

REVIEW ARTICLE

Histamine, histamine H₃ receptor, and alcohol use disorder

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Alcohol use disorder is associated with several mental, physical, and social problems. Its treatment is difficult and often requires a combination of pharmacological and behavioural therapy. The brain histaminergic system, one of the wake-active systems that controls whole-brain activity, operates through three neuronal GPCRs. The histamine H₃ receptor (Hrh3), which is expressed in many brain areas involved in alcohol drinking and alcohol reward, can be targeted with a number of drugs developed initially for cognitive disorders and/or disorders related to sleep, wakefulness, and alertness. In all rodent alcohol drinking models tested so far, H₃ receptor antagonists have reduced alcohol drinking and alcohol-induced place preference and cue-induced alcohol reinstatement. Several H₃ receptor antagonists tested and found to be safe for humans could be subjected to clinical tests to treat alcohol use disorder. Preference should be given to short-acting drugs to avoid the sleep problems associated with the wake-maintaining effects of the drugs.

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1 | ALCOHOL AND BRAIN NEUROTRANSMITTER SYSTEMS

Alcohol use disorder (AUD) is a complex disease, which is despite recent developments still a major health problem (Abrahamo, Salinas, & Lovinger, 2017). Drug treatments, based on known targets or circuits, including those tested or already in use (disulphiram, naltrexone, acamprosate, topiramate, baclofen, and gabapentin) all require complementary behavioural therapy, and the results are often still not satisfactory (Abrahamo et al., 2017; Korpi et al., 2015; Vuoristo-Myllys, Lipsanen, Lahti, Kalska, & Alho, 2014).

The brain histaminergic system in mammals comprises cell bodies in the posterior basal hypothalamus in an area named the tuberomammillary nucleus (TMN; Panula, Airaksinen, Pirvola, & Kotilainen, 1990; Panula,

Yang, & Costa, 1984; Watanabe et al., 1984), which sends projections to all major parts of the brain (Inagaki et al., 1988; Panula, Pirvola, Auvinen, & Airaksinen, 1989). Alcohol is a simple compound that interacts with target cells mainly through hydrogen bonding and weak hydrophobic interactions (Abrahamo et al., 2017) in addition to specific neurotransmitter receptors, and thus, high concentrations are needed for reinforcing and sedative effects. Most brain areas are thus affected by systemic intake of alcohol, which affects cells and circuits in many brain areas that receive histaminergic innervation (Inagaki et al., 1988; Panula, Pirvola, Auvinen, & Airaksinen, 1989). Alcohol has well-characterized effects on GABA and glycine receptors and less well-understood effects at the glutamate **NMDA receptor** (Abrahamo et al., 2017; Korpi et al., 2015). Since these receptors and some of the signalling pathways also directly affected by alcohol are found in many aminergic neurons, these neurons are among the direct or indirect targets of alcohol.

Initial acute effects of alcohol include increased inhibition through **GABA_A receptor** potentiation, reduced excitation through block of NMDA and **AMPA** receptors, activation of the mesolimbic system through

Abbreviations: AA, ALKO alcohol (type of alcohol-preferring rat); ANA, ALKO non-alcohol (type of alcohol non-preferring rat); AUD, alcohol use disorder; NAcc, nucleus accumbens; RT, randomized treatment; SN, substantia nigra; TMN, tuberomammillary nucleus; VTA, ventral tegmental area

increased **dopamine** release, and effects (relaxation, euphoria, and anxiolysis) mediated by neuropeptide systems (Korpi et al., 2015). Withdrawal symptoms are associated with reduced GABA_A receptor signalling, increased excitation mediated by NMDA and AMPA receptor activation, and reduced dopamine release in the mesolimbic system. These plastic changes affect a number of brain areas, including the orbitofrontal and prefrontal cortex, dorsomedial, dorsolateral and ventral striatum (nucleus accumbens [Acb]), lateral habenula, amygdala, bed nucleus of the stria terminalis, substantia nigra (SN), ventral tegmentum, and some brainstem areas. Although none of the well-known behavioural effects of alcohol are directly linked to the histaminergic neuron system, many of these areas express high levels of at least one of the three neuronal G-protein-coupled histamine receptors, postsynaptic **H₁ receptor**, **H₂ receptor**, or pre or postsynaptic **H₃ receptor** (Hrh3). In the neurons that express H₃ receptors, neurotransmitter release is likely affected by histamine through this receptor or by constitutive activity of the H₃ receptor (Panula et al., 2015).

