BJP British Journal of Pharmacology

DOI:10.1111/bph.12221
www.brjpharmacol.org

Themed Issue: Histamine Pharmacology Update

REVIEW

Histamine H_3 receptors, the complex interaction with dopamine and its implications for addiction

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Keywords
histamine; H_3 receptors; D_1 receptors; D_2 receptors; drugs of abuse; cocaine; psychostimulants; direct pathway; indirect pathway; dorsal striatum; ventral striatum

Received
30 November 2012
Revised
10 April 2013
Accepted
18 April 2013

Histamine H_3 receptors are best known as presynaptic receptors inhibiting the release of histamine, as well as other neurotransmitters including acetylcholine and dopamine. However, in the dorsal and ventral striatum, the vast majority of H_3 receptors are actually located postsynaptically on medium sized spiny output neurons. These cells also contain large numbers of dopamine (D_1 and D_2) receptors and it has been shown that H_3 receptors form heterodimers with both D_1 and D_2 receptors. Thus, the anatomical localization of H_3 receptors suggests a complex interaction that could both enhance and inhibit dopaminergic neurotransmission. Dopamine, especially within the striatal complex, plays a crucial role in the development of addiction, both in the initial reinforcing effects of drugs of abuse, as well as in maintenance, relapse and reinstatement of drug taking behaviour. It is, therefore, conceivable that H_3 receptors can moderate the development and maintenance of drug addiction. In the present review, we appraise the current literature on the involvement of H_3 receptors in drug addiction and try to explain these data within a theoretical framework, as well as provide suggestions for further research.

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Abbreviations
CPP, conditioned place preference; GSK3, glycogen synthase kinase 3; TMN, tuberomammillary nucleus; TMM, medial tuberomammillary nucleus; TMV, ventral tuberomammillary nucleus

Introduction

Drug addiction is a major economic and health problem especially among young people. According to the United Nation's World Drug Report, about 210 million people use illicit drugs each year and about 200 000 die because of that (UNODC, 2010). The misuse or abuse of licit drugs, especially nicotine and alcohol, is much more common, with 23% of the American population currently being classified as smokers, although the trend to smoke is decreasing. With respect to alcohol, a recent study showed that 31% of all males and 16% of all females in the USA have been reported to binge drink and an estimated 18 million Americans (7%) are dependent on alcohol or have problems related to their use of alcohol (http://www.drugabuse.gov/sites/default/files/drugfactsnationtrends_1.pdf), a percentage that has not changed since 2002.

Although drug addiction is multifaceted, its most prominent characteristic is loss of control of drug consumption (Hyman *et al.*, 2006). As a direct result of this, addicted individuals continue to consume the addictive drug (usually in large amounts and in most cases other addictive drugs as well) in spite of the obvious and well-recognized negative influence on their general health and well-being. Moreover, as a result of the large amounts of drugs consumed, the brain and body of the addicted individual adapts, leading to withdrawal signs when the drug is withheld. Although these withdrawal signs can be very severe, the more problematic aspect of drug addiction is relapse. Even after a prolonged period of drug abstinence, long after the withdrawal symptoms have subsided, drug addicts have an increased risk of relapsing into drug taking again.

In spite of the massive problems associated with drug addiction (legal, health and economic to name just a few),

very few successful therapeutic approaches have so far been developed. Most of these are aimed at replacing the addictive drug by a less dangerous, less potent substitute, such as methadone as a substitute for heroin and nicotine patches or gum as a substitute for cigarette smoking. The recently marketed partial nicotine receptor agonist varenicline also falls within this category. With respect to alcohol addiction, several drugs have been marketed and these include disulfiram, acamprosate and naltrexone. Naltrexone blocks opiate receptors. Acamprosate is known to block NMDA receptors and has beneficial effects, especially when combined with a non-pharmacological treatment. However, the mode of action of acamprosate is not yet completely understood. Disulfiram interferes with the metabolism of alcohol by inhibiting the enzyme acetaldehyde dehydrogenase. This leads to an accumulation of acetaldehyde, which induces unpleasant effects such as flushing, palpitations and nausea. In addition to these, a large number of different treatment options have been or are currently being investigated, including vaccines. For a recent overview of the pharmacological treatment of addiction see vandenBrink (2012).

The nomenclature used for receptors conforms to BJP's *Guide to Receptors and Channels* (Alexander *et al.*, 2011).

The neurobiology of drug addiction and the role of dopamine

Given the complicated nature of drug addiction and the protracted nature of its course, it is no surprise that the neurobiology of addiction is highly complicated and is still far from being understood. Although we have made considerable progress in studying the commonalities of addictive drugs, we still have yet to understand the risk factor that leads to addictive behaviour and what exactly governs the switch from recreational to compulsive drug use. It is far beyond the scope of this paper to provide a detailed overview of the many findings and theories in this area. For this, the reader is referred to several excellent papers (Everitt and Robbins, 2005; Koob and Volkow, 2010; Dalley *et al.*, 2011).

One of the most important neurotransmitters in the field of drug addiction is dopamine (Wise and Rompre, 1989; Adinoff, 2004; Feltenstein and See, 2008). This is based on the finding that both experimenter administration (Di Chiara and Imperato, 1988) and self-administration (Wise *et al.*, 1995) of drugs of abuse leads to an increase in dopamine release. Moreover, this increased release occurs with virtually all drugs of abuse, in spite of the fact that they act through different mechanisms. Thus, whereas psychostimulants such as cocaine and (meth)amphetamine directly increase extracellular dopamine by blocking and/or reversing the dopamine transporter, opiates, nicotine and ethanol indirectly activate the dopaminergic cells. In line with the increase in dopamine release after (self)-administration of drugs of abuse, dopamine antagonists have been shown to block the maintenance of self-administration, especially after local administration in the ventral striatum (Yokel and Wise, 1976; Bergman *et al.*, 1990; Hubner and Moreton, 1991). Likewise, lesioning the dopaminergic cells in the mesolimbic pathway (that principally innervates the ventral striatum) also blocks drug self-administration, although this effect seems more prominent with psychostimulants than with opiates (Pettit *et al.*, 1984; Dworkin *et al.*, 1988; Gerrits and Van Ree, 1996). The blockade of self-administration by dopamine antagonists is probably due to a reduction in the rewarding (reinforcing) properties of the drugs of abuse, as the same antagonists also reduce the breaking point in a progressive ratio schedule (Fletcher, 1998; Izzo *et al.*, 2001) and block the conditioned place preference (CPP) (Tzschentke, 2007; Tzschentke, 1998).

