in 5-HT₃ receptor function, DA levels were elevated, as measured by quantitative no-net-flux microdialysis, in both the AD and ND groups compared with the WC group, with no changes in extraction fractions [128]. These data suggest that chronic ethanol administration reduces 5-HT₃ receptor regulation of extracellular DA levels and may serve as an adaptive mechanism to return the system to a more normal state [128,129]. In a study examining 5-HT₃ receptor regulation of somatodendritic DA levels in the VTA, reverse microdialysis of m-CPBG increased extracellular DA levels to a greater extent in the posterior VTA of alcohol preferring rats than that seen in outbred Wistar rats [130]. In addition, the posterior subregion was more sensitive to m-CPBG perfusion than the anterior subregion. Other studies have shown that chronic administration of 5-HT₃ antagonists alters their reduction of extracellular DA levels in the NAc [100,131]. These data are consistent with substantial evidence indicating that chronic administration of 5-HT₃ antagonists results in reduced firing rates, or number of active DA neurons in the VTA [97,98,100,132-134]. Therefore, chronic administration of ethanol and/or 5-HT₃ antagonists produces neuroadaptive changes in the ability of 5-HT₃ receptors to regulate mesolimbic DA neurotransmission.

5-HT₃ receptor activity may also be changed by chronic administration of other drugs of abuse as well. Chronic cocaine treatment reduces the effectiveness of the 5-HT₃ agonist m-CPBG to increase K⁺-induced release of DA in slice preparations of rat NAc [111,135]. Moreover, ondansetron co-administered with the cocaine reverses the effect of continuous cocaine treatment [135]. These results suggest that chronic cocaine treatment may downregulate 5-HT₃ receptors, possibly *via* elevated 5-HT levels, and this may play a role in the development of tolerance to certain cocaine-associated effects [111,135].

5. 5-HT₃ Receptors in Animal Models of Addiction

5.1. Self-Administration

5.1.1. Ethanol Drinking—In early work, it was shown that ondansetron reduced ethanol intake in Wistar rats and C57BL/6 mice under limited access conditions [136]. Bilateral amygdaloid infusions of 5-HT₃ antagonists, tropisetron and ondansetron, significantly reduced ethanol intake in Wistar rats under limited access conditions [137]. In a subsequent study, bilateral intra-accumbal infusions of 2-Me-5-HT, a 5-HT₃ agonist, significantly reduced ethanol intake under limited access conditions as well [138]. Despite these reports on the efficacy of 5-HT₃ antagonists in reducing ethanol intake under limited access conditions, zacopride, a 5-HT₃ antagonist, did not affect limited access ethanol intake but did reduce 24-hr free-choice access to ethanol Sprague-Dawley rats [139,140]. In another study using alcohol-preferring P rats, it was shown that MDL 72222 reduced ethanol under limited access conditions if the time of the access period changed daily, but this 5-HT₃ antagonist did not affect ethanol intake under limited access conditions, if the access period was at the same time every day [141]. Therefore, the conditions of ethanol access are an important variable when determining the efficacy of 5-HT₃ antagonists in reducing ethanol intake. However, the compound and line or strain of rodent may have also played a role in the mixed results discussed above. When assessed under continuous access conditions, 5-HT₃ antagonists consistently reduce ethanol intake. As indicated above, zacopride reduced 24-hr ethanol intake in Sprague-Dawley rats [139]. In heterogeneous stock rats that developed a preference for ethanol, high, but not low, doses of ICS 205-930 reduced 24-hr ethanol intake [142]. Both MDL 72222 and ICS205-930 have been shown to reduce ethanol consumption in P-rats under acquisition, maintenance, and relapse conditions [143]. Also, in alcohol-preferring sP rats, MDL 72222 administered three times a day dose-dependently reduced 24-hr ethanol intake [144]. When assessed under operant oral self-administration, MDL 72222 significantly reduced ethanol self-administration in C57BL/6 mice [145]. Operant oral ethanol self-administration was also reduced with systemic administration of MDL 72222 in P-rats [146], or with ICS205-930 in outbred rats [147].

There is also evidence that 5-HT₃ antagonists reduce stress-induced reinstatement of ethanol self-administration. One study examined the effects of ondansetron and tropisetron on foot-shock reinstatement of ethanol seeking. Wistar rats were trained to operantly self-administer 12% ethanol for 28-31 days and the behavior was extinguished over 9-10 days. Rats pretreated with a 5-HT₃ antagonist prior to ethanol reinstatement displayed a significant reduction in ethanol-seeking behavior [148].

