



Review

5-HT receptors and reward-related behaviour: A review

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ABSTRACT

The brain's serotonin (5-HT) system is key in the regulation of reward-related behaviours, from eating and drinking to sexual activity. The complexity of studying this system is due, in part, to the fact that 5-HT acts at many receptor subtypes throughout the brain. The recent development of drugs with greater selectivity for individual receptor subtypes has allowed for rapid advancements in our understanding of this system. Use of these drugs in combination with animal models entailing selective reward measures (i.e. intracranial self-stimulation, drug self-administration, conditioned place preference) have resulted in a greater understanding of the pharmacology of reward-related processing and behaviour (particularly regarding drugs of abuse). The putative roles of each 5-HT receptor subtype in the pharmacology of reward are outlined and discussed here. It is concluded that the actions of 5-HT in reward are receptor subtype-dependent (and thus should not be generalized) and that all studied subtypes appear to have a unique profile which is determined by content (e.g. receptor function, localization – both throughout the brain and within the synapse) and context (e.g. type of behavioural paradigm, type of drug). Given evidence of altered reward-related processing and serotonergic function in numerous neuropsychiatric disorders, such as depression, schizophrenia, and addiction, a clearer understanding of the role of 5-HT receptor subtypes in this context may lead to improved drug development and therapeutic approaches.

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1. Introduction

1.1. Serotonin in reward-related processing

In its most basic form, a reward (an object or event, regardless of its origin) is something that an organism will expend energy to obtain or approach; in this context, it is operationally opposite to an aversive stimulus (e.g. Wise, 2004). A rich animal literature has shown that the brain neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) plays an important role in the regulation of reward-related processing. For instance, 5-HT is involved in natural reward-related physiology and behaviour, from feeding to sexual activity (for reviews, see Pfau, 2009; Wirtshafter, 2001). Recent studies in humans have supported this notion, showing for instance that 5-HT is involved in emotional regulation (see Cools et al., 2008 for review) and experiences as varied as the pleasantness of warmth (Lowry et al., 2009) or chocolate (McCabe et al., 2010).

Given 5-HT's role in reward-related functioning (Kranz et al., 2010), and that altered reward processing has been proposed in many psychiatric disorders (as reflected, for instance, by reduced motivation to obtain rewards in depression and schizophrenia), it should not be surprising that serotonergic dysfunction has been associated with numerous neuropsychiatric pathologies and, as such, has been a main target for therapeutic drug development. Most notably, extensive research has implicated this system in depression (e.g. a typical first-line treatment is the use of selective serotonergic reuptake inhibitors) (Trivedi et al., 2006), anxiety (Hood et al., 2010), schizophrenia (Emsley, 2009) and addiction (Rothman et al., 2008). Nonetheless, there is an incomplete understanding of the pharmacological mechanisms underlying the role of 5-HT in reward-related processing; this is necessary for a full understanding of both healthy and pathological reward system functioning and for the development of future effective drug therapies for disorders that entail dysfunction of brain reward systems.

Serotonin-containing neurons make extensive connections to other neural systems in reward-related brain areas. Clusters of serotonergic cell bodies are divided into nine nuclei or cell groups (B1–B9) (Dahlstrom and Fuxe, 1964) along the midline (or raphe) from the medulla to the midbrain. The primary ascending projections originate from the anterior (i.e. dorsal and median) raphe nuclei and account for the majority of 5-HT innervation of the forebrain (Azmitia and Segal, 1978). Innervation by these anterior raphe nuclei is extensive, diffuse, and overlapping, and includes areas known to be involved in aversion- and reward-related regulation such as the nucleus accumbens septi (NAc), ventral tegmental area (VTA), substantia nigra, hippocampus, amygdala, and prefrontal cortex (Hensler, 2006; Ikemoto, 2010; Lechin et al., 2006). In addition to having reciprocal connections with many reward-related brain areas, 5-HT regulates the transmission of all major neurotransmitters (Fink and Gothert, 2007), including the well-studied dopamine (Alex and Pehek, 2007). In a recent review by Kranz et al. (2010), the authors present converging evidence, particularly from pharmacology, electrophysiology, and human brain imaging, that the 5-HT system is as important for reward processing as dopamine. The current review focuses on the specific putative roles of individual 5-HT receptor subtypes in this processing.

1.2. The pharmacology of reward-related serotonergic mechanisms

The idea that 5-HT may be involved in the regulation of reward-related behaviours likely began with the work of James Olds and his colleagues. They showed that rats decreased their motivated responding following lateral hypothalamic microinjections of 5-HT (Olds et al., 1964), about a decade following their discovery that rats would self-administer electrical stimulation into similar regions (Olds and Milner, 1954). Indeed, many studies have since shown that stimulation of serotonin-rich nuclei of the brain (i.e. median and dorsal raphe nuclei) can sustain intracranial self-stimulation (ICSS) (e.g. Broadbent and Greenshaw, 1985; Van Der Kooy et al., 1978). At least one study has demonstrated that perfusion of 5-HT close to the ventral tegmental area (a key area of the mesolimbic system which contains the cell bodies of mesocorticolimbic dopamine-containing projections) increases rates of ICSS of the medial forebrain bundle (Redgrave and Horrell, 1976). Paradoxically, selective lesioning of serotonergic cells appears to facilitate ICSS (Poschel et al., 1974). In addition, increased reward is seen with conditioned place preference following administration of drugs that increase brain 5-HT (Subhan et al., 2000), although increases in 5-HT generally correlate with decreases in self-administration (Lyness et al., 1980; Yu et al., 1986). These conflicting, and often difficult to interpret, results are likely due to the high number of 5-HT targets (which can be located on multiple cell types within and/or across brain regions – resulting in the potential for each receptor subtype to have opposing effects on reward; for an excellent narrative review on the history of 5-HT and the discovery of its receptor subtypes, see Green, 2006). The use of behavioural models with reward-selective measures are discussed below in Section 2.4.

The rapid growth of knowledge around existing 5-HT receptor subtypes, in conjunction with improved techniques and a more collaborative environment among fields encompassing biomedical research and chemical engineering, allowed for the rapid development of numerous ligands in the 1980s and 1990s (Green, 2006). The early identification of 5-HT receptor selective ligands – such as mianserin and eltopazine, which were originally considered antagonists for the 5-HT₂ receptor family, though eltopazine was also known to be an agonist for the 5-HT_{1B} receptor – allowed for a more detailed investigation of 5-HT receptor subtype function (Peroutka and Snyder, 1981; Schipper et al., 1990). Although some studies using these compounds reported reward-related findings consistent with more recent studies (for instance, the finding by Risinger and Oakes (1996) showing that mianserin did not induce place conditioning alone, but did enhance alcohol-induced place preference), others had seemingly contradictory findings (Rocha et al., 1993). These were later clarified through the use of additional, more selective, ligands (e.g. Mosher et al., 2005; Hayes et al., 2009a,b), and an improved knowledge of 5-HT receptor pharmacology.