As briefly discussed above, after chronic (self)-administration, a large variety of adaptive changes occur in the brain of animals (and humans), leading to long-term changes in neurochemistry (Haensel *et al.*, 1991; Freeman *et al.*, 2008; Schmidt *et al.*, 2012) and morphology (Robinson *et al.*, 2001; Crombag *et al.*, 2005; Ballesteros-Yanez *et al.*, 2007), resembling in many ways the changes seen during memory formation. Many of these changes are very long lasting and can be observed many months after drug taking has stopped. This has led many researchers to suggest that these changes result from epigenetic alterations, leading to persistent increases and/or decreases in gene expression (Feng and Nestler, 2010; Im *et al.*, 2010; Russo *et al.*, 2010; Robison and Nestler, 2011). In spite of these complex changes, which involve many genes and neurotransmitters, dopamine is also known to play an important role in craving, especially in models of relapse and reinstatement of drug seeking after prolonged periods of withdrawal. Drug reinstatement in animals can be induced by either a single priming injection of the drug (or one with similar properties) or by exposing animals to a stressor or the drug-associated cues (Shaham *et al.*, 2003). Although there are subtle (although important) differences in the neurobiology of the different reinstatement paradigms, dopamine seems to function as a final common pathway in all of them. Similar to their effects on self-administration, dopamine antagonists block reinstatement of drug seeking behaviour (Alleweireldt *et al.*, 2003; Bossert *et al.*, 2007; Brennan *et al.*, 2009; Liu *et al.*, 2010; Schenk *et al.*, 2011).

Dopamine can bind to five different receptors, generally subdivided into two families: the D_1 family (encompassing D_1 and D_5 receptors) and the D_2 receptor family (encompassing D_2, D_3 and D_4 receptors). There is accumulating evidence that both receptor families are involved in the development and maintenance of drug addiction. Dopamine has higher affinity for the receptors belonging to the D_2 than those belonging to the D_1 family, and especially for the so-called D_{2S} (a short splice variant of the D_2 receptor) which is mainly located presynaptically (Usiello *et al.*, 2000). Given the limited selectivity of most drugs for the different receptors within each family, the receptors are often referred to as D_1-like and D_2-like receptors.

It is important to note that dopaminergic cells can fire in two distinct modes, tonically and phasically (bursting), with the latter occurring when the cells are activated leading to high levels of dopamine release (Grace *et al.*, 2007). Thus under baseline (tonic) conditions, the D_2 receptors will be (at least partially) stimulated by dopamine to maintain a basal level of cellular communication, while the D_1 receptors are only activated when the dopaminergic cells switch to bursting mode. As discussed above, all drugs of abuse enhance dopamine release, either by a blockade/reversal of the dopa-

mine transporter, or by increasing the firing of dopaminergic cells. There is mounting evidence that the availability of D_2-like receptors is lower in people addicted to drugs of abuse (Hikida *et al.*, 2010; Groman and Jentsch, 2012). Although this could at least in part be the result of the chronic drug use, studies in animals have shown that animals with pre-existing low levels of D_2-like receptors also exhibit more cocaine self-administration (Nader *et al.*, 2006; Dalley *et al.*, 2007). These data have lead to the hypothesis that individuals with low D_2-like receptor availability use the dopamine enhancing effects of drugs of abuse in order to compensate for their relatively low levels of dopamine neurotransmission.

Although fewer studies have looked at the role of dopamine D_1-like receptors, it has been shown, especially in behavioural studies, that selective blockade of the D_1-like receptors inhibits drug self-administration, reinstatement and CPP (Beninger and Miller, 1998; Bossert *et al.*, 2007; Brennan *et al.*, 2009; Carati and Schenk, 2011). Moreover, cocaine self-administration is abolished in mice lacking the D_1 receptor, suggesting that this receptor also plays an important role in the development of drug addiction (Caine *et al.*, 2007). Interestingly, recent imaging studies have further corroborated the significance of D_1-like receptors in drug addiction. In a recent PET study, it was found that, in cocaine addicts, low occupancy of D_1 receptors was associated with a greater tendency to choose cocaine self-administration over a monetary reward (Martinez *et al.*, 2009). Likewise, individuals with low striatal D_1 receptor availability showed more risk-seeking behaviour, a character trait known to be associated with an increased risk of addiction (Takahashi *et al.*, 2010; 2012). Thus, on consideration of all the evidence, it is concluded that both the D_1 and the D_2 family of receptors play important roles in the development, maintenance and reinstatement of drug addiction. Although a detailed analysis of the literature shows that there are differences between the roles of both families of receptors, it is beyond the scope of this paper to discuss this.

Even though the effects of dopamine receptors ligands in the various phases of drug self-administration (i.e. acquisition, maintenance, reinstatement) seem to be very similar, it is important to note that significant changes take place within the brain during these phases. As the individual moves from recreational use to abuse, a shift from impulsive to compulsive drug use is thought to occur (Koob *et al.*, 2004) and, with it, a shift in involvement of the ventral striatum to the dorsal striatum (Everitt and Robbins, 2005; Dalley *et al.*, 2011). However, dopamine plays a crucial role in gating information from cortical and subcortical regions in both parts of the circuitry and thus, it is not surprising that it also plays an important role in all aspects of drug addiction.