2 | GPCRS AS TARGETS FOR AUD

GPCRs are among the most utilized drug targets. Not surprisingly, several GPCRs have been tested in rodents as potential targets to treat AUD. Selective receptor agonists and antagonists and gene-modified animals have been used in these experiments. Since several methods have been used with variable controls, the results have not always been easy to interpret. Among the most studied receptor are the **opioid receptors** (Contet, Kieffer, & Befort, 2004; Matthes et al., 1996), dopamine **D₁** and **D₂ receptors** (Cunningham et al., 2000; El-Ghundi et al., 1998), **5-HT receptors** (Crabbe et al., 1996; de Bruin et al., 2013), **metabotropic glutamate receptors** (Zhou et al., 2013), **cannabinoid receptors** (Hungund, Szakall, Adam, Basavarajappa, & Vadasz, 2003; Naassila, Pierrefiche, Ledent, & Daoust, 2004), and **muscarinic receptors** (de la Cour et al., 2015). Indeed, repeated alcohol administration increases levels of methionine enkephalin-Arg-Phe levels in the periaqueductal gray (Lindholm, Ploj, Franck, & Nylander, 2000), and acute moderate doses induce release of methionine-enkephalin in the NAcc (Marinelli, Bai, Quirion, & Gianoulakis, 2005). **Naltrexone**, which preferentially blocks opioid **μ receptors**, is one of the few accepted treatments for AUD. Naltrexone decreases alcohol consumption in rhesus monkeys (Altshuler, Phillips, & Feinhandler, 1980) and rats (Stromberg, Casale, Volpicelli, Volpicelli, & O'Brien, 1998) and is one of the few available drugs currently accepted for treatment of AUD despite challenges met when treating heavy drinkers (Vuoristo-Myllys, Lahti, Alho, & Julkunen, 2013). The H₃ receptor was not initially among the targets predicted to treat AUD, but the findings on a robust reduction in alcohol drinking in both rats (Lintunen et al., 2001) and mice (Nuutinen, Karlstedt, Aitta-Aho, Korpi, & Panula, 2010) were initially unexpected, but have since been independently verified.

3 | HISTAMINE AND H₃ RECEPTORS IN BRAIN AREAS RELEVANT FOR AUD

The H₃ receptor is widely expressed in the brain of all vertebrates studied (Pillot et al., 2002; Sallmen, Lozada, Anichtchik, Beckman, & Panula, 2003; Sundvik et al., 2011; Tardivel-Lacombe et al., 2000). In rat brain, the

different isoforms show slightly different expression patterns (Drutel et al., 2001), but the significance of this and detailed roles of the isoforms are not known. In general, the H₃ receptor is expressed in histaminergic neurons, which is in agreement with its role as an autoreceptor, and in many brain regions. One of the most consistent findings is its abundant expression in telencephalic structures (Figure 1), such as the striatum and cerebral cortex, and dorsal thalamus (Jin, Kalimo, & Panula, 2002; Jin & Panula, 2005; Panula & Nuutinen, 2013; Panula, Sundvik, & Karlstedt, 2014). A comparison of H₃ receptor mRNA and receptor radioligand binding studies and the knowledge of neuronal pathways suggests that this receptor is found in several critically important brain structures and pathways related to cognitive functions, motivation, aversion and pleasure, and locomotion, such as the thalamocortical, hypothalamocortical, and striatonigral systems (Panula & Nuutinen, 2013; Figure 2). Both the expression of this receptor and receptor radioligand binding are high in limbic structures such as the hippocampus and amygdala (Haas & Panula, 2003). Interestingly, the tuberomammillary nucleus in which the histaminergic neurons reside receives its heaviest innervation from the infralimbic or medial prefrontal cortex in the rat (Ericson, Blomqvist, & Kohler, 1991), suggesting that the histaminergic neurons get direct inputs from this brain region, which is in a key area for decision making and executive functions. The H₃ receptor is highly expressed in this area of the brain.