Taken together, these data underscore the need to clarify the role of 5-HT in reward-related processing and behaviour. An increase in the number and development of much more selective pharmacological agonists and antagonists, and refinement of reward-related behavioural measures, over the past two decades has been essential to this endeavour. As a result of this advancement of knowledge on many fronts (e.g. multiple, readily available, selective ligands; improved understanding of 5-HT receptor subtypes) this is perhaps

the first opportunity to extensively review the literature on this topic – although the authors' acknowledge that future advancements may result in conceptual revisions to the present work. Nonetheless, this review aims to add clarity and insight to our current understanding of the role of 5-HT receptor subtypes in reward-related behaviour and to underscore the relevant contents (e.g. subtype function and localization, drug delivery parameters, species under investigation) and contexts (e.g. type of reward-related paradigm used; mechanism of drug used to produce reward, such as cocaine vs. ethanol) which are likely important in this regard.

2. Review methods and criteria

2.1. Inclusion criteria

We aimed to identify all studies which focused on the functionally selective agonism or antagonism of 5-HT receptor subtypes (discussed briefly below in Section 2.3) on the reward-related paradigms of intracranial self-stimulation (ICSS), self-administration, and place conditioning (described briefly below in Section 2.4) through numerous PubMed searches and subsequent searches through relevant reference sections and review papers.

In order to clarify the role of specific 5-HT receptor subtypes in reward, this review includes only studies which investigated the effects of selective 5-HT receptor agonists and antagonists, administered systemically or intracranially, on place conditioning, ICSS and drug self-administration. Some compounds with actions at multiple 5-HT receptor subtypes (sometimes referred to as 'mixed' 5-HT compounds) have been selectively included for completeness (for instance, where there is a lack of data using more selective ligands or when a mixed antagonist is used to block the effects of a putatively selective agonist), where their actions are believed to be predominantly at one or two receptor subtypes. In addition, effects of 5-HT receptor ligands on behaviours induced by drugs of abuse such as cocaine, nicotine, amphetamine, morphine and ethanol, and ligands that act at targeted receptor subtypes were also included; their putative mechanisms of action, and their many interactions with other neurochemical systems, can be found elsewhere in a number of reviews. In addition, studies involving genetically manipulated mice whose manipulations involved only the specific alteration of 5-HT receptor subtypes (i.e. knock out or transgenic mice) and animals bred for increased response to a drug of abuse (e.g. alcohol preferring rats) are also included where appropriate. However, the reader is cautioned to consider these results in light of the potential compensatory and/or developmental alterations which may be associated with such manipulations. There is a paucity of studies dealing with the role of 5-HT receptors in the context of reward in non-adult organisms – because of this, only studies involving adult mammals were considered for inclusion. The authors acknowledge that a review of the literature on adolescents/developmental stages and 5-HT receptors would be of value, but recognize, as recently pointed out, we do not yet know the manner in which “alterations in serotonin signaling [may] differentially influence circuit formation in the CNS in early and later development. . . [and] . . . the critical developmental windows for these effects and how [they] translate into complex behaviours in the adult” (Daubert and Condrón, 2010).

2.2. Exclusion criteria

Studies that have used receptor ligands whose predominant actions are on multiple neurotransmitter systems (so-called 'mixed' compounds) are difficult to interpret, and thus have been largely excluded. However, some studies using selective ligands in conjunction with ligands that act directly at a putatively small

number of receptor sites (e.g. non-specific dopamine or 5-HT receptor antagonists, such as sulpiride) have been included for clarity and comparison at the authors' discretion. Although studies involving drugs of abuse (in conjunction with selective 5-HT ligands) were included in this review, those investigating their withdrawal effects and effects related to chronic exposure are not (see Section 2.4 below for additional related comments). This is because any effects which are, in part, the result of circuitry neuroadaptations (e.g. changes in synaptic plasticity or receptor expression) become increasingly difficult to interpret. In addition, the effects of compounds that alter 5-HT related enzymes, induce serotonergic lesions, interfere with 5-HT precursors or broadly affect 5-HT release or reuptake are beyond the scope of this review as they all have broad effects on 5-HT neurotransmission and, as such, will obscure any interpretations related to specific receptor subtype function. For similar reasons, studies looking at natural reward behaviours, such as feeding or sexual activity, are not included (but see Dayan and Huys, 2009 for a recent review of 5-HT in that broad context).

2.3. Serotonin receptors and their ligands

The characterization of 5-HT receptor subtypes (including their putative roles in some neuropsychiatric disorders) has been reviewed extensively elsewhere (Barnes and Sharp, 1999; Hoyer et al., 2002; Kitson, 2007). Briefly, 5-HT receptors are currently divided into seven receptor families (5-HT₁₋₇) based on amino acid sequence, signal transduction mechanisms, pharmacology and functional criteria (see Table 1). Within each family, receptors are further divided into receptor subtypes designated by a letter (e.g. 5-HT_{1A} receptor). Their various roles in regulating reward-related behaviour is likely, in part, due to their effects on second messengers and ionic conductance as well as their differential distributions throughout the nervous system. A summary of 5-HT receptor subtypes, their mechanism of action, high-density brain localization, and currently suggested reward-related localizations are found in Table 1. For an indication, beyond what is noted in the present review, of the putative locations of reward-related 5-HT receptors, the reader is referred to excellent reviews by Alex and Pehek (2007) and McBride et al. (1999). In addition, Supplementary Table 1 outlines the receptor profile of ligands mentioned in this review, as well as some commonly used 'mixed' ligands which were excluded.

2.4. Animal models of reward-related behaviour

Changes in reward-related behaviour are measured largely by three paradigms: place conditioning, intracranial self-stimulation (ICSS), and drug self-administration. These paradigms were chosen as they directly activate the brain's reward-related circuitry – either through electrical stimulation (ICSS) or receptor activation (systemic or local drug injection) – and they are sensitive to changes in the rewarding properties of drugs, especially drugs of abuse (Wise, 2002).

Repeated administration of many drugs (e.g. amphetamine) can result in enhanced sensitivity (i.e. sensitization) to the future use of similar drug doses – which is often, but not always, reflected in increased locomotor activity and ostensibly parallel increases in reward. Studies that focused on the repeated administration of selective 5-HT ligands are included in this review (e.g. Davidson et al., 2002, 2004) as we believe that this inclusion helps to provide additional clarity. Similarly, experiments specifically targeting learning and memory processes are only included if they focus on selective measures of reward.