Histamine and the histamine receptors

Histamine, a small imidazole-containing chemical was first detected by Sir Henry Dale and his colleagues (Dale and Laidlaw, 1910), as a mediator of the smooth muscle contractions of the gut and vasodilatation. In 1941, Kwiatkowski first detected histamine in the brain (Kwiatkowski, 1941), and it was later found that histamine is both synthesized and metabolized in neurons (White, 1959), although it was not until the actual identification of the histaminergic cells and their axonal distribution within the brain (Panula *et al.*, 1984) that histamine was considered a neurotransmitter similar to other amines such as dopamine and noradrenaline. However, before the actual identification of histamine as a neurotransmitter, antihistamine drugs were already being used for the treatment of allergies and among the most prominent side effects was sedation and sleepiness, coining histamine as the 'waking substance' (Monnier *et al.*, 1967; Haas *et al.*, 2008).

Like dopamine, the cell bodies that use histamine as a neurotransmitter are located in a small cluster in the midbrain, the tuberomammillary nucleus (TMN). In humans, this cell cluster contains approximately 64 000 neurons, whereas in the rat, the number of histaminergic cells is estimated to be only 2300. Ericson subdivided this cluster into three different parts, a ventral part (TMV, about 1500 cells) a medial part (TMM, approximately 600 cells) and a diffuse part of about 200 cells (Ericson *et al.*, 1987). Inagaki and colleagues further subdivided the TMV into rostral and caudal, and the TMM into dorsal and ventral, leading to five distinct cell groups: E1–E5 (Inagaki *et al.*, 1990). Although these subdivisions are predominantly based on anatomical/morphological characteristics, there is increasing evidence that there is also functional heterogeneity in the histaminergic cells. Thus, injections of the H_3 receptor antagonist thioperamide into the TMN enhances histamine release in the prefrontal cortex, but not the dorsal or ventral striatum, suggesting that the TMN cells projecting to the latter two areas may be devoid of functional H_3 autoreceptors (Giannoni *et al.*, 2009). Experiments with an H_3 agonist are clearly needed to elucidate the function of H_3 receptors in these pathways.

Although there are only a very small number of histaminergic cells, they have a very widespread projection, innervating the majority of the cerebral cortical areas as well as many subcortical regions, including the (hypo)thalamus, hippocampus, amygdala and the dorsal and ventral striatum (Haas *et al.*, 2008). In line with this widespread distribution, histamine is known to be involved in several general brain functions, including arousal, sleep-wake regulation, thermoregulation, pain perception and feeding. In addition, studies have shown histamine to be involved in higher cognitive functions and mood (Haas *et al.*, 2008).

Once released, histamine can interact with four different receptors, conveniently labelled H_1 to H_4. All four receptors belong to the rhodopsin family of GPCRs, even though there are clear differences between them. The histamine H_1 receptor is found throughout the body and the brain and is coupled to a $G_{q/11}$ protein. The binding of histamine to the receptor therefore leads to activation of PLC promoting the formation of inositol triphosphates and DAG. Like the H_1 receptor, the histamine H_2 receptor is also widespread in both the brain and the body. It is coupled to a $G_{\alpha s}$ protein, thus leading to an increased activity of adenylate cyclase and a concomitant rise in cAMP upon stimulation.

The histamine H_3 receptor was first discovered by Jean Charles Schwartz and his colleagues, in 1983 (Arrang *et al.*, 1983), and subsequently cloned by Tim Lovenberg *et al.*, (1999). It is primarily coupled to a Gi/o protein, implying that stimulation of the H_3 receptor leads to an inhibition of adenylate cyclase and a reduction in intracellular cAMP production (Torrent *et al.*, 2005). However, they can also engage

in $G_{q/11}$ signalling and activate the PLA_2, Akt/glycogen synthase kinase 3 (GSK3; Bongers *et al.*, 2007) and MAP kinase pathways (Drutel *et al.*, 2001; Giovannini *et al.*, 2003). In contrast to the H_1 and H_2 receptors, H_3 receptors are almost exclusively located within the CNS, although some H_3 receptors are found outside the CNS, particularly in the heart (Chan *et al.*, 2012). The last of the histamine receptors is the H_4 receptor, which is predominantly located in the blood, spleen, lung, liver and gut (Breunig *et al.*, 2007), although there is also evidence that it is present in the CNS (Connelly *et al.*, 2009). Like the H_1, H_2 and H_3 subtypes, the H_4 receptor is also a GPCR, and like the H_3 receptor, its stimulation leads to a reduction in adenylate cyclase activity and cAMP production (due to its coupling to a $G_{i/o}$ protein). At present, it is receiving more and more attention due to its potential role in pain and inflammation (Morgan *et al.*, 2007).

The H_3 receptor and its interaction with dopamine

The H_3 receptor is predominantly, although not exclusively located in the CNS, with high levels in the frontal cortex, hippocampus, amygdala, TMN and especially in dopamine rich areas including the substantia nigra, the dorsal and ventral striatum and the olfactory tubercle (Pillot *et al.*, 2002). An interesting characteristic of the H_3 receptor is its very high constitutive activity. In other words, the $G_{i/o}$ protein is continuously activated, even in the absence of histamine binding to the receptor. Although this is not unique, in fact all histamine receptors show some degree of constitutive activity (Haas *et al.*, 2008), it seems particularly high for the H_3 receptor. This implies that in addition to agonists and antagonists, inverse agonists also exist. Indeed, many of the traditional (neutral) antagonists have now been reclassified as inverse agonists.