Brain areas important in AUD include the mesocorticolimbic system and extended amygdala including the nucleus of the stria terminalis and habenula (Abraham et al., 2017; Koob & Volkow, 2016; Korpi et al., 2015; Figure 2). H₃ receptor mRNA expression and receptor radioligand binding are high in almost all of these areas (Figures 1 and 2), which render it difficult to identify a sole site of action of H₃ receptor antagonists on alcohol drinking or alcohol-induced place preference. One of the few sites where these drugs affect a significant signalling pathway for these behaviours is the striatum, where an H₃ receptor antagonist has been shown to regulate dopaminergic signalling (Nuutinen et al., 2016). In the striatum, dopamine receptor signalling was increased by dopamine receptor agonists **quinpirole** and **SKF38393** in wild type but not in H₃ receptor knockout mice (Kononoff Vanhanen, Nuutinen, Tuominen, & Panula, 2016). Even in this location, several H₃ receptor expressing pathways merge (Panula & Nuutinen, 2013). Obviously, systemic administration of H₃ receptor antagonists, which is also the most appropriate route for evaluating mechanisms intended to be clinically relevant, affects all the circuits in the brain in which the H₃ receptor is active. The behavioural consequences of systemic administration naturally represents the sum effect of all these targeted brain areas and circuits. Site targeted administration schedules to study the contribution of distinct H₃ receptor-expressing cell types have not yet been applied to address alcohol-related behaviours. Since these H₃ receptor-expressing cells release many other neurotransmitters regulated by H₃ receptors, the role of H₃ receptor antagonists in alcohol-related behaviours is likely due to circuits involving many of these transmitters.

4 | ALCOHOL AND HISTAMINE–DOPAMINE INTERACTIONS

The ventral tegmentum, which harbors dopaminergic and GABAergic neurons, is crucial for the development of alcohol-related behaviours:

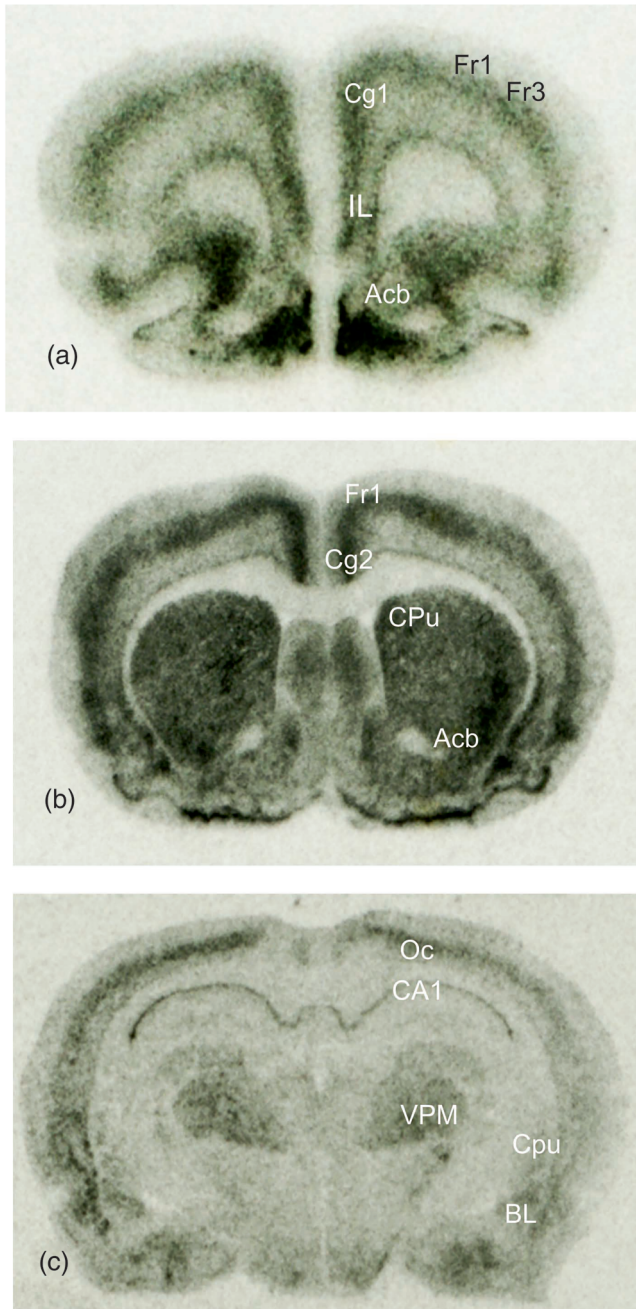


FIGURE 1 In situ hybridization of rat brain sections with ^{35}S -labelled oligonucleotide probes for histamine H_3 receptor at (a) 2.70, (b) 0.70, and (c) -3.60 mm from bregma shows a clear laminar expression of H_3 receptor mRNA in various parts of the cortex (infralimbic cortex [IL], cingulate cortex area 1 [Cg1], frontal cortex, area 1 [Fr1], frontal cortex, area 3 [Fr3], and occipital cortex [Oc]) and high expression throughout the caudate-putamen (striatum; CPu) and nucleus accumbens (Acb). IL and Cg1 represent parts of rat brain area thought to correspond to parts of prefrontal cortex in humans. BL: basolateral amygdaloid nucleus; CA1: field 1 of cornu ammonis in hippocampus; Cg2: cingulate cortex area 2; VPM: ventral posteromedial thalamic nucleus

an injection of the opioid antagonist methylnaloxonium (a non-selective opioid antagonist) or **baclofen** (a GABA_B receptor agonist) into the ventral tegmental area (VTA) but not into the NAcc decreases

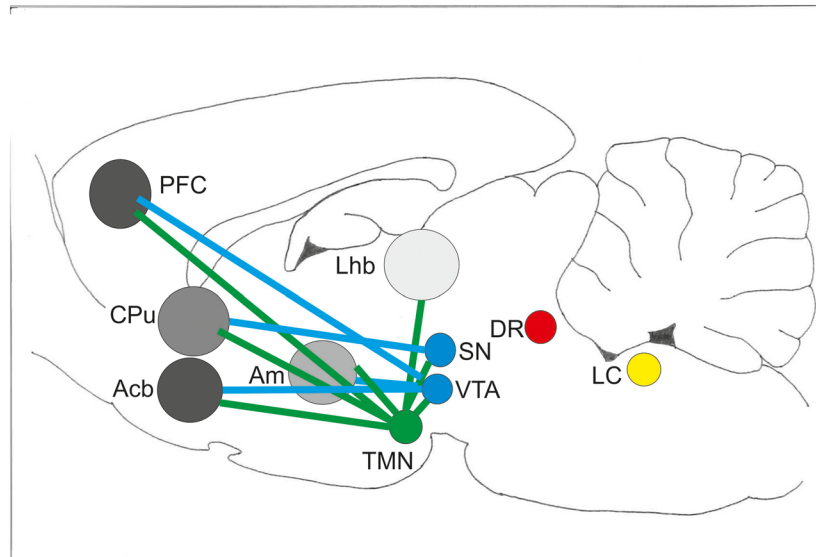
alcohol-induced place preference (Bechtholt & Cunningham, 2005). Wistar rats also self-administer alcohol into the posterior VTA but not the anterior VTA (Rodd-Henricks, McKinzie, Crile, Murphy, & McBride, 2000). In the VTA, a single dose of alcohol induces a long-lasting potentiation of GABAergic synapses in dopaminergic neurons (Melis, Camarini, Ungless, & Bonci, 2002).