Place conditioning measures the conditioned rewarding properties of a stimulus (e.g. pharmacological compound). There are typically three phases to a place conditioning experiment:

Table 1
5-HT receptor subtypes. List of 5-HT receptor subtypes, major localization, and their effects on metabotropic G-protein coupled receptor-activated second messengers or on ion channels (i.e. 5-HT₃ receptors). In addition, the putative reward-related localization of these pre- and/or post-synaptic receptors is also indicated – though it is important to note that most are unknown (as denoted by –) and other sites may yet be discovered.

Receptor family (subtype)	Effect	High-density localization	Suggested reward-related localization	Selected references
5-HT _{1A}	G _{ij/o} (↓ cAMP)	C, HC, RN	Pre- (and possibly post) synaptic RN	Ahn et al. (2005), Muller et al. (2007), and Ogren et al. (2008)
5-HT _{1B}		Col, GP, HC, SN, VP	Post- and/or pre-synaptic NAc, VTA	Hoplight et al. (2006), Sari (2004), and Sari et al. (1999)
5-HT _{1D}		Low expression in BG, DR, GP, SN, VP	–	Bonaventure et al. (1998)
5-HT _{1E}		C, CD	–	Klein and Teitler (2009)
5-HT _{1F}		C, CD, EC, NAc, OB, OT, RN, T	–	Lucaites et al. (2005)
5-HT _{2A}	G _q (↑ IP ₃ /DAG)	C, BG, EC, OB, PN	Post-synaptic VTA	Ding et al., 2009 and Fletcher et al. (2007)
5-HT _{2B}		PN, stomach, low expression in brain	–	Bonhaus et al. (1995) and Kursar et al. (1994)
5-HT _{2C}		AM, CP, HC, NAc, RN, SN, VTA	Post-synaptic RN, VTA, (likely not NAc)	Berg et al. (2008a), Fletcher et al. (2004), Giorgetti and Tecott (2004), and Hayes et al. (2009a)
5-HT ₃	Non-selective cation channel (mainly Na ⁺ , K ⁺)	AP, EC, PN	Post-synaptic posterior (not anterior) VTA	Rodd et al. (2010) and Thompson and Lummis (2007)
5-HT ₄	G _S (↑ cAMP)	BG, Col, HC, PN	–	Fayyaz and Lackner (2008) and King et al. (2008)
5-HT _{5A}	G _{ij/o} or G _S ? (↓ cAMP)	C, CB, HC, OB	–	Nelson (2004)
5-HT _{5B}		–	–	Nelson (2004)
5-HT ₆	G _S (↑ cAMP)	AM, C, CD, HC, NAc, OT	Post-synaptic VTA	Ferguson et al. (2008) and King et al. (2008)
5-HT ₇	G _S (↑ cAMP)	C, HC, HT, T	–	Cifariello et al. (2008)

Source: Adapted from Ciranna (2006) and Hannon and Hoyer (2008).

Abbr.: AM, amygdala; AP, area postrema; BG, basal ganglia; C, cortex; CB, cerebellum; Col, colliculi; CD, caudate putamen; CP, choroid plexus; RN, raphe nuclei; EC, entorhinal cortex; GP, globus pallidus; HC, hippocampus; HT, hypothalamus; NAc, nucleus accumbens; OB, olfactory bulb; OT, olfactory tubercle; PN, peripheral neurons; SN, substantia nigra; T, thalamus; VP, ventral pallidum; VTA, ventral tegmental area.

pre-conditioning, conditioning, and post-conditioning. Place conditioning occurs when two or more previously neutral but distinct environments (referred to as the pre-conditioning phase) are paired with different unconditioned stimuli (e.g. drugs of abuse; referred to as the conditioning phase). When animals are subsequently given free-access (referred to as the post-conditioning phase), the time spent in each environment is used as an index of the rewarding/aversive properties of the unconditioned stimulus (the reader is referred to Tzschenke, 2007 for a comprehensive review of this paradigm). The effects of a test drug (e.g. one targeting a receptor subtype) alone on place conditioning, as well as its effects on reward or aversion processing induced by another drug (particularly drugs of abuse), is commonly investigated. Also, the acquisition (where drugs are co-administered during the conditioning phase of the experiment) or the expression (where the drugs of interest are administered only on the test or post-conditioning day; to investigate context-dependent effects) of place conditioning can also be investigated.

Intracranial self-stimulation (ICSS) studies have employed a number of methods throughout the past fifty years, though mainly they can be divided into two main groups: those methods that are currently believed to be rate-free and reward-selective and those that are not (Greenshaw and Wishart, 1987; Stellar and Rice, 1989). In the ICSS paradigm, animals are trained to perform a behaviour (e.g. pressing a lever) contingent on the delivery of electrical stimulation to specific brain areas that acts as a reinforcer or reward. Some studies employing measures of ICSS based on response rate are included in this review; the reader should interpret these data with caution, as they are not considered independent of performance effects (e.g. drug-induced effects on performance and response rates do not necessarily indicate changes in reinforcement or reward). These studies have been indicated in Table 2A by the

footnote 'a'. The most commonly used methods, the rate-frequency or rate-current curve-shift method, measures the frequency or current, respectively, of stimulation that produces half-maximal responding, as this is sensitive to changes in reinforcement induced by drugs, such as drugs of abuse (see Miliareisis et al., 1986; for review, see Carlezon and Chartoff, 2007; Wise, 1996). Of these two methods, the rate-frequency shift method is considered superior as changes in the magnitude of stimulation current will alter the volume of tissue affected by the electrical stimulus (Ranck, 1975).

Drug self-administration has emerged as a paradigm in which a variety of operant schedules of reinforcement can be used. Each schedule may provide important manipulations aimed at investigating different facets of the behaviour. As such, while the use of various schedules may provide convergent verification, they may also reveal important differences in self-administration behaviour. Most commonly, in the simple fixed-ratio schedule a fixed number of responses are required for drug delivery (e.g. FR4 requires 4 responses for one delivery), while the progressive ratio (PR) schedule requires incremental increases in responding to achieve each drug delivery. It is suggested that this schedule is best at determining the rank-order effectiveness for reinforcers, as determined mainly by the breaking point (the point at which the animal will no longer respond). For a correct interpretation of the data, it is imperative to note that dose–response curves for self-administered drugs are nearly all inverted U shaped (i.e. there is a dose at which animals will respond maximally, and lower/higher doses typically lead to progressively decreased responses). This suggests that, for instance, modulatory treatments (e.g. other co-administered drugs) that enhance the effects of the self-administered compound may actually result in increased responding at low doses and decreased responding at higher doses, or vice versa. In depth discussion of

these schedules is covered extensively elsewhere (Boulton et al., 1993; Shippenberg and Koob, 2002).