A closer inspection of the localization of H_3 receptors shows that many of the receptors are located presynaptically, both on histaminergic cells as well as on terminals of neurons using other neurotransmitter. H_3 autoreceptors are found both on the cell body (i.e. in the TMN) and the terminals of histaminergic cells, although as mentioned before, not all histaminergic cells contain (active) H_3 receptors. In a recent study, it was shown, using a dual probe microdialysis technique, that local administration of the selective H_3 antagonist GSK18254 in the TMN increased histamine release in this nucleus as well as in the basal nucleus of Meynert and the cortex, but not in the dorsal and ventral striatum (Giannoni *et al.*, 2010), further supporting the theory that the histaminergic innervation of the basal ganglia is devoid of functional H_3 autoreceptors (Giannoni *et al.*, 2009). However, so far, studies with selective H_3 agonists have not been performed.

In addition, to regulating the release of histamine, H_3 receptor activation has been found to inhibit the release of many other neurotransmitters, including acetylcholine, glutamate, GABA, 5-HT, noradrenaline and dopamine (Blandina *et al.*, 1996; Brown and Reymann, 1996; Schlicker *et al.*, 1999; Jang *et al.*, 2001; Fox *et al.*, 2005; Medhurst *et al.*, 2007). As with the effect of H_3 receptors on histamine release, there appear to be regional differences in the regulation of other neurotransmitters, although this has been less systematically investigated. However, with respect to its influence on dopamine release, virtually all studies have found that H_3 antagonist/inverse agonists increase the release of dopamine in the prefrontal cortex (Fox *et al.*, 2005; Medhurst *et al.*, 2007), but do not affect dopamine release in the dorsal or ventral striatum (Munzar *et al.*, 2004; Fox *et al.*, 2005; Giannoni *et al.*, 2010; Galici *et al.*, 2011). Given the high concentration of H_3 receptors within the dorsal and ventral striatum, this may seem somewhat surprising. However, it is important to note that the vast majority of H_3 receptors are located postsynaptically within the dorsal striatum on the medium spiny output-neurons (Ryu *et al.*, 1994; Pillot *et al.*, 2002). A detailed analysis has shown that H_3 receptors are found both on D_1 and D_2 receptors of the direct and indirect output pathways respectively. In fact 95% of all D_1 positive and 89% of all D_2 positive cells in the striatum also contain H_3 receptors (Moreno *et al.*, 2011). Nonetheless, it has also been suggested that H_3 receptor mRNA may be present in the dopaminergic nigrostriatal neurons (Anichtchik *et al.*, 2001; Arias-Montano, 2007), although this awaits further confirmation.

It is also important to realize that there are substantial differences between the dopaminergic cells in the mesocortical and the mesolimbic and nigrostriatal pathway, Thus, it has been known for a long time that a subset, at least, of mesocortical cells do not possess D_{2S} autoreceptors (Chiodo *et al.*, 1984; Lammel *et al.*, 2008) and also show several other pharmacological and molecular differences (Ungless and Grace, 2012). For instance, whereas κ-agonists affect the mesocortical but not the mesolimbic dopaminergic cells (Margolis *et al.*, 2006), the reverse holds true for cocaine (Lammel *et al.*, 2011). It is, therefore, not surprising that H_3 receptors also differentially influence these two dopaminergic projection systems, with, in this case a direct effect on the mesocortical, but not the mesolimbic or the nigrostriatal pathway. On the other hand, it has been shown that H_3 receptors, although ineffective by themselves, enhance methamphetamine-induced dopamine release in the ventral striatum (Munzar *et al.*, 2004), suggesting that the difference between the mesocortical and mesolimbic system may be more quantitative than qualitative. In addition, it is well-established that there is an inverse relationship between dopamine release in the frontal cortex and that in the subcortical areas (Pycock *et al.*, 1980). Given that all H_3 antagonists potently increase frontal cortex dopamine, this may provide an additional reason why the subcortical increase is not so pronounced.

Thus, the interaction between H_3 receptors and dopamine is very complex. On the one hand, presynaptic H_3 receptors regulate the release of dopamine, with H_3 agonists inhibiting and antagonists enhancing the release, especially in the frontal cortex and in the striatum in the presence of dopamine releasing drugs. On the other hand, H_3 and D_2 receptors co-operate with each other in the indirect pathway (since both are coupled to a $G_{i/o}$ protein), while H_3 and D_1 receptors oppose each other in the direct pathway (since D_1 is coupled to a G_s and H_3 to a $G_{i/o}$ protein). In agreement with this, it was found that whereas both D_2 and H_3 agonists reduce striatal GABA release, D_1 agonists enhance it, and the effects of a

D_1 agonist were reversed by the H_3 agonist immepip (Arias-Montano *et al.*, 2001). Since this effect was seen in reserpine-treated rats (i.e. rats without active dopamine release), the effects of the H_3 agonist are most likely postsynaptic rather than through an inhibitory action on dopamine release (i.e. a presynaptic effect). Overall, these data suggest that within the striatum, H_3 receptors potentiate the dopamine (D_2)-induced inhibition of the indirect pathway and inhibit the dopamine (D_1)-induced excitation of the direct pathway (see Figure 1).