In a drug combination study, it was shown that administration of tropisetron (ICS-205-930) 5.6 mg/kg given in combination with naltrexone significantly reduced ethanol intake more than naltrexone given alone (1.0 mg/kg) without affecting food intake in Sprague-Dawley rats using the sucrose-fade method [149]. In a previous study, a combination of subthreshold doses, doses that were ineffective when given alone, of naltrexone and ondansetron potentially reduced ethanol intake in both mice and rats [150]. These results suggest that the effects of naltrexone may be augmented by 5-HT₃ receptor antagonism by two different mechanisms, which appear to interact, and that the combination treatment may be a promising strategy for the treatment of alcoholism. These findings are consistent with some preliminary studies in humans [151, 152]

Fawn-Hooded rats (FH/Wjd), which display elevated ethanol intake and are a putative animal model of depression, have reduced 5-HT₃ receptor densities in the frontal cortex, hippocampal CA1 region, as well as the medial and lateral amygdala compared with ACI/N rats [153]. In investigations of 5-HT₃ receptor levels of selectively bred rats, it was found that alcohol-preferring AA rats did not differ from their –nonpreferring ANA counterparts, whereas alcohol-

preferring P rats had lower levels in the lateral nucleus and posteromedial cortical nucleus of the amygdala, but not in subregions of the cortex or hippocampus, than their – nonpreferring NP counterparts [154]. However, the latter finding is at odds with a previous report indicating no differences between P and NP rats [95]. Given 5-HT₃ receptor densities are low in limbic regions, including the amygdala, and there were methodological differences between the two studies, it appears the 5-HT₃ is not a strong candidate mediating the genetic propensity for high ethanol consumption in selectively bred rats.

In a study using knock-out mice, it was reported that mice lacking the 5-HT_{3A} receptor subunit drank less ethanol (sweetened or unsweetened) than the wild-type control mouse, and administration of the 5-HT₃ receptor antagonist LY-278-584 reduced ethanol intake in the WT mice but had no effect in the mutant mice [155]. An examination of 5-HT₃ receptor overexpression, which was limited to the forebrain, revealed over-expressing mice drank less ethanol than their non-transgenic counterparts [156]. In a subsequent study, it was reported that 5-HT₃ receptor overexpressing mice have increased sensitivity to the low dose activating, but not the high dose sedating, effects of ethanol compared with the non-transgenic mice [157].

In summary, these studies indicate that the 5-HT_{3A} receptor subunit plays a permissive role in alcohol self-administration in mice and that ethanol self-administration and seeking behavior can be reduced by administration of 5-HT₃ receptor antagonists. However, the efficacy of the antagonist treatment may be dependent on the schedule of ethanol access employed.

5.1.2. 5-HT₃ Receptors and Self-Administration of Drugs of Abuse—Few reports utilizing animal models have demonstrated that 5-HT₃ receptors are significantly involved in self-administration of other drugs of abuse. In combination with pergolide, ondansetron reduced methamphetamine sensitization and reinstatement of i.v. self-administration of methamphetamine during withdrawal in rats [158]. In studies of cocaine self-administration, the 5-HT₃ receptor antagonist ondansetron had no significant effect on cocaine self-administration in rats [159-161], and MDL72222 had no effect on the break point of i.v. cocaine administration in a progressive ratio self-administration paradigm in rats [162]. Also, i.v. nicotine self-administration in rats was not affected by administration of MDL 72222 or ICS205-930 [163]. Using an intravenous self-administration model, Higgins and colleagues [164] found that 5-HT₃ receptor antagonist treatment (ondansetron or MDL72222) had no effect on self-administration of heroin in rats. Conversely, others have reported that treatment with ondansetron or tropisetron reduced oral morphine intake in both acquisition and relapse of morphine intake [165]. In the limited number of preclinical studies conducted thus far, 5-HT₃ receptors appear to be involved in the self-administration of morphine and methamphetamine, but not cocaine, nicotine, or heroin. However, given that environmental factors and cues can influence the outcome of self-administration experiments, as observed with ethanol self-administration, further research is needed to determine if these factors also affect 5-HT₃ regulation of abused drug self-administration.