3. Results of review

The specific results of the review are outlined in three tables. All tables use the symbols ● and ○ to identify agonists and antagonists, respectively. Table 2A lists the results of studies that looked at 5-HT receptor subtype function in intracranial self-stimulation (ICSS), note that the symbol Φ is used to identify studies that do not clearly distinguish between reward and motor effects; Table 2B lists the results related to self-administration; Table 2C lists the results related to place conditioning (note that unless otherwise specified, results of conditioned place preferences, CPP, or aversions, CPA, reflect the expression phase (in the absence of drug treatments), as opposed to the acquisition phase during which drugs are administered. A general comparison of receptor subtype agonism/antagonism across the three reward-related models is presented in Table 3. For a summary of all 5-HT receptor subtypes and their function and localization, the reader is referred to Table 1.

4. Discussion

This review compared the roles of 5-HT receptor subtypes, using pharmacologically selective manipulations, in animal models of reward-related behaviour (i.e. intracranial self-stimulation (ICSS), self-administration, place conditioning). These behavioural models were chosen as they involve the direct activation of the brain's reward-related circuitry (either through electrical or receptor stimulation), have reward-selective measures, and are sensitive to the reinforcing properties of drugs of abuse (for extensive reviews, see Carlezon and Chartoff, 2007; Sanchis-Segura and Spanagel, 2006; Tzschentke, 2007). Overall, the results underscore the importance of 5-HT in reward-related processing, and show that its role is content-related (e.g. receptor subtype and function) and context-related (e.g. type of reward-related paradigm; mechanism of drug producing reward, such as cocaine vs. ethanol; relative amount/concentration of ligand used) dependent.

In terms of content, the most important determinants of reward effects appear to be those related to individual receptor subtypes (e.g. mechanism of action, constitutive/tonic receptor activity), although which species are under investigation (e.g. alcohol preferring rats, monkeys), and other model-specific parameters (e.g. route and timing of drug administration; type of reward measures) must also be taken into careful consideration – these can be compared across Tables 2A–2C. In terms of context, these results demonstrate clearly that the role of each 5-HT receptor subtype must be considered carefully within the context of the behavioural approach and experimental conditions under investigation. For instance, while 5-HT_{1B} receptor stimulation enhances the rewarding-properties of cocaine and may even support self-administration alone at low levels (Parsons et al., 1998), it cannot be predicted that it will enhance reward-related measures when investigated with ICSS (Hayes et al., 2009b), place conditioning (Cervo et al., 2002), or the self-administration of other drugs of abuse (Fletcher et al., 2002a; Maurel et al., 1999).

Taken together, results across studies reveal that general conclusions can be made about the role of many receptor subtypes in relation to individual reward-related models and drugs of abuse – as seen in Table 3 – while broader claims about 5-HT in reward are difficult to make (as discussed below). Interestingly, while the ongoing development of highly selective ligands is adding substantively to our knowledge in this regard, all 5-HT receptor subtypes that have been reasonably investigated to date appear to play some role in mediating reward-related behaviours. Thus, although the

role of 5-HT in reward-related processing is highly complex, clearer patterns have emerged following a closer examination of the function of each receptor subtype across behaviours (for a detailed comparison across studies, the reader is referred to the results listed in Tables 2A–2C). The individual receptor profiles regarding the pharmacology of reward-related behaviour (indicating which specific contents and contexts are likely most important in each profile), and their potential implications, are discussed below with regard to each 5-HT receptor subtype.

4.1. Serotonin 1A receptors

Along with the 5-HT₃ receptors, 5-HT_{1A} receptors have been the most widely studied of the 5-HT family in the context of reward-related behaviour. This is largely due to the early development of the selective agonists, 8-OH-DPAT and buspirone. However, it is important to note that these ligands have putatively weak pharmacological and behavioural effects at 5-HT₇ (Raully-Lestienne et al., 2007; Vanhoenacker et al., 2000) and dopamine D2 receptors (van Wijngaarden et al., 1990), respectively, which may account for some past discrepancies. Nonetheless, these ligands, along with highly selective receptor antagonists such as WAY 100635, have been used extensively to provide insight into the role of 5-HT_{1A} receptors in reward-related behaviours.

In several studies, following systemic administration, low doses of the 5-HT_{1A} receptor agonist 8-OHDPAT decreased stimulation thresholds, suggesting facilitation of the rewarding effects of intracranial self-stimulation (but see Ahn et al., 2005 for an exception), and produce a conditioned place preference (CPP), while high doses have the opposite effect (Harrison and Markou, 2001; Papp and Willner, 1991). Receptor antagonists appear to have no effect on their own (e.g. Budygin et al., 2004; Markou et al., 2005). The effect of low doses of 5-HT_{1A} agonists appears to be mediated by 5-HT_{1A} receptors in the midbrain raphe nuclei (which contain the cell bodies of ascending 5-HT containing neurons; e.g. Ahn et al., 2005; Fletcher et al., 1993, 1995) as suggested by studies which found increased reward following the microinjection of 8-OHDPAT (e.g. Fletcher et al., 1993, 1995; Ahn et al., 2005), these effects are behaviourally specific as microinjections of 8-OHDPAT into these raphe nuclei have opposite effects on locomotion *per se* (Ahn et al., 2005). It has been postulated that these biphasic effects are due to the higher affinity of somatodendritic autoreceptors (i.e. pre-synaptic or cell body 5-HT_{1A} receptors that inhibit 5-HT release) over post-synaptic receptors. This preference for pre- vs. post-synaptic receptors may also, in part, be due to the fact that there is a receptor reserve in the cells of the raphe nuclei but not in postsynaptic cells (Yocca et al., 1992). Additionally, it has also been shown that 5-HT_{1A} receptors in the anterior raphe preferentially may couple to different types of G proteins compared to their target regions (e.g. hippocampus) (Mannoury la Cour et al., 2006).

While 5-HT_{1A} receptor agonists and antagonists are not self-administered alone, they may attenuate the effects of cocaine and ethanol self-administration. Their inhibitory effects on cocaine self-administration are largely found with the use of higher doses (e.g. Parsons et al., 1998; Peltier and Schenk, 1993), strongly implicating the activation of post-synaptic receptors. Studies in monkeys using far lower doses also reported increased cocaine reward (Czoty et al., 2005; Nader and Woolverton, 1990). Although many studies have also found that 5-HT_{1A} receptor activation decreases ethanol self-administration, in general, it is concluded that these effects are likely non-specific (e.g. Roberts et al., 1998; Silvestre et al., 1998) as decreases in alcohol intake or preference are typically paired with overall reductions in non-alcohol-related fluid intake or responding. Although one study has suggested that receptor antagonism may decrease consumption (Zhou et al., 1998), another has demonstrated antagonist-induced CPP when combined with subthreshold

Table 2A

The effect of 5-HT receptor subtype ligands on intracranial self-stimulation.