However, recent data suggest that the situation is further complicated by the fact that at least some of the H_3 receptors form heteromers with the D_1 (Ferrada *et al.*, 2009) and D_2 receptors (Ferrada *et al.*, 2008). Although the functional consequences of this heteromerization are not yet fully understood, studies in rats show that in the presence of an H_3 agonist, the affinity of quinpirole for the D_2 receptors is markedly decreased (from a K_{Dh} of 0.9 nM to 52 nM, see Figure 1B), an effect counteracted by the addition of an H_3 antagonist (Ferrada *et al.*, 2008). The interaction between H_3 and D_1 receptors is even more interesting. Whereas D_1 receptors are normally coupled to adenylate cyclase via a G_s protein, this switches to a $G_{i/o}$ protein when the D_1 dimerizes with the H_3 receptor (Ferrada *et al.*, 2009). Moreover, whereas in wild-type mice H_3 and D_1 agonists increase the phosphorylation of $ERK_{1/2}$, this effect is absent in D_1 knock-out mice, suggesting it is a direct consequence of the D_1-H_3 heterodimer (Moreno *et al.*, 2011). Thus, in cells where D_1-H_3 dimers are more prevalent, dopamine and histamine work cooperatively rather than antagonistically, as would be the case in cells where both receptors are present but do not form heteromers (see Figure 1D). However, it is important to note that in those cells that contain the D_1-H_3 heterodimer, it is the D_1 receptor rather than the H_3 receptor that changes its second messenger system. In other words, whereas normally dopamine would enhance the activity of the direct pathway by stimulating the D_1 receptor, it would inhibit those cells of the direct pathway that are equipped with the D_1-H_3 heterodimer, thereby producing a further imbalance between the direct and indirect pathway. Although it has been shown that these heterodimers do indeed exist *in vivo* (Moreno *et al.*, 2011), it is currently unknown how prevalent they are and to what extent they contribute to the overall effect of dopamine within the dorsal striatum.

It should be noted that all these effects were found in the dorsal striatum and, so far, data concerning the ventral striatum are lacking. Although there are clear differences between the mesolimbic and nigrostriatal dopaminergic cells and even within the ventral striatum between the dopaminergic cells projecting to the shell and the core (Lammel *et al.*, 2011), the data published so far show that within the ventral striatum (like the dorsal striatum), H_3 antagonists/inverse agonists do not increase dopamine release (Giannoni *et al.*, 2010; Galici *et al.*, 2011), making it likely that the interaction between H_3 receptors and dopamine receptors in this region is similar to that seen in the dorsal striatum. Obviously, more research is warranted in this respect, also focusing on possible differences between the core and the shell region of the ventral striatum (Lammel *et al.*, 2011).

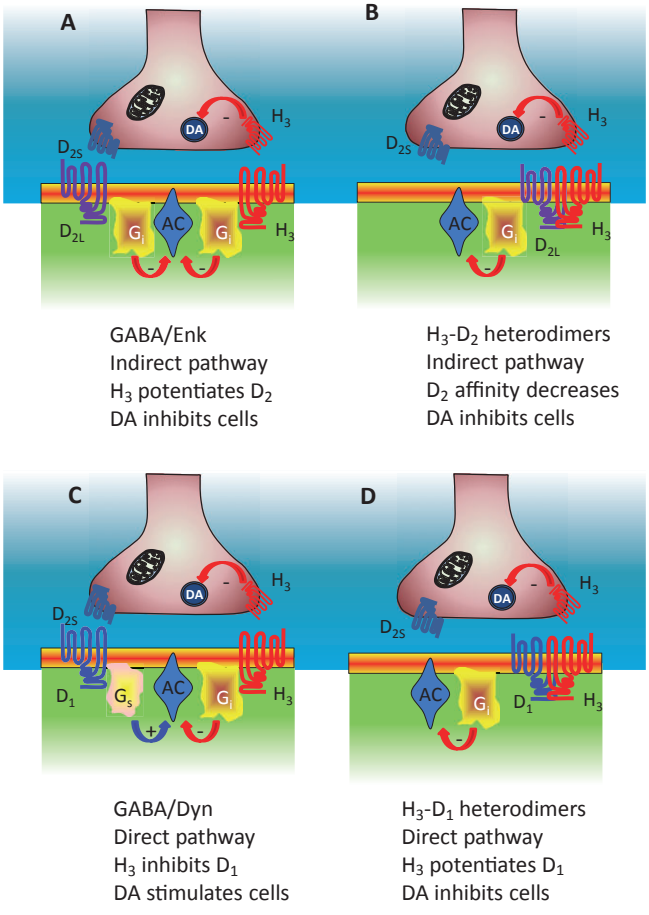

Figure 1

A diagram illustrating the intricate and complex relationship within the striatum between histamine H_3 receptors and dopaminergic neurotransmission. In the upper panel, the interaction between H_3 and D_2 receptors in the indirect pathway is represented with (A) showing the situation in which the receptor are monomers and (B) where the receptors form heterodimers. The lower panel shows the interaction between H_3 and D_1 receptors in the direct pathway, with (C) showing the situation where both receptors are monomers, and (D) the situation where they form a heterodimer. Note that in case of the H_3-D_1 heterodimer, the effect of dopamine on the direct pathway changes from excitation to inhibition. It is important to note that, although D_1-H_3 receptor dimers have been reported *in vivo*, their relevance for the behavioural effects of drugs of abuse is still virtually unknown. Abbreviations: DA: dopamine; AC: adenylate cyclase; Enk: enkephalin; Dyn: dynorphin.

H_3 receptors and drugs of abuse

Table 1 gives an overview of the studies that have investigated the role of H_3 receptors in the behavioural effects of drugs of abuse. In line with the complex interaction described above, it is clear from Table 1 that the literature is far from unanimous about the role of H_3 receptors in the addictive properties of these drugs. To illustrate this with just a few examples (see also Table 1): (i) whereas the CPP induced by ethanol in DBA/2J mice is reduced by H_3 antagonists/inverse agonists, these drugs increase CPP induced by ethanol in 129Sv mice and CPP induced by cocaine in C57BL/6J mice;

Table 1

A summary of the literature on the influence of H_3 receptor antagonists/inverse agonists on the behavioural effects induced by drugs of abuse