5.1.3. Intracranial Self-Administration (ICSA)—Intracranial self-administration is a method by which animals directly administer drugs into discrete sites within the brain [166]. This method provides insight into the neuroanatomical pathways that support the ICSA of drugs of abuse and the pharmacology associated with this self-administration behavior. In addition, the technique may be used as a model to implicate neurobiological trigger points in human addiction and identify possible targets for therapeutic intervention. Previous studies have shown that several sites within the mesolimbic DA system support the ICSA of drugs of abuse [2,167]. One pathway of particular interest that shows clear ICSA of drugs of abuse and regional heterogeneity of this behavior is the pathway from the posterior VTA to the shell of the NAc [47,168,169]. It has been shown that ICSA of ethanol directly into the posterior VTA

is blocked by co-infusion with either of the selective 5-HT₃ receptor antagonists zacopride or ICS205-930, indicating that 5-HT₃ receptor activation is necessary for the reinforcing effects of ethanol in this brain region [170]. Similarly, the posterior VTA supports the ICSA of a metabolite of ethanol, acetaldehyde [171], and a condensation product of this metabolite with DA, salsolinol [172]. ICSA of each substance was attenuated by co-administration with ICS 205-930, which indicates 5-HT₃ receptors play a permissive role in acetaldehyde and salsolinol self-administration [171,172]. These data also suggest that acetaldehyde and salsolinol may play a role in the reinforcing properties of ethanol. The posterior, but not anterior, VTA also supports ICSA of cocaine and this behavior is blocked by co-administration of the 5-HT₃ receptor antagonist ICS 205-930 [169]. In a demonstration of the reinforcing properties mediated by 5-HT₃ receptors within the mesolimbic DA system, Rodd and colleagues [173] reported that the posterior, but not anterior, VTA supports the ICSA of the 5-HT₃ agonist m-CPBG. These authors also reported that alcohol-preferring P rats self-infused m-CPBG at lower concentrations than outbred Wistar rats, and this ICSA was attenuated by co-infusion with ICS205-930 or the dopamine D₂ receptor agonist quinpirole.

Related to ICSA, intracranial self-stimulation (ICSS) evaluates brain areas that support direct electrical stimulation, initiated by the subject, through an implanted electrode [48]. Relatively few studies have examined the effects of 5-HT₃ receptor agents on ICSS. Administration of the 5-HT₃ antagonist Y-25130 attenuated the cocaine-induced reduction in reward threshold for ICSS in the MFB [174], suggesting that the rewarding effects of cocaine, as measured by this paradigm, are mediated, at least in part, through 5-HT₃ receptors. However, nicotine-induced reductions in the ICSS threshold in the VTA were blocked by haloperidol and mecamylamine but not ondansetron [175]. Overall, data from ICSA and ICSS studies implicate 5-HT₃ receptors in the reinforcing effects of ethanol and cocaine and suggest that selection for ethanol preference may enhance the role that 5-HT₃ receptors play in self-administration behavior.

5.2. Place Conditioning

As discussed in more detail above, conditioned place preference (CPP) is one paradigm used to assess a drug's abuse liability. A compound that reduces, or abolishes a CPP would also be expected to reduce self-administration of the drug. Low doses of ethanol resulted in a CPP in rats that had been conditioned to fear stimuli, and ondansetron pretreatment before conditioning trials significantly reduced the CPP [176]. Moreover, ondansetron also significantly attenuated enhancement of an ethanol-induced CPP by morphine, or a delta opioid agonist, suggesting that 5-HT₃ receptors may play a role in mediating the rewarding properties of ethanol observed under psychological stress. In addition, both MDL72222 and ICS205930 blocked an ethanol CPP in which pyrazole was co-administered with ethanol during the training sessions [177].

Mice overexpressing the 5-HT₃ receptor in brain show reduced CPP for cocaine at 10 mg/kg but not 4 mg/kg [125]. Since these animals show increased sensitivity to cocaine in a variety of other behavioral and neurochemical tests, one explanation for this finding is that the place-conditioning dose-response curve is shifted to the left for cocaine preference and the 10 mg/kg dose produced an excessive response that resulted in a reduced place preference score [125]. Administration of MDL72222 attenuated a CPP induced with cocaine and mazindol, but not methylphenidate in rats [121]. Similarly, both MDL72222 and ICS205-930 reduced a CPP induced by both cocaine and methamphetamine [178]. Others have found no effects of 5-HT₃ antagonists on cocaine-induced CPP, with MDL72222, tropisetron, nor ondansetron affecting a CPP induced by cocaine [179]. Moreover, these authors reported that ondansetron had no effect on cocaine-induced increases in extracellular DA in the NAc. Administration of MDL72222 attenuated a CPP induced by methylenedioxymethamphetamine (MDMA) in rats [180]. In other work, administration of 5-HT₃ antagonists was found to reduce a CPP

induced by nicotine and morphine but not amphetamine [181,182]. Using an unbiased place-conditioning protocol the 5-HT₃ antagonism of a CPP induced by morphine has been confirmed by others [183]. In addition, administration of the 5-HT₃ antagonist MDL-72222 was found to dose dependently block a CPP induced by the drug of abuse 1-benzylpiperazine in rats [184]. The different findings reported above may stem from differences in the experimental methodology of CPP induction as well as different doses of the drug(s) administered.