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species (strain)	Additional drug or treatment	Effective doses (route and timing)	Electrode stimulation site	Method type	Reward effects	Motor effects	References
1A	● Buspirone (0–3 mg/kg)	1, 3 mg/kg; i.p.	Lister rats	–	–	Mid-LH	Fixed-current/frequency (response rate)	Φ Decreased response rate		Montgomery et al. (1991)
	● 8-OH-DPAT (0–0.3 mg/kg)	0.003 mg/kg; i.p. 0.1, 0.3 mg/kg; i.p.						Φ Increased response rate		
	● 8-OH-DPAT (0–5.0 μg)	1.0, 2.5, 5.0 μg (intra-median raphe)	Wistar rats	–	–	MFB	Frequency-thresholds	Decreased thresholds (increased reward)	No effect	Fletcher et al. (1995)
	● 8-OH-DPAT (0–0.3 mg/kg)	(s.c.; –30 min)	Wistar rats	● p-MPPI	0.03, 0.3, 1.0 mg/kg (s.c.; –135 min)	Posterior LH	Current-thresholds	0.03 mg/kg decreased thresholds; 0.1, 0.3 mg/kg increased thresholds; effects attenuated by p-MPPI	No effect	Harrison and Markou et al. (2005)
	● p-MPPI (0–10 mg/kg)	(s.c.; –135 min)		–	–			No effect		
	● 8-OH-DPAT (0–5.0 μg)	(intra-dorsal raphe)						1.0, 2.5 μg decreased thresholds		
	● 8-OH-DPAT (0–0.3 mg/kg)	0.1, 0.3 mg/kg (s.c.; –10 min)	SD rats	● WAY 100635	0.1 mg/kg (s.c.; –30 min)	VTA	Frequency-thresholds	Increased thresholds; blocked by WAY 100635 (no effect alone)	Decreased (impaired motor responding); blocked by WAY 100635 (no effect alone)	Ahn et al. (2005)
● 8-OH-DPAT (5.0 μg)	(intra-dorsal raphe)						Decreased thresholds; blocked by WAY	No effect, but decrease in locomotion in a separate experiment		
		(intra-median raphe)					Decreased thresholds; blocked by WAY	No effect, but decrease in locomotion in a separate experiment		
1B	● CP 94253 (0–5 mg/kg)	5 mg/kg (s.c.; –20 min)	SD rats	● GR 127935	10 mg/kg (s.c.; –40 min)	VTA	Frequency-thresholds	Increased thresholds; attenuated by GR 127935 (no effect alone)	No effect	Hayes et al. (2009b)
	● MDL 100907 (0–2 mg/kg)	(s.c.; –30 min)	SD rats	Amphetamine (0–1 mg/kg)	(i.p.; –15 min)	VTA	Thresholds (defined as the shortest train duration that maintained 50% of the mean maximal response rate)	Φ Amphetamine reduced thresholds (significant doses not specified); administration of MDL 100907 did not alter the effects of amphetamine		Moser et al. (1996)

2A	● MDL 100907 (0–0.33 mg/kg)	(s.c.; 0 min; testing every 30 min over 4 h)	SD rats	–	–	LH	Frequency- thresholds	No effect	No effect	Benaliouad et al. (2007)
	● TCB 2 (0–0.3 mg/kg)	0.3 mg/kg (i.p.; –20 min)	SD rats	Cocaine ● R 96544 (0–3 mg/kg)	5 mg/kg (i.p.; –5 min) (s.c.; –20 min)	MFB	Frequency- thresholds	TCB increased thresholds, but did not affect cocaine-induced reward; attenuated by R 96544 (no effect alone)	No effect	Katsidoni et al. (2010)
2C	● Ro 60-0175 (0–3 mg/kg)	3 mg/kg (i.p.; –30 min)	Wistar rats	–	–	VTA	Chronic stress-induced increases in frequency- thresholds	∅ Ro compounds attenuate stress-induced increases in thresholds; no effect on controls		Moreau et al. (1996)
	● Ro 60-0332 (3 mg/kg)	3 mg/kg (i.p.; –30 min)								
	● WAY 161503 (0–1 mg/kg)	1 mg/kg (s.c.; –10 min)	SD rats	–	–	VTA	Frequency- thresholds	Increased thresholds	No effect	Hayes et al. (2009a)
	● WAY 161503 (0–1.5 µg/side)	(bilateral nucleus accumbens shell)						No effect	No effect	
	● WAY 161503 (0–3 mg/kg)	1, 3 mg/kg (s.c.; –20 min)	SD rats	Cocaine	5 mg/kg (i.p.; –5 min)	MFB	Frequency- thresholds	WAY increased thresholds; attenuated by SB (no effect alone); cocaine-induced reward was attenuated by WAY and enhanced by SB	No effect (although the highest dose of WAY decreased RMAX)	Katsidoni et al. (2010)
	● WAY 161503 (0.15–0.3 µg/side)	0.3 µg/side (bilateral medial prefrontal cortex, VTA, NAc shell and core)		● SB 242084 (0–1 mg/kg)	(i.p.; –20 min)			The highest dose of intra-NAc shell/core and medial prefrontal cortex (but not VTA) WAY attenuated cocaine-induced reward (without having an effect alone)		
	● Ondansetron (0–1 mg/kg)	(s.c.; –30 min)	Lister hooded rats; PVG hooded rats	Amphetamine (0.5 mg/kg)	(s.c.; 0 min)	LH Nicotine (0.4 mg/kg)	Current- thresholds	∅ Ondansetron had no effect on amphetamine-induced increased responding; it blocked the early depressant effects of nicotine in naïve rats but had no effect on increased responding seen in the late phase; it had no effect alone		Herberg et al. (1992) and Montgomery et al. (1993)
	● Ondansetron (0–0.2 mg/kg)	(s.c.; –30 min)	SD rats	Nicotine (0.6 mg/kg)	0.6 mg/kg (s.c.; –20 min)	VTA	Frequency- thresholds	No effect on nicotine-induced threshold decreases or alone	No effect	Greenshaw (1993b) and Ivanova and Greenshaw (1997)

Table 2A Continued

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species (strain)	Additional drug or treatment	Effective doses (route and timing)	Electrode stimulation site	Method type	Reward effects	Motor effects	References
3	● Ondansetron (0–0.1 mg/kg)	–	Wistar rats	–	–	MFB	Current-thresholds	∅ No effect	No effects	Borisenko et al. (1996) Rompre et al. (1995)
	● Granisetron (0–3 mg/kg)	0.003, 3 mg/kg (s.c.; 0 min)	Lister hooded rats	Morphine (2.5 µg)	2.5 µg (unilateral intra-VTA; –30 min)	A caudal mesencephalic site above the VTA	Frequency-thresholds	3 mg/kg Granisetron blocks morphine-induced threshold decreases; 0.003 mg/kg Granisetron increased thresholds alone (though at no other doses)		
	● Y-25130 (0–3 mg/kg)	0.3, 3 mg/kg (i.p.; –30 min)	Long-Evans rats	Cocaine (0, 4 mg/kg)	(i.p.; 0 min)	MFB-LH	Current-thresholds	Threshold decreasing effects of cocaine were blocked by Y-25130; no effects alone	Did not alter response latencies	Kelley and Hodge (2003)
4	● SB 204070A (0–10 mg/kg)	(i.p.; –10 min)	Lister Hooded rats	–	–	LH	Frequency-thresholds	No effects were noted		Reavill et al. (1998)

∅ Study cannot distinguish between reward and motor effects.