Species	Strain	Drug of abuse	H_3 antagonist	Paradigm	Results	Reference
Mice	DBA/2J	Ethanol	Ciproxifan	CPP	CPP ↓	Nuutinen *et al.*, 2011b
Mice	DBA/2J	Ethanol	JNJ10181457	CPP	CPP ↓	Nuutinen *et al.*, 2011b
Mice	129Sv	Ethanol	Ciproxifan	CPP	CPP ↑	Nuutinen *et al.*, 2010
Mice	DBA/2J	Ethanol	Ciproxifan	LMA	Hyperactivity ↑	Nuutinen *et al.*, 2011b
Mice	C57Bl/6J	Ethanol	Ciproxifan	SA	SA ↓	Nuutinen *et al.*, 2011a
Mice	H_3KO	Ethanol		CPP	CPP ↓	Nuutinen *et al.*, 2011a
Mice	H_3KO	Ethanol		SA	Ethanol intake ↓	Nuutinen *et al.*, 2011a
Mice	H_3KO	Ethanol		LMA	Hyperactivity ↓	Nuutinen *et al.*, 2011a
Rats	Alc-P	Ethanol	JNJ-39220675	SA	Intake and preference ↓	Galici *et al.*, 2011
Rats	Alc-P	Ethanol	Thioperamide	SA	SA ↓	Lintunen *et al.*, 2001
Rats	Alc-P	Ethanol	Clobenpropit	SA	SA ↓	Lintunen *et al.*, 2001
Mice	Swiss	Amphetamine	Thioperamide	LMA	Hyperactivity ↓	Akhtar *et al.*, 2006
Rats	SD	Amphetamine	GSK207040	LMA	Hyperactivity -	Southam *et al.*, 2009
Rats	Wistar	Amphetamine	Ciproxifan	LMA	Hyperactivity ↓	Mahmood *et al.*, 2012
Rats	Wistar	Amphetamine	Clobenpropit	LMA	Hyperactivity ↓	Mahmood *et al.*, 2012
Mice	C57Bl/6J	Cocaine	Thioperamide	CPP	CPP ↑	Brabant *et al.*, 2005
Mice	C57Bl/6J	Cocaine	Thioperamide	LMA	Sensitization -	Brabant *et al.*, 2006
Mice	C57Bl/6J	Cocaine	Thioperamide	LMA	Hyperactivity ↑	Brabant *et al.*, 2005
Mice	C57Bl/6J	Cocaine	A-331440	LMA	Hyperactivity -	Brabant *et al.*, 2009
Mice	H_3KO	Methamphetamine		CPP	CPP -	Okuda *et al.*, 2009
Mice	H_3KO	Methamphetamine		LMA	Sensitization (↓)	Okuda *et al.*, 2009
Mice	Swiss	Methamphetamine	Ciproxifan	LMA	Hyperactivity ↓	Motawaj and Arrang, 2011
Mice	Swiss	Methamphetamine	Ciproxifan	LMA	Sensitization (↓)	Motawaj and Arrang, 2011
Mice	CD-1	Methamphetamine	ABT-239	LMA	Hyperactivity ↓	Fox *et al.*, 2005
Mice	Swiss	Methamphetamine	BF2.649	LMA	Hyperactivity ↓	Ligneau *et al.*, 2007
Rats	SD	Methamphetamine	Thioperamide	SA	SA ↑	Munzar *et al.*, 2004
Rats	SD	Methamphetamine	Clobenpropit	SA	SA ↑	Munzar *et al.*, 2004
Mice	H_3KO	MDMA		CPP	CPP -	Okuda *et al.*, 2009
Mice	H_3KO	MDMA		LMA	Sensitization ↓	Okuda *et al.*, 2009
Rats	?	Morphine	Thioperamide	CPP	CPP ↓	Perez-Garcia *et al.*, 1999

Abbreviations: CPP, conditioned place preference; H_3KO, H_3 receptor knock-out mice; LMA, locomotor activity; SA, self-administration. Symbols: ↑, H_3 antagonists/inverse agonists enhance the effects of the drug of abuse; ↓, H_3 antagonists/inverse agonists reduce the effects of the drug of abuse; -, H_3 antagonists/inverse agonists do not affect the effects of the drug of abuse. Symbols in parentheses indicate a small trend in the effects of H_3 receptors antagonists/inverse agonists.

(ii) whereas H_3 antagonists/inverse agonists reduce the acute locomotor hyperactivity induced by methamphetamine, it seems to have only marginal effects on the sensitization response to methamphetamine and enhances methamphetamine-induced self-administration; (iii) whereas the amphetamine-induced hyperactivity is reversed by clobenpropit and ciproxifan, it is unaffected by GSK207040. These observed differences could be due to differences in methodology, differences between different drugs of abuse and H_3 receptor ligands (leading to differences in pharmacokinetic interactions) and differences between strains and/or species. Therefore, it is worthwhile discussing these points in more detail.

Methodological considerations

With respect to the methodology, there are several ways to measure (aspects of) the rewarding/reinforcing properties of drugs of abuse. We have already discussed self-administration with its different phases (acquisition, maintenance, reinstatement, progressive ratio) and so far most studies involving H_3 receptors have focused on maintenance. Animals are first trained to obtain a stable level of drug intake and then challenged with an H_3 ligand. Although this is an established procedure, it is not without limitations. The first, and major limitation is that drug intake usually follows an inverted U-shaped curve, with low and very high doses leading to