5.3. Drug Discrimination

The ability of a rat to discriminate between the effects of ethanol or drugs of abuse and saline (known as discriminative stimulus effects) is positively associated with their abuse liability. A compound that reduces drug discrimination would be a candidate for the treatment of ethanol and/or drug abuse [185]. Although one study found that 5-HT₃ agonists and antagonists appear to have no discriminative stimulus properties [186], an earlier study [187] reported that the partial 5-HT₃ agonist meta-chlorophenylguanidine (MD-354) has discriminative stimulus properties that generalized to quipazine (ED₅₀=0.2 mg/kg), m-CPBG, ED₅₀=1.4 mg/kg), 2-methyl 5-HT (ED₅₀=4.5 mg/kg), 1-(2-naphthyl)biguanide (2-NBG, ED₅₀=1.9 mg/kg), and N-(2-naphthyl)guanidine (2-NG, ED₅₀=0.7 mg/kg). Moreover, these stimulus properties of MD-354 were attenuated by the administration of either zacopride or tropisetron [187].

Several studies have examined the potential role of 5-HT₃ receptors in mediating the discriminative stimulus properties of ethanol. Both ICS205-930 and MDL72222, but not zacopride, attenuated the discriminative stimulus properties of ethanol in pigeons [73]. In a study with rats trained to discriminate ethanol (1.25 g/kg, i.p.) from saline, there were biphasic effects of the 5-HT₃ antagonist ICS 205-930 [188]. Administration of 0.01 mg/kg ICS 205-930 significantly reduced ethanol's discriminative stimulus effects while higher doses showed enhancement without affecting response rates or ethanol elimination. In a study with mice which examined both operant self-administration and ethanol discrimination, MDL 72222 significantly reduced operant ethanol self-administration but did not affect ethanol discrimination [145]. In rats, discriminative stimulus effects of a 1.0 g/kg, i.p. ethanol administration was not attenuated by tropisetron or ondansetron, and m-CPBG did not substitute for the stimulus with central or peripheral administration [189]. A comprehensive examination of both 5-HT₃ receptor over-expression and 5-HT₃ antagonism in mice revealed neither 5-HT₃ receptor over-expression nor treatment with MDL 72222 or ondansetron altered GABAergic agonist or glutamatergic antagonist ethanol-like discriminative stimulus effects [190].

The partial 5-HT₃ agonist MD-354 was shown to enhance the discriminative stimulus properties of low doses of (+) amphetamine [191], similar to a finding with the 5-HT₃ antagonist ICS205-930 [192]. Conversely, the discriminative stimulus properties of methamphetamine in pigeons were unaffected by administration of 5-HT₃ antagonists including MDL72222 [193]. Similarly, the discriminative stimulus effects of amphetamine were not affected by administration of a number of selective 5-HT₃ receptor antagonists in rats [194].

In most studies, 5-HT₃ receptors do not mediate the discriminative stimulus effects of cocaine [195-198], with MDL72222, ondansetron, and ICS205-930 not affecting the discriminative stimulus effects of cocaine. Moreover, m-CPBG did not show robust substitution for the cocaine cue, and cocaine did not substitute for m-CPBG in m-CPBG trained rats [195,197, 198]; although see [199]. Systemic administration of 5-HT₃ antagonists including MDL 72222, LY 278584 and ondansetron had no significant effects on the discriminative stimulus properties of cocaine in pigeons [196]. The discriminative stimulus properties of morphine were also unaffected by systemic administration of MDL72222, ICS205-930, or ondansetron in rats

[200], with MDL72222 also not blocking the discriminative stimulus properties of the NMDA agonist ketamine in rats [201].

5.4. Locomotor Activity

The behavioral measure locomotor activity is often used to assess the pharmacology of the activating effects of drugs of abuse. Using DBA/2N mice, it has been reported that neither ondansetron nor ICS205-930 had any effect on the locomotor activating effects of ethanol or cocaine [202]. In other work, m-CPBG modestly enhanced the locomotor activating effects of ethanol in rats [203], with MDL 72222 also reducing hyperlocomotion induced by ethanol in adult female rats and in adolescent male and female rats [204]. Microinjection of the 5-HT₃ agonist 2-Methyl-5HT or d-amphetamine into the VTA, but not NAcB, increased locomotor activity with both being blocked by co-administration of ondansetron, but not granisetron, in rats [205,206]. Mice overexpressing the 5-HT₃ receptor were more sensitive than wild-type mice to the locomotor activating effects of cocaine and methamphetamine [125]. Also, targeted deletion of the 5-HT_{3A} receptor subunit gene reduced the induction of cocaine sensitization in mice [207]. Administration of zacopride, ICS205-930, MDL72222, or ondansetron reduced cocaine-induced hyperlocomotion in rats [208,209]. Similar effects of ICS205-930 and zacopride have also been found in mice [210]. Regarding central pharmacological blockade, bilateral microinjections of ondansetron into the core of the NAcB attenuated increased locomotor activity induced by cocaine [211] or amphetamine [212] administration in rats.