● Agonist.

● Antagonist.

Table 2B

The effect of 5-HT receptor subtype ligands on self-administration.

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species	Self-administered drug (dose range and route)	Effective doses	Schedule of reinforcement	Effects	References
1A	● 8-OH-DPAT (0–0.5 mg/kg)	0.5 mg/kg (s.c.; –30 min)	SD rats	Cocaine (0–0.5 mg/kg/infusion)	0.125 mg/kg/infusion	FR1	Decreased responding	Peltier and Schenk (1993)
	● 8-OH-DPAT (0–1.0 mg/kg)	0.3 mg/kg (s.c.; –15 min)	Wistar rats	Cocaine (0.125 mg/kg/infusion)	0.125 mg/kg/infusion	PR	Reduced intake (no change in break point)	Parsons et al. (1998)
	● 8-OH-DPAT (0–0.003 mg/kg)	0.0003–0.003 mg/kg	Squirrel monkeys (n = 3)	Cocaine (0.3, 1.0, 2.0 mg/kg; i.m.)	–	Second-order	Dose-dependent increased responding	Nader and Woolverton (1990)
	● Buspirone (0–0.03 mg/kg)	0.001–0.03 mg/kg						
	● 8-OH-DPAT (0.01–0.1 mg/kg)	0.01 mg/kg (i.v.; –5 min)	Cynomolgus monkeys (n = 5)	Cocaine (0.003–0.03 mg/kg/infusion)	0.003 mg/kg	FR50	Increased rates of responding (though decreased rates in one monkey)	Czoty et al. (2005)
	● 8-OH-DPAT (0–1.0 mg/kg)	0.3, 1.0 mg/kg (s.c.; –15 min)	Wistar rats	Cocaine (0.125 mg/infusion)	–	PR	Decreased cocaine intake (0.3 mg/kg) and break points (0.3, 1.0 mg/kg); no change in time to reach break point	Parsons et al. (1998)
	● m-MPPI (0–10 mg/kg)	10 mg/kg (s.c.; –25 min)					Decreased intake with reduced break point and an increase in time to reach break point	
	● WAY 100635 (0–1.0 mg/kg)	0.3, 1.0 mg/kg (s.c.; –30 min)	SD rats	Cocaine (0.5 mg/kg/infusion); priming 10, 20 mg/kg	0.5 mg/kg/infusion	FR5	Decreased reinstatement responding	Schenk (2000)
	● Buspirone (0–1 mg/kg)	0.1–1.0 mg/kg (i.v.; –15 min) (i.v.; –15 min)	Rhesus monkeys (n = 4)	Cocaine (0–0.05 mg/kg/infusion)	0.02 or 0.05 mg/kg (to maintain 40–100 infusions/session)	FR10	Agonist increased cocaine responding at 0.1 and 0.56 mg/kg; decreased responding at 1.0 mg/kg	Gold and Balster (1992)
	● Gepirone (0–1 mg/kg)						Gepirone had no effect at any dose	
	● 8-OH-DPAT (0–1.0 mg/kg)	0.3, 1.0 mg/kg (s.c.; twice daily over 4 days)	SD rats	Ethanol (10%, oral) + 3% glucose	–	Two-bottle choice (water vs. ethanol)	Decreased preference and consumption of ethanol + sucrose solution	Silvestre et al. (1998)
	● Buspirone (0–1.0 mg/kg)	–					Non-specific decrease in fluid intake	
	● 8-OH-DPAT (0–1.0 mg/kg)	0.5, 1.0 mg/kg (i.p.; –30 min)	SD rats	Ethanol (8%, oral)	–	FR2	Reduced responding and intake	Wilson et al. (1996, 1998)
	● Buspirone (0–10 mg/kg)	1, 5, 10 mg/kg (i.p.; –30 min)						
● 8-OH-DPAT (0.1 mg/kg)	0.1 mg/kg (i.p.; –30 min)	SD rats	Ethanol (8%, oral)	–	Secondary reinforcer (light)	Reduced lever responding	Wilson et al. (2000)	
● Buspirone (0–5 mg/kg)	1.0, 5.0 mg/kg (i.p.; –30 min)							
● 8-OH-DPAT (0–1.0 mg/kg)	0.5, 1.0 mg/kg (s.c.; –15 min)	Wistar rats	Ethanol (10%, oral)	–	Two-bottle choice (water vs. ethanol)	Decreased ethanol and water responding	Roberts et al. (1998)	
						Increased water responding only		
● Ipsapirone (0–20 mg/kg)	0.25 mg/kg (s.c.; –15 min)	Wistar rats	Ethanol (0–20%, oral)	1.25–20%	FR1	Decreased ethanol responding (irrespective of % ethanol); decreased water responding only at the 20 mg/kg dose	Schreiber et al. (1999)	

Table 2B (Continued)