Alcohol increases the firing of VTA dopaminergic neurons in both C57BL/6J and DBA/2J mice (Brodie & Appel, 2000). Alcohol also increases postsynaptic GABA_A receptor sensitivity and enhances action potential-independent GABA release onto VTA dopaminergic neurons (Theile, Morikawa, Gonzales, & Morrisett, 2008), which in turn may limit the direct excitation of these neurons. The role of H_3 receptors in the regulation of VTA dopaminergic neurons may be complex: Local GABAergic neurons and afferents from the NAcc are potential direct targets of H_3 receptor antagonists, since the expression of H_3 receptors in NAcc is abundant and VTA GABAergic cells may form the population that expresses H_3 receptors. In addition, **5-HT** through **5-HT $_2\text{C}$ receptors** modulates GABA release on dopaminergic neurons (Theile, Morikawa, Gonzales, & Morrisett, 2009), and H_3 receptor agonists inhibit electrically-evoked 5-HT release at least in the SN (Threlfell et al., 2004). Although it is possible that one of the key sites of H_3 receptor ligands' action on alcohol-related behaviours is the VTA, this is unlikely because of the sparsity of H_3 receptor radioligand binding and gene expression in this region compared to the SN (Pillot et al., 2002).

During the operant alcohol self-administration procedure, dopamine release in the NAcc increases in both trained rats and handling controls during placement in the operant chamber, but only in alcohol-consuming rats during alcohol but not water self-administration (Doyon et al., 2003). Intraperitoneal alcohol also increases dopamine release in the posterior VTA in rats (Deehan et al., 2016). In mice, alcohol increases dopamine release in the NAcc without affecting histamine release (Nuutinen et al., 2016).

The location of the H_3 receptor in many aminergic neurons allows its release from terminals to be directly regulated by histamine and H_3 receptor ligands (for a review, see Panula & Nuutinen, 2013). Although in vitro evidence suggests that histamine inhibits the electrically-evoked release of [^3H] dopamine from striatal slices in a manner that is abolished by the H_3 receptor antagonist **thioperamide** and thus may suggest the presence of presynaptic H_3 receptors on striatal dopaminergic terminals (Schlicker, Fink, Detzner, & Gothert, 1993), in vivo microdialysis has not revealed an evidence of dopamine release in the striatum by H_3 receptor antagonists (Aquino-Miranda, Escamilla-Sanchez, Gonzalez-Pantoja, Bueno-Nava, & Arias-Montano, 2016; Nuutinen et al., 2016). The H_3 receptor antagonist GSK189254 did not evoke the release of dopamine in the NAcc (Giannoni et al., 2010), and **ABT-239**, another H_3 receptor antagonist, induced the release of dopamine in the cortex but not the striatum (Fox et al., 2005). Furthermore, the expression of H_3 receptor mRNA in the VTA and SN is low in rats and normal humans (Anichtchik, Huotari et al., 2000; Anichtchik, Rinne et al., 2000; Drutel et al., 2001), although H_3 receptor radioligand binding is high in the SN (Anichtchik et al., 2001; Anichtchik, Huotari et al., 2000; Pillot et al., 2002). At the cellular level, the expression of H_3 receptor mRNA has

FIGURE 2 Dopaminergic (blue) and histaminergic (green) projections target many brain areas essential in alcohol-related rewarding and drug-seeking or aversive behaviours. Dopaminergic projections to the prefrontal cortex (PFC), nucleus accumbens (Acb), and amygdala (Am) originate in the ventral tegmental area (VTA); those directed to the caudate-putamen (CPu) originate in the SN. All histaminergic projections originate in the tuberomammillary nucleus (TMN). 5-HT-containing dorsal raphe nucleus (DR; red) and noradrenaline-containing locus coeruleus (LC; yellow) are also labelled, but their projections are not included. The intensity of the grey scale in target areas lateral habenular nucleus (Lhb), PFC, CPu, Am, and Acb indicates the intensity of the H₃ receptor radioligand binding density in autoradiographic films in rat brain. SN: substantia nigra pars compacta



been reported in the SN, although the transmitter phenotype of the cells was not determined, whereas in the VTA, little if any H₃ receptor mRNA was detected (Pillot et al., 2002). Microarray analysis has not verified H₃ receptor gene (Hrh3) as one that distinguishes A9 and A10 dopaminergic neurons (Chung et al., 2005), and the gene is not among those which distinguish different clusters of mesencephalic dopaminergic neurons (Poulin et al., 2014).