Other investigators have focused on the sensitization of the activating effects of drugs of abuse. One group found that cocaine-induced sensitization was blocked by co-administration of azasetron during the cocaine pretreatments in mice [213,214]. Azasetron administration attenuated the expression of sensitization induced with repeated methamphetamine administration as well [214]. Similarly, MDL72222 reduced methamphetamine-induced sensitization of its hyperactivating effects in mice [215]. However, in other work, although administration of 5-HT₃ receptor antagonists partially blocked the acute locomotor activating effects of cocaine, the 5-HT₃ antagonists did not block sensitization of cocaine-induced hyperlocomotion in rats [216a].

Studies thus far do not support a role for 5-HT₃ receptors in nicotine-induced locomotor activation. A series of 5-HT₃ receptor antagonists including ondansetron, bemisetron, granisetron and tropisetron were tested for effects on nicotine-induced hyperlocomotion in rats. None of the antagonists tested showed any effect on either acute or chronic nicotine-induced motor activity [216b]. A similar lack of effect was observed with MDL72222 and ICS205-930 [163]. Regarding morphine, ICS205-930, ondansetron, and zacopride have all been shown to attenuate morphine-induced hyperactivity in rats [123].

5.5. Other Behaviors

In a study addressing ethanol-induced aggression, it was found that the 5-HT₃ receptor antagonists ondansetron and zacopride reduced ethanol-induced aggression in ethanol-exposed CFW mice with both highly aggressive and mildly aggressive reactions to intruders. Zacopride also reduced aggression in B6SJL/F2 wild-type and transgenic 5-HT₃ over-expressing mice, but at a much higher dose as compared with the CFW mice [217]. This and other studies underscore the importance of genetic background in the analysis of alcohol or drug self-administration phenotypes in transgenic and selected animals [218].

6. Clinical Effects of 5-HT₃ Antagonist Treatment

6.1. Alcohol Drinking

In a six week, double-blind, placebo-controlled study of alcohol-dependent males, ondansetron treatment of 0.5 mg (but not 4 mg) reduced alcohol consumption in a heavy drinking subgroup [219]. In a larger placebo-controlled, double-blind study conducted over 12 weeks, ondansetron treatment reduced ethanol consumption in early onset alcoholics but not late onset alcoholics given a twice daily dosage between 1 and 16 ug/kg [79]. The differential effect of ondansetron in early vs late onset alcoholics was also found in an open-label study [220]. Ondansetron treatment also reduces ethanol craving in early onset alcoholics [221]. Since 5-HT systems are thought to have reduced function in early onset alcoholics [222,223], 5-HT₃ receptors may be upregulated in these individuals, and treatment with 5-HT₃ receptor antagonists may be particularly effective in treating this subgroup of alcoholics [79,222,224]. This may also explain why fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) reduce drinking in heavy drinking social drinkers [225], but SSRI treatment actually increased ethanol intake [226] or was not different from placebo [227] in early-onset alcoholics. In an open-label study, ondansetron treatment was also effective in reducing ethanol drinking in alcohol-dependent adolescents [228]. Ondansetron may also be a candidate for combination therapy with other drugs that reduce alcohol drinking. Combined with naltrexone, ondansetron significantly reduced measures of ethanol drinking [151] and craving [152,229] in early onset alcoholics. In social drinkers, ondansetron treatment increased the stimulant, sedative, and discriminative effects of ethanol without affecting the psychomotor effects, suggesting that ondansetron may reduce ethanol drinking by increasing subjective intoxication and/or the aversive effects of ethanol [230]. Overall, the clinical studies to date suggest that 5-HT₃ receptor antagonist administration may be an effective treatment for alcoholism. This treatment shows particular effectiveness in alcoholics that are considered early-onset and high-risk (type II), and as an adjunctive treatment with naltrexone. Although the results are promising, additional controlled studies are needed with different antagonists to better establish the relationship between 5-HT₃ receptor antagonism and alcohol drinking, craving, and relapse in different sub-groups of alcoholics.

6.2. Cocaine Use

Few studies have examined the effects of 5-HT₃ agents on human cocaine use. One recent placebo-controlled double-blind study in male cocaine users showed that ondansetron treatment (4.0 mg/twice a day) resulted in an improvement in the weekly percentage of non-use days compared with placebo [231]. Although much more study is needed to determine the effectiveness of 5-HT₃ receptor antagonists in treating cocaine addiction, this study suggests that ondansetron may have some clinical treatment value.