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species	Self-administered drug (dose range and route)	Effective doses	Schedule of reinforcement	Effects	References
1B	● Buspirone (0–10 mg/kg)	0.0025–0.16 mg/kg (s.c.) 2.5, 10 mg/kg (s.c.)	Wistar (high and medium alcohol preferring)	Ethanol (3%, oral)	–	Two-bottle choice (water vs. ethanol)	Decreased ethanol (and total fluid) intake in medium alcohol preferring rats; no effect in high p-rats Increased ethanol (and total fluid) intake in medium alcohol preferring rats; no effect in high p-rats	Meert (1993)
	● WAY 100635 (0–1.0 mg/kg)	0.05–0.5 mg/kg (s.c.)	Wistar (high and medium alcohol preferring)	Ethanol (10%, oral)	–	Two-bottle choice (water vs. ethanol)	Decreased ethanol intake (without total volume change)	Zhou et al. (1998)
	● WAY 100635	(i.p.; –30 min)	Wistar rats	Ethanol (12%, oral)	–	FR4 lever press, two choice (water vs. ethanol)	No effects	Tomkins and O'Neill (2000)
	● WAY 100135 (both 1 mg/kg) ● 8-OH-DPAT (5 μg)	5 μg (bilateral intra-nucleus accumbens)	SD rats	d-Amphetamine (bilateral intra-nucleus accumbens)	60 μg/kg/infusion	PR	No effect	Fletcher et al. (2002a)
	● CP 94253 (0–3 mg/kg) ● GR 127935 (3, 10 mg/kg; s.c.; –25 min)	1, 3 mg/kg (s.c.; –15 min)	Wistar rats	Cocaine (0.015–0.25 mg/infusion)	0.03, 0.125 mg/infusion	FR5; PR	CP (1, 3 mg/kg) reduced cocaine intake (0.125 mg/infusion) and increased break points and time to reach break point; CP (1 mg/kg) enhanced infusion of subthreshold dose of cocaine (0.03 mg/infusion); GR 127935 blocked effect of CP 94253 (1 mg/kg) on PR	Parsons et al. (1998)
	● CP 93129 (3.0 and 10 μg)	3.0 and 10 μg (intra-cerebro-ventricular)					CP (3, 10 μg) reduced cocaine intake (0.125 mg/infusion) and increased break points and time to reach break point; CP (10 μg) enhanced infusion of subthreshold dose of cocaine (0.03 mg/infusion)	
	● GR 127935 (10 mg/kg)	(i.p.; –10 min)	Wildtype 129/Sv-ter and KO mice	Cocaine (2.0 mg/kg/infusion)	–	PR	No effects in wildtype or KO mice	Castanon et al. (2000)
	● GR 127935 (0.5 mg/kg)	(i.p.; –20 min)	C57/BL6 mice	Cocaine (30, 150 pmol/injection; intra-VTA)	–	Y-maze self-administration	Decreased self-administration and increased latency to enter cocaine-paired arm of maze	David et al. (2004)
	● CP 94253 (0–2.5 mg/kg) ● SB 216641 (0–7.5 mg/kg)	7.5 mg/kg (i.p.; –30 min) 7.5 mg/kg (i.p.; –45 min)	Wistar rats	Cocaine (0–0.5 mg/kg/infusion)	0.125, 0.25, 0.5 mg/kg/infusion	FR5	CP 94253 reduced cocaine responding SB had no effect on cocaine responding (0.125, 0.25 mg/kg/infusion), but attenuated the effects of CP	Przegalinski et al. (2007)
	● CP 94253 (5.6 mg/kg)	5.6 mg/kg (s.c.; –15 min)	SD rats	Cocaine (0–1.5 mg/kg/infusion)	–	FR5	CP attenuated cocaine responding at 0.188, 0.375, 0.750 mg/kg/infusion	Pentkowski et al. (2009)

-	-	Wildtype 129/Sv-ter and KO mice	Cocaine (0–4 mg/kg/infusion)	-	FR2	Wildtype and KO mice self-administer cocaine similarly	Rocha et al. (1997)
● CP 94253 (0–10.0 mg/kg)	3, 10 mg/kg (i.p.; –60 min)	Wistar rats	Ethanol (10%, oral)	-	PR	KO mice show higher break points compared to wildtypes	Rocha et al. (1998)
● GR 127935 (1 mg/kg)	(i.p.; –30 min)	Wistar rats	Ethanol (12%, oral)	-	Two-bottle choice (water vs. ethanol)	CP non-selectively decreased responding; slight decrease in ethanol at the highest dose (10 mg/kg)	Maurel et al. (1999)
● GR 55562 (0–200 μM)	(intra-posterior VTA)	Wistar rats	Ethanol (200 mg%; intra-posterior VTA)	-	FR 4 lever press, two choice (water vs. ethanol)	No effects	Tomkins and O'Neill (2000)
-	-	Wildtype 129/Sv-ter and KO mice	Ethanol (3–20%, each for 8–12-day periods, oral)	6, 10, 20%	FR1	No effects	Ding et al. (2009)
-	-	Wildtype 129/Sv-ter and KO mice	Ethanol (0–20%, unsweetened and saccharin sweetened, oral)	-	Two-bottle choice (water vs. ethanol)	KO's drank twice as much ethanol as wildtypes over a 36 day period	Crabbe et al. (1996)
-	-	Long Evans rats	Ethanol (6, 12%)	6, 12%	FR 4 lever press, two choice (water vs. ethanol)	KO's and wildtypes responded similarly	Risinger et al. (1999)
-	5-HT(1B) protein viral particles (bilateral intra-NAc resulting in VTA receptor expression; 2 μl)	SD rats	Amphetamine (bilateral intra-nucleus accumbens)	60 μg/kg/infusion	Three-bottle choice (water vs. 6 or 12% ethanol)	Rats with overexpressed VTA 5-HT(1B) receptors showed increased ethanol (12%) preference without effects on total liquid volume intake	Hoplight et al. (2006)
● CP 93129 (0–2.5 μg)	1.25, 2.5 μg	SD rats	Amphetamine (bilateral intra-nucleus accumbens)	60 μg/kg/infusion	PR	CP 93129 reduced cocaine responding without altering the latency to begin responding; GR attenuated the effects of 1.25 μg CP (2.5 μg not tested) and 5 μg 5-HT; GR had no effect alone	Fletcher et al. (2002a)
● GR 127935 (1 mg/kg)	3.0 mg/kg (s.c.)	Wistar rats	● CP 94253 (0–1.0 mg/infusion)	0.1 mg/infusion	FR5	Self-administration of CP was never maintained for more than 90 min	Parsons et al. (1998)
● CP 94253 (0–1.0 mg/infusion)	-	Wistar rats	● CP 94253 (0–1.0 mg/infusion)	0.1 mg/infusion	FR5	Self-administration of CP was never maintained for more than 90 min	Parsons et al. (1998)
2A ● MDL 100907 (0–2 mg/kg)	(s.c.; –30 min)	SD rats	Cocaine (0.0625–0.25 mg/infusion)	-	PR	MDL did not alter the rewarding effects of cocaine	Fletcher et al. (2002b)
● SR 46349B (0–1.0 mg/kg)	0.5, 1.0 mg/kg (s.c.)	Wistar rats	Cocaine (0.5 mg/kg/infusion)	-	FR5	No effect on self administration; though it did decrease responding for a cocaine priming dose (10 mg/kg; i.p.) and reduced cue-induced reinstatement of lever pressing	Filip (2005)
● MDL 100907 (0–0.3 mg/kg)	(i.m.; –15 min)	Rhesus monkeys	Cocaine (0.001–0.3 mg/kg/infusion)	-	FR30	No effect	Fantegrossi et al. (2002)
● R-96544 (0–200 μM)	100, 200 μM (intra-posterior VTA)	Wistar rats	MDMA (0.001–0.3 mg/kg/infusion)	0.003–0.1 mg/kg/infusion	FR1	MDL abolished responding for R(-)-MDMA and attenuated responding for S(+)-MDMA	Ding et al. (2009)
● R-96544 (0–200 μM)	100, 200 μM (intra-posterior VTA)	Wistar rats	Ethanol (200 mg%; intra-posterior VTA)	-	FR1	Antagonist attenuated ethanol-maintained responding on active lever	Ding et al. (2009)