significantly less intake than intermediate doses (Mello and Negus, 1996). The reasoning behind this is that at high doses, animals 'titrate their needs'. Thus, only a few sips or lever presses are necessary to obtain the amount of reward they need at higher concentrations of the rewarding drug. On the one hand, this poses questions concerning the validity of such self-administration paradigms as models for addiction, after all one of the most essential aspects of drug addiction is loss-of-control. While the animal obviously shows a degree of control; on the other hand, testing a drug such as an H_3 antagonist against a single dose of the addictive compound does not provide adequate information of how the drug alters the rewarding value. For instance, if an H_3 antagonist reduces self-administration of a drug of abuse, it might be because it reduces or increases the rewarding value of the drug. It is therefore important to test a compound against multiple doses of the addictive drug, in order to obtain a dose-response curve. Indeed, Munzar and colleagues, in their study with methamphetamine, looked at the effects of thioperamide and ciproxifan on the responses to several doses of methamphetamine and found clear evidence for a shift to the left of the dose-response curve, that is, both H_3 receptor ligands increased the rewarding properties of methamphetamine. In line with this, the authors found that thioperamide, although ineffective by itself, increased the methamphetamine-induced release of dopamine in the nucleus accumbens (Munzar *et al.*, 2004). In contrast, in studies on ethanol intake generally only the effects of drugs on one specific concentration of alcohol are investigated and invariably H_3 antagonist have been reported to decrease alcohol intake in both rats and mice. Whether this implies that H_3 antagonists/inverse agonists indeed reduce the rewarding value of ethanol, as has been suggested by Panula and Nuutinen (2011), cannot be firmly established from the present findings. It would be of interest to see whether the intake also decreases at lower concentrations of ethanol. In this respect, it is important that in the study with H_3 knock-out mice, different doses of ethanol are used (Nuutinen *et al.*, 2011a). Alternatively, the H_3 antagonists/inverse agonists could be given during acquisition. Then, if they do decrease the rewarding value of ethanol, the acquisition would be slower. However, if, like methamphetamine, the H_3 antagonists/inverse agonists increase the rewarding value of alcohol, the acquisition would be faster.

Another approach for assessing the effects of a drug on the rewarding properties of a drug of abuse is to use the (CPP) paradigm (Tzschentke, 1998; Tzschentke, 2007). Although there are various forms of the CPP paradigm, the basic principle is that animals will spend more time in a formally neutral environment once this has been paired with a drug of abuse. One potentially relevant methodological consideration is the use of a biased or an unbiased approach. In both approaches, rats are first tested for their spontaneous preference for one of the two compartments. However, whereas in an unbiased approach only animals without a clear biased are used, in a biased approach, all animals are included and the drug of abuse is usually given in the least preferred compartment. It would go beyond the scope of this paper to discuss the potential differences between the biased and unbiased approach. The reader is referred to other reviews on this subject (Tzschentke, 1998, 2007).

In general, dose-response curves for drugs of abuse are much simpler for CPP than for self-administration, and thus a change in CPP after pretreatment with an H_3 antagonist can be more easily interpreted. However, it is important to understand that CPP and self-administration are two different processes and therefore rely on (in part) different neurobiological substrates. Studies in which the effects of H_3 antagonists/inverse agonists on drug-induced CPP are examined have led to mixed results. Mostly, the H_3 antagonists/inverse agonists were found to reduce the ethanol-induced CPP (Nuutinen *et al.*, 2011a; b). Although in 129Sv mice, the ethanol-induced CPP was actually enhanced by ciproxifan (Nuutinen *et al.*, 2010). So far, only two studies have been done with other drugs of abuse, both using thioperamide: one found an increase in CPP induced by cocaine in mice (Brabant *et al.*, 2005) and the other showed a decrease in CPP induced by morphine in rats (Perez-Garcia *et al.*, 1999).

In addition to CPP and self-administration, many drugs of abuse also increase locomotor activity, a phenomenon that has traditionally been linked to the reinforcing properties of these drugs (Wise and Bozarth, 1987). Perhaps more important than the acute hyperactivity response, is the increase seen with repeated administration. This sensitization has been regarded as an essential prerequisite for drug self-administration, especially with the psychostimulant class of drugs (Robinson and Berridge, 1993). With respect to drug-induced hyperactivity, most studies using H_3 antagonists/inverse agonists seem to find either no effect or a small decrease. This was not only seen with the traditional imidazole-type drugs such as thioperamide and ciproxifan, but also with more novel non-imidazole drugs such as ABT-239 and BF2.649. A noticeable exception is GSK207040, which did not appear to reduce amphetamine-induced hyperactivity. When looking at sensitization, in most studies the H_3 antagonists/inverse agonists did not have a noticeable effect on this parameter (see Table 1). It is important in this respect to differentiate between a reduction in hyperactivity and a reduction in sensitization. The latter would imply a significant interaction between treatment and sessions. For instance, whereas two studies using cocaine and methamphetamine found clear effects on hyperactivity *per se* (albeit in the opposite direction) they did not find a significant drug × session interaction, suggesting that the sensitization as such remained unaffected (Brabant *et al.*, 2006; Motawaj and Arrang, 2011).

Pharmacological considerations

With respect to the different drugs of abuse, most studies evaluating the role of H_3 receptor antagonists/inverse agonists used either ethanol or psychostimulants (especially cocaine and methamphetamine) with two studies using H_3 knock-out mice, one where the effects on 3,4 methylene dioxymethamphetamine (MDMA) were examined and the other morphine. Moreover, the vast majority of the studies on alcohol were performed by only one group of researchers, as were the studies on cocaine. Given the differences in (design of the) paradigms used in the different laboratories, it is difficult to draw a firm conclusion. However, in general the data suggest that whereas H_3 receptor antagonists/inverse agonists tend to reduce the rewarding effects of ethanol, they seem to increase those for cocaine and methamphetamine. One possible explanation for this might be the difference in

the influence of these drugs on the dopaminergic system. Thus, whereas cocaine and methamphetamine directly increase the extracellular dopamine by blocking and/or reversing the dopamine transporter, ethanol indirectly increases dopamine, most likely via an indirect action on the dopaminergic cell bodies. In this respect, it should be remembered that whereas thioperamide by itself does not affect striatal dopamine release (Munzar *et al.*, 2004; Fox *et al.*, 2005; Giannoni *et al.*, 2010; Galici *et al.*, 2011), it does enhance the methamphetamine-induced release of dopamine (Munzar *et al.*, 2004), thereby possibly contributing to the rewarding properties of methamphetamine. Given that ethanol increases dopamine by altering the firing rate of dopaminergic cells, it is conceivable that H_3 antagonists/inverse agonists do not enhance the dopamine releasing effects (although this still needs to be investigated). An alternative (or additional) potential explanation for the differences may be related to the differences in pharmacokinetics between psychostimulants and ethanol (especially the role of cytochrome P450, see below).