6.3. Amphetamine, Nicotine, Benzodiazepines, and Opiates

Ondansetron has also been studied in the treatment of amphetamine addiction. In some preliminary studies, increases in positive subjective mood and euphoria [232,233] and anorexia [234] induced with d-amphetamine were reduced with ondansetron treatment. However, recently, a double-blind, placebo-controlled study of 150 methamphetamine-dependent subjects given ondansetron (0.25 to 4.0 mg, b.i.d) in an 8-week trial, in conjunction with cognitive behavioral therapy, had no effect on any parameters of methamphetamine use, craving, or clinical signs [235]. Together these studies suggest that while some characteristic psychological and physiological responses to d-amphetamine may be reduced with ondansetron treatment, it appears to be ineffective in the treatment of methamphetamine addiction, at least in the dose range administered. In the few published reports that have examined the ability of 5-HT₃ receptor antagonists to reduce nicotine [236-238], benzodiazepine [239], and opiate [240] addiction, 5-HT₃ antagonist treatment was found to

be ineffective in reducing drug use, withdrawal effects, or craving. Overall, clinical treatment with 5-HT₃ antagonists was well tolerated and resulted in few adverse effects, the most common being constipation, headache, and dizziness.

Conclusions

Current evidence indicates that the 5-HT₃ receptor plays a role in the actions of drugs of abuse, and the preclinical and clinical data show many parallels (see Tables 1 and 2). Although the density of this ligand-gated ion channel is relatively low in most areas of the mesolimbic DA system, 5-HT₃ receptors clearly regulate the activity of DA neurons within this system. Activation of these receptors generally enhances both mesolimbic DA neuronal activity and DA release. As a drug of abuse, ethanol has been shown to interact in a unique way with the 5-HT₃ receptor. Ethanol directly potentiates agonist-induced activity of the 5-HT₃ receptor, and this may be an important mechanism by which ethanol produces effects on the mesolimbic reward system and may play a role in the development of alcoholism as well. There is some evidence that other drugs of abuse may activate this system, at least partially, through 5-HT₃ receptors. Chronic administration of ethanol, cocaine, or 5-HT₃ receptor antagonists produces neuroadaptive changes in mesolimbic DA neurotransmission. The data also suggest that chronic ethanol or cocaine treatment may downregulate 5-HT₃ receptor function resulting in altered basal DA release, and reduced ability of 5-HT₃ agonists to enhance DA release. In addition, chronic administration with 5-HT₃ antagonists reduces the firing rates, or number, of active DA neurons in the VTA.

In preclinical drug self-administration studies, the 5-HT₃ receptor is clearly involved in ethanol self-administration. Mice lacking the 5-HT_{3A} receptor subunit do not self-administer ethanol and ethanol drinking and seeking behavior can be attenuated by administration of 5-HT₃ receptor antagonists. However, the efficacy of 5-HT₃ receptor antagonists appears to be dependent, at least in part, on environmental cues and the schedule of ethanol access. Treatment with 5-HT₃ antagonists also reduces the self-administration of morphine and methamphetamine, but has consistently shown no affect on systemic self-administration of other drugs of abuse including cocaine, nicotine, or heroin, suggesting that 5-HT₃ receptors may not be as effective in treating addiction to these substances.

Evidence from ICSSA and ICSS studies implicate 5-HT₃ receptors in mesolimbic reinforcement and suggest that activation of 5-HT₃ receptors is necessary for the central reinforcing properties of cocaine and ethanol. Moreover, selection for ethanol preference may lead to an enhanced role for 5-HT₃ receptors in ethanol reinforcement. Similarly, studies employing place-conditioning have found that 5-HT₃ antagonist administration reduces a CPP induced with ethanol, morphine, nicotine, and 1-benzylpiperazine, and in some studies with cocaine and methamphetamine as well, suggesting that some drug-induced reward, as assessed by the CPP paradigm, may be mediated by 5-HT₃ receptors.

In the majority of studies, the discriminative stimulus effects of ethanol are at least partially mediated through 5-HT₃ receptors as these effects are attenuated by administration of 5-HT₃ receptor antagonists. However, most evidence indicates that 5-HT₃ receptors do not mediate the discriminative stimulus properties of cocaine, morphine, or ketamine. Conversely, a majority of studies indicate that 5-HT₃ receptors are involved with the locomotor activating effects of cocaine and methamphetamine, but not nicotine.