It is thus unlikely that H₃ receptor antagonists would as such be habit-forming. The histaminergic neuron population may be heterogeneous, since H₃ receptor antagonists administered intracerebrally directly to the TMN induce the release of histamine from the prefrontal cortex and nucleus basalis magnocellularis but not from the NAcc or dorsal striatum (Blandina, Munari, Provensi, & Passani, 2012).

5 | H₃ RECEPTOR, ALCOHOL DRINKING AND CONDITIONED PLACE PREFERENCE

The first report on the possible role of H₃ receptors in AUD was the report by Lintunen et al. (2001) on alcohol-preferring (AA) rats. In this rat line, the levels and turnover of histamine in the brain were significantly higher than those in the Wistar rats or alcohol non-preferring (ANA) rats, and in the two-bottle choice self-administration test, two H₃ receptor antagonists, **clobenpropit** and thioperamide, significantly suppressed alcohol intake, whereas the H₁ receptor antagonist **mepyramine** had no effect on self-administration. The H₃ receptor agonist **R- α -methylhistamine** increased alcohol self-administration in AA rats, suggesting that H₃ receptors regulate this behaviour in a bidirectional manner. This finding was surprising and unexpected and opened up the questions related to the potential mechanisms and clinical use. Interestingly, the AA rats also had higher histamine H₃ receptor expression in two relevant brain areas, the primary motor cortex and NAcc, and higher tele-methylhistamine content in the frontal cortex than that of the ANA rats (Lintunen et al., 2001).

Histamine content in AA rat brains was higher than that in ANA rats in the frontal cortex, septum, hippocampus, and mesencephalon (Lintunen et al., 2001). Although the activity of the histaminergic system was clearly higher in AA than in ANA rats, it is not certain that the effect of H₃ receptor ligands on alcohol self-administration is mediated by autoreceptors on projections of TMN histaminergic neurons, because the expression of the H₃ receptor is abundant in many different neurons in relevant brain areas (Panula et al., 2015; Panula & Nuutinen, 2013).

The effect of H₃ receptor antagonists on alcohol consumption or other AUD-related behaviours has been reported for a number of H₃ receptor antagonists, including thiperamide, clobenpropit, **ciproxifan**, JNJ-39220675, JNJ-10181475, DL77, and ST1283, consisting of both imidazole- and non-imidazole-based molecules (Bahı, Sadek, Nurulain, Lazewska, & Kiec-Kononowicz, 2015; Bahı, Sadek, Schwed, Walter, & Stark, 2013; Nuutinen et al., 2011). These studies also utilized a number of different drinking models, suggesting that possible caveats related to a specific method or non-specific effects of some ligands do not explain the findings.

6 | CLINICAL TREATMENT TRIALS WITH H₃ RECEPTOR ANTAGONISTS FOR AUD

Since several companies have produced H₃ receptor antagonists with high potency, good kinetic properties, and no observed toxicity, two clinical trials have been announced at clinicaltrials.com, but none have yet been initiated or completed. In addition, several companies have developed effective drugs, which have been removed from further development due to adverse side effects or lack of positive effects.

A single centre, randomized, double-blind, placebo-controlled parallel group Phase 2 study with bavisant (JNJ 31001074) was announced in 2011 with Janssen Research & Development as sponsor. The intention was to study a primary outcome, the urge to drink.