A somewhat surprising finding is the difference between the psychostimulants with respect to the inhibitory effects of H_3 antagonists/inverse agonists on hyperactivity. Whereas these drugs block the hyperactivity induced by amphetamine and methamphetamine, they enhance the cocaine-induced hyperactivity (see Table 1). Also, in addition to potential differences in strain and species, dissimilarities between the H_3 receptor antagonists/inverse agonists may also underlie some of the discrepancies in the results obtained.

It is important to realize that the traditional H_3 receptor antagonists/inverse agonists such as thioperamide and ciproxifan are imidazole-containing compounds are metabolized by cytochrome P450, which also metabolizes some of the psychostimulants, most notably cocaine. In line with this, thioperamide has been shown to enhance plasma levels of cocaine in mice (Brabant *et al.*, 2009). This might (at least in part) explain why this drug enhanced cocaine-induced hyperactivity, especially since these potentiating effects of thioperamide could only be partially reversed by the H_3 agonists immepip, and the non-imidazole H_3 antagonist A-331440 did not influence cocaine induced hyperactivity. It has yet to be investigated whether these imidazole-containing drugs also affect the plasma levels of other psychostimulants. However, since both imidazole (thioperamide and ciproxifan) and non-imidazole (ABT-239 and BF2.649) type H_3 antagonists reduce methamphetamine-induced hyperactivity (see Table 1), it seems unlikely that pharmacokinetics play an important role here. Likewise, the potentiation of the methamphetamine-induced release of dopamine in the nucleus accumbens was seen after both peripheral and direct administration of the H_3 antagonists into the nucleus accumbens (Munzar *et al.*, 2004), also pointing to a pharmacodynamic rather than a pharmacokinetic interaction between the two drugs.

Species/strain considerations

A last factor that might contribute to the discrepancies found in the literature on the interactions between H_3 receptors and drugs of abuse is differences in strains and species. This is perhaps best illustrated by the finding that ciproxifan decreases ethanol-induced CPP in DBA/2J mice (Nuutinen *et al.*, 2011b) but increases it in the 129Sv strain (Nuutinen *et al.*, 2010). Species differences may also underlie some of the differences found in studies with methamphetamine. Thus, whereas most studies in mice found that methamphetamine-induced hyperactivity is decreased by H_3 antagonists/inverse agonists (see Table 1), the one study published in rats showed that thioperamide and ciproxifan actually increased methamphetamine-induced dopamine release and self-administration. Although this may also be in part due to differences in paradigms used, there are important differences between rats and mice with respect to the dopaminergic regulation of locomotor activity (Ralph-Williams *et al.*, 2002; Ralph and Caine, 2005). In mice D_1 agonists strongly enhance locomotor activity, whereas in rats they only induced only a weak hyperactivity. Given the intricate relationship between H_3 and D_1 and D_2 receptors (see also Figure 1), the species differences are not surprising. In line with this, we recently found that both thioperamide and a non-imidazole type H_3 antagonist did not affect methamphetamine-induced hyperactivity in Sprague Dawley rats (unpublished data).

Conclusions and outlook

Given the high levels of H_3 receptors in the dorsal and ventral striatum, and the intricate relationship between the H_3 receptors and the dopamine D_1 and D_2 receptors, it is not surprising that H_3 receptors have been studied in relation to drug addiction. Unfortunately, as evidenced by the summary in Table 1, there are quite a number of discrepancies in the literature, making it, at present impossible to determine unequivocally whether H_3 receptor antagonists/inverse agonists may be of relevance for the treatment of addiction. The most consistent findings have been reported for ethanol, where H_3 receptor antagonists/inverse agonists have generally been found to reduce intake and CPP (with the exception of the 129Sv strain). However, it should be noted that the vast majority of these data have been obtained by only one research group and it is important to see whether this can also be replicated by other laboratories. The recent study showing that the novel H_3 receptor antagonist/inverse agonist JNJ-39220675 inhibits ethanol self-administration in alcohol-preferring rats is encouraging in this respect (Galici *et al.*, 2011).

With respect to other drugs of abuse, the situation is less clear. Only one study has looked at self-administration (showing an enhancement of methamphetamine) and two at CPP (one showing an enhancement of cocaine the other showing a reduction of morphine). Thus, with respect to psychostimulants, H_3 receptor antagonists may be useful as substitution therapy, although more data with respect to self-administration and CPP is certainly necessary. Finally, an important issue that needs to be addressed is the potential role of pharmacokinetic interactions, since most studies have so far used imidazole-like compounds such as thioperamide and ciproxifan. Fortunately, more and more non-imidazole like compounds are now becoming available, many of which have already successfully been tested in phase I studies (such as BF2.649, GSK189254 and MK-0249). It will be important to determine whether these drugs have a similar effect compared to those observed with the traditionally used H_3

antagonists/inverse agonists. These new drugs are also more selective for the H_3 receptor, especially compared to thioperamide, which also shows affinity for H_4 receptors.

In summary, whereas there is a strong theoretical rationale for a role for H_3 receptors in drug addiction, so far with the possible exception of ethanol, the current literature does not allow us to draw any firm conclusion. In particular, further studies looking at drug self-administration using a range of different concentrations of the addictive drug need to be undertaken. In addition, given the differences found between the psychostimulants and ethanol, it would be of interest to see whether H_3 receptors also play a role in the actions of opiates such as morphine and heroin.

Acknowledgements

The author would like to thank Dr. Mark Gemkow (Evotec AG Hamburg, Germany) for valuable discussions.

Conflict of interests

I have no conflict of interest to declare.

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