Clinical studies with 5-HT₃ receptor antagonist treatment in drug abuse show it may be an effective treatment for alcohol abuse in certain subgroups of alcoholics. Consistently, the administration of ondansetron to early-onset alcoholics appears effective in reducing relapse-associated behavior. It may also be effective in treatment of alcohol dependent adolescents and

as a complementary treatment with naltrexone. However, additional studies with different selective antagonists in different populations and subgroups of alcoholics will be needed to determine if 5-HT₃ receptor antagonism is an effective treatment for alcoholism in general. One recent study suggests that ondansetron may also be a potential treatment for cocaine-dependent individuals. However, in studies with chemically dependent individuals, 5-HT₃ antagonist treatment appears to be ineffective in treating nicotine, amphetamine, benzodiazepine, or opiate addiction.

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Abbreviations

5-HT	5-Hydroxytryptamine, serotonin
DA	Dopamine
VTA	Ventral tegmental area
PFC	Prefrontal cortex
GABA	Gamma aminobutyric acid
ICSA	Intracranial self-administration
NAcb	Nucleus accumbens
ICSS	Intracranial self-stimulation
MFB	Medial forebrain bundle
CPP	Conditioned place preference
nACh	Nicotinic acetylcholine
DRN	Dorsal raphe nucleus
PBG	Phenylbiguanide
m-CPBG	Methyl-cyanophenylbiguanide
DAT	Dopamine transporter
CP	Caudate putamen
BDZ	Benzodiazepine
SSRI	Selective serotonin re-uptake inhibitor

Table 1
Effect of 5-HT₃ Receptor Antagonists on Dopamine Neurotransmission

Antagonist	Measurement	Brain area	Effect	Duration	Reference
Ondansetron (GR38032F)	MD	NAcb	↔ Basal levels	Acute	[99]
	MD	NAcb	↓ Agonist effect *	Acute	[106]
	MD	NAcb	↓ Agonist effect	Acute	[107]
	MD	NAcb	↓ Morphine effect	Acute	[123]
	MD	NAcb	↓ Morphine effect	Acute	[124]
	MD	NAcb	↔ Cocaine effect	Acute	[124]
	MD	NAcb	↔ Amphetamine effect	Acute	[124]
	SF	NAcb	↓ Cocaine DR of 5-HT ₃ Receptors	Chronic	[135]
Tropisetron (ICS205-930)	SF	NAcb, STR	↔ Agonist effect	Acute	[102]
	MD	NAcb	↓ Agonist effect	Acute	[101]
	MD	VTA	↓ Agonist effect	Acute	[104]
	SF	STR	↓ Agonist effect	Acute	[108,109]
	SF	NAcb	↓ Agonist effect	Acute	[111]
	MD	PFC	↑ Basal levels	Acute	[112]
	MD	NAcb, STR	↓ EtOH effect	Acute	[119]
	MD	NAcb	↓ EtOH effect	Acute	[101]
	MD	VTA	↓ EtOH effect	Acute	[104]
	MD	NAcb, VTA	↓ Morphine effect	Acute	[122]
	MD	NAcb	↓ Morphine effect	Acute	[123]
	MD	VTA	↓ Basal levels	Acute	[104]
	MD	NAcb	↔ Basal levels	Acute	[101]
Zacopride	MD	NAcb	↓ Agonist effect *	Acute	[106]
	MD	PFC	↓ Agonist effect	Acute	[115]
	MD	NAcb	↓ Agonist effect	Acute	[107]
	MD	NAcb	↓ Cocaine effect	Acute	[120]
MDL72222	SF	NAcb, STR	↔ Agonist effect	Acute	[102]
	MD	PFC	↔ Agonist effect	Acute	[113]

Antagonist	Measurement	Brain area	Effect	Duration	Reference
	MD	NAcb	↓ Cocaine effect	Acute	[121]
	MD	NAcb	↓ Morphine effect	Acute	[124]
	MD	NAcb	↔ Cocaine effect	Acute	[124]
	MD	NAcb	↔ Amphetamine effect	Acute	[124]
Granisetron	EC	NAcb	↓ Agonist effect	Acute	[105]
	MD	NAcb	↓ Morphine effect	Acute	[123]
BRL 46470A	EP	VTA	↔ Neuron firing rates	Acute	[126]
Zatosetron (LY277359)	EP	VTA	↓ # Of active neurons	Acute	[97,133]
	EP	VTA	↓ # Of active neurons	Chronic	[133]
Itasetron (DAU6215)	EP	VTA	↑ # Of active neurons	Acute	[98]
	EP	VTA	↓ # Of active neurons	Chronic	[98]
	MD	NAcb	↔ Basal levels	Acute	[100]
	MD	NAcb	↓ Basal levels	Chronic	[100]
MDL 73,147EF	EP	VTA	↓# Of active neurons	Chronic	[132]
	EP	VTA	↔ # Of active neurons	Acute	[132]

EC = electrochemistry; EP = electrophysiology; MD = microdialysis; SF = superfusion; DR = downregulation;
* effect of DRN stimulation; all studies performed in rats.