The secondary outcome measures were the number of patients reporting adverse events; abnormal findings from eye examinations were performed as a measure of safety and tolerability, as well as vital signs measurements, electrocardiograms, and clinical laboratory tests. The planned experimental setup included adult (21–62 years) non-treatment-seeking currently alcohol-dependent individuals. In the test setup, the individuals would be shown various computer images and then presented with either a favourite alcohol-containing drink or water (without drinking the offered drink). Study subjects would have taken one 3 mg tablet of bavisant or matching placebo in the morning of each day. However, the study was withdrawn before enrolment following re-prioritization (Panula et al., 2015).

The outcome of a second trial on **pitolisant** by Bioprojet were published in 2016. The multisite, double-blind, placebo-controlled study, which was withdrawn by the sponsor before recruitment, was planned on male or female moderate or severe *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition AUD patients 18–65 years of age, who were treatment-seeking subjects. The planned primary outcome measure was a decrease in the number of monthly heavy drinking days (HDDs). Secondary end-points included total alcohol consumption from baseline to end of treatment, % of patients without HDDs during the 24 weeks of randomized treatment (RT) phase, % of abstinence days during the RT phase, continuous abstinence duration from baseline during the 24 weeks of RT phase, 4-week point prevalence abstinence at the end of treatment, improvement in alcohol biomarkers during the 24-week RT phase, craving during the 24-week RT phase, Beck depression inventory during the 24-week RT phase, quality of sleep, % of patients without HDDs during the open label (OL) follow-up period, quality of life (SF-12) during the RT phase, and quality of sleep (Pittsburgh Sleep Quality Index) during OL phase. Neither of these prospective clinical trials was cancelled or discontinued because of undesired side effects of lack of efficacy but rather they were withdrawn due to altered company policies.

Based on information on in vivo properties in human subjects available, the most suitable drug for clinical tests in AUD would be AZD5213 developed by Astra-Zeneca. This compound has shown high occupancy at H₃ receptors in human brain, good tolerance after repeated doses (~14 mg·day⁻¹) and short (about 5 hr) half-life (Jucaite et al., 2013). The short half-life is particularly important for an H₃ receptor antagonist in clinical use, because drug accumulation in plasma can be significant. The most likely side effects, which include sleep disturbance, may be less prominent than with other H₃ receptor drugs.

7 | CONCLUDING REMARKS: CURRENT STATE OF RESEARCH AND THE FUTURE

The surprising finding that H₃ receptor antagonists can reduce alcohol intake in AA rats has led to a series of rodent studies. These studies have found that several H₃ receptor antagonists inhibit alcohol intake in at least three different drinking models and also inhibit alcohol-induced reward. Similar findings have been obtained in mice lacking

H₃ receptors. No evidence of habit-forming properties of H₃ receptor antagonists have been reported, although these drugs stimulate the release of several neurotransmitters in different brain regions. Although the H₃ receptor is an autoreceptor, which regulates histamine release, its role in regulating several other transmitters including GABA and glutamate renders it possible that histamine itself might not be the key transmitter in the neuronal circuits involved in AUD. Since the H₃ receptor is expressed in many important brain areas, it is not obvious where the effects of H₃ receptor antagonists occur that then regulate alcohol-related behaviours. The most probable site is the cortico-striato-mesencephalic system. Alcohol is known to release dopamine in the striatum, and H₃ receptor antagonists regulate dopamine signalling in the striatum possibly through receptor oligomers consisting of H₃ and dopamine receptors. Experiments on animals in vivo using, for example, optogenetic inhibition or excitation of specific neuronal assemblies in freely behaving animals would be needed to address the potential involvement of these and other areas, for example, the habenula and amygdala. Drug companies have produced potentially useful and safe H₃ receptor antagonists for clinical testing. Two clinical trials have been planned to test the use of these drugs to treat AUD. Both have been withdrawn before starting due to company policy reasons. The clinical potential of these drugs is thus still not tested. Such trials would be the obvious next step to open a new area of application.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander, Christopoulos et al., 2017; Alexander, Peters et al., 2017).

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CONFLICT OF INTEREST

The author declares no conflicts of interest.

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