Table 2
Effect of 5-HT₃ Antagonists on Drug Self-Administration Models

Antagonist	Behavior	Schedule	Drug	Effect	Species	Reference
Ondansetron (GR38032F) Ondansetron ⁿ	Seeking	Continuous	EtOH	↓	Rat	[148]
	Drinking	Scheduled	EtOH	↔	Rat	[140]
	Drinking	Scheduled ^{\$}	EtOH	↓	Mice	[136]
	i.v SA	Scheduled	Methamphetamine	↓	Rat	[158]
	i.v SA	Scheduled	Cocaine	↔	Rat	[159-161]
	i.v SA	Scheduled	Heroin	↔	Rat	[164]
	Drinking	Continuous	Morphine	↓	Rat	[165]
	Drinking	Continuous	EtOH	↓	Human ^h	[219]
	Drinking	Continuous	EtOH	↓	Human ^e	[79]
	Drinking	Continuous	EtOH	↔	Human ^l	[79]
	Drinking	Continuous	EtOH	↓	Human ^e	[220]
	Drinking	Continuous	EtOH	↔	Human ^l	[220]
	Drinking	Continuous	EtOH	↓	Human ^c	[228]
	Drinking	Continuous	EtOH	↓	Human	[151]
	SA ^d	Continuous	Cocaine	↓	Human	[231]
	SA ^m	Continuous	Methamphetamine	↔	Human	[235]
	Smoking	Continuous	Nicotine	↔	Human	[236-238]
	Oral SA	Continuous	Benzodiazepine	↔	Human	[239]
Tropisetron (ICS205-930)	Drinking	Continuous	EtOH [*]	↓	Rat	[149]
	Seeking	Continuous	EtOH	↓	Rat	[148]
	Drinking	Continuous	EtOH	↓	Rat	[142]
	Drinking	Continuous	EtOH	↓	Rat ^a	[141,143]
	Drinking	Scheduled	EtOH	↔	Rat ^a	[141]
	Drinking	Variable	EtOH	↓	Rat ^a	[141]
	Drinking	Scheduled	EtOH	↓	Rat	[147]
	Drinking	Continuous	Morphine	↓	Rat	[165]

Antagonist	Behavior	Schedule	Drug	Effect	Species	Reference
	iv SA	Scheduled	Nicotine	↔	Rat	[163]
	ICSA/pVTA	Scheduled	EtOH	↓	Rat	[170]
	ICSA/pVTA	Scheduled	Acetaldehyde	↓	Rat ^a	[171]
	ICSA/pVTA	Scheduled	Salsolinol	↓	Rat	[172]
	ICSA/pVTA	Scheduled	Cocaine	↓	Rat	[169]
	ICSA/pVTA	Scheduled	m-CPBG	↓	Rat	[173]
Zacopride	Drinking	Continuous	EtOH	↓	Rat	[139]
	Drinking	Scheduled	EtOH	↔	Rat	[139]
	Drinking	Scheduled	EtOH	↔	Rat	[217]
	ICSA/pVTA	Scheduled	EtOH	↓	Rat	[170]
MDL72222	Drinking	Continuous	EtOH	↓	Rat ^a	[144]
	Drinking	Continuous	EtOH	↓	Rat ^a	[141,143]
	Drinking	Scheduled	EtOH	↔	Rat ^a	[141,146]
	Drinking	Variable	EtOH	↓	Rat ^a	[141,146]
	iv SA BP	Scheduled	Cocaine	↔	Rat	[162]
	iv SA	Scheduled	Heroin	↔	Rat	[164]
	iv SA	Scheduled	Nicotine	↔	Rat	[163]
Granisetron	Drinking	Scheduled	EtOH	↔	Rat	[140]
SC-51296	Drinking	Scheduled	EtOH	↔	Rat	[140]
LY278-584	Drinking	Continuous	EtOH	↓	Mice	[155]
	Drinking	Continuous	EtOH	↔	Mice ^b	[155]

iv SA = intravenous self-administration; BP = break point;

* Enhanced naltrexone effect on EtOH intake;

^a Alcohol-preferring line;

^b 5-HT3A knock-out mice;

[§] Chronic;

^h Heavy drinkers;
^e Early onset alcoholics;
^l Late onset alcoholics;
^c adolescent alcoholics;
ⁿ in combination with naltrexone;
^d smoking, i.v., or intranasal;
^m oral, nasal, smoking, i.v; non-i.v. injection.