Table 2B (Continued)

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species	Self-administered drug (dose range and route)	Effective doses	Schedule of reinforcement	Effects	References
	● SR 46349B (eplivanserin; 0.25, 0.5 mg/kg)	0.25, 0.5 mg/kg (i.p.)	Wildtype C57BL/6J and KO mice	MDMA (0–0.25 mg/kg/infusion); 5, 10 mg/kg (i.p.) priming doses	0.125, 0.25 mg/kg/infusion	FR1	KO mice showed reduced responding compared to wildtype littermates; cue-induced reinstatement of responding in wildtype mice was blocked by SR at 0.5 (but not 0.25) mg/kg	Orejaarena et al. (2010)
2C	● SB 242084 (0–1 mg/kg)	0.5, 1.0 mg/kg (i.p.; –60 min)	SD rats	Cocaine (0.0625–0.25 mg/infusion)	–	PR	SB (0.5, 1.0 mg/kg) increased responding and break points for cocaine (0.125 mg/infusion); SB (0.5 mg/kg) increased responding for cocaine at the lowest (0.063, 0.125 mg/infusion) but not highest (0.25 mg/infusion) dose	Fletcher et al. (2002b)
	–	–	Wildtype 129 C57BL/6J and KO mice	Cocaine (1.0 mg/kg/infusion)	–	PR	KO mice pressed a cocaine-paired lever twice as much as wildtypes and showed an increase in break points	Rocha et al. (2002)
	● SDZ SER-082 (0–1 mg/kg)	(s.c.; 0 min)	Wistar rats	Cocaine (0.5 mg/kg/infusion)	–	FR5	No effect on self-administration, cocaine priming dose (10 mg/kg; i.p.), or cue-induced reinstatement of lever pressing	Filip (2005)
	● Ro 60-0175 (0–10 μg)	3, 10 μg (Intra-VTA)	SD rats	Cocaine (0.25 mg/kg/infusion)	–	FR5, PR	Agonist reduced responding on both FR5 and PR schedules; 3 μg effects were blocked by SB 242084 (0.5 mg/kg)	Fletcher et al. (2004)
	● SB 242084 (0.5 mg/kg)	0.5 mg/kg (i.p.; –30 min)						
	● Ro 60-0175 (0–1 mg/kg)	0.3, 1.0 mg/kg (s.c.; –30 min)	Wistar rats	Ethanol (12%, oral)	–	FR4	Decreased active lever responding and overall ethanol intake; blocked by SB 242084 (0.5 mg/kg)	Tomkins et al. (2002)
	● SB 242084 (0.5 mg/kg)	(i.p.; –40 min)						
	● SB 242084 (0–1 mg/kg)	0.5, 1.0 mg/kg (i.p.; –40 min)					SB 242084 increased responding and intake of ethanol in low-responding, but not high-responding rats	
3	● Ondansetron (0–1 mg/kg)	(i.p.; –30 min)	SD rats	Cocaine (0.5 mg/kg/infusion)	0.5 mg/kg/infusion	FI1	No effect on cocaine responding or alone	Peltier and Schenk (1991)
	● Ondansetron (0–1 mg/kg)	(i.p.; –30 min)	SD rats	Cocaine (0–0.5 mg/infusion)	0.125–0.5 mg/infusion	FR2	No effect on cocaine responding or alone	Lane et al. (1992)
	● Ondansetron (0.2 mg/kg)	0.2 mg/kg (s.c.; first 5 days of withdrawal; 3.5 h following cocaine exposure during PR)	SD rats	Cocaine (2.0 mg/kg/infusion)	2.0 mg/kg/infusion	PR; 10 days withdrawal (with ondansetron administration for the first 5 days); 12 days on cocaine PR (followed by acute ondansetron administrations)	Decreased self-administration during PR on days following ondansetron administration	Davidson et al. (2002)
	● Ondansetron (0.2 mg/kg)	0.2 mg/kg (s.c.; –30 min)	SD rats	Cocaine (0.2 mg/ml; oral)	0.2 mg/ml	Two-bottle 14 h free-choice (water vs. cocaine)	No effect with antagonist pretreatment	Davidson et al. (2004)

	0.2 mg/kg (s.c.; 3.5 h following cocaine exposure) (s.c.; -30 min)	Wistar rats	Cocaine (0.6 mg/infusion)	0.6 mg/infusion	PR	Reduced cocaine intake up to two days following antagonist administration	
● MDL 72222 (0-1920 µg/kg)						No effect on cocaine responding or alone	Lacosta and Roberts (1993)
● ICS 205930 (0-200 µM)	100, 200 µM	Wistar rats	Cocaine (0-1600 pmol/100 nl; intra-posterior VTA; NOT intra-anterior VTA)	50-200 pmol/100 nl	FR1	Antagonist reduced number of active lever responses and cocaine infusions	Rodd et al. (2005a)
● Zacopride (0-10 mg/kg)	(i.p.; -45 min)	SD rats	Ethanol (6%, oral)	-	Two-bottle 1 h free-choice (water vs. ethanol)	No effect	Knapp and Pohorecky (1992)
	5, 10 mg/kg (i.p.; -45 min; twice daily over 5 days)				Two-bottle 24 h free-choice (water vs. ethanol)	Decreased ethanol preference and intake without affecting total fluid intake	
● Ondansetron (0-0.16 mg/kg)	0.01, 0.16 mg/kg (s.c.; -24 h)	Wistar rats with high (>85%) and medium (60-85%) preference	Ethanol (3%; oral)	-	Two-bottle free-choice (water vs. ethanol)	No effect on ethanol preference or intake; total fluid intake was reduced	Meert (1993)
● Ondansetron (0-0.1 mg/kg)	(s.c.; -30 min)	SD rats	Ethanol (8%; oral)	-	FR 2 lever press	No effect on ethanol or total volume intake	Wilson et al. (1998)
● Tropisetron (0-17 mg/kg)	1.0, 10 mg/kg (s.c.; -30 min)	Long-Evans rats	Ethanol (10%; oral)	-	FR4 single choice	Decreased self-administration following 10 mg/kg dose of antagonist	Hodge et al. (1993)
					FR4 two-lever choice (water vs. ethanol)	Decreased ethanol self-administration with 1.0 mg/kg dose of antagonist without affecting water-lever responding	
● Tropisetron (0-17 mg/kg)	1.0, 10, 17 mg/kg (s.c.; -30 min)	Long-Evans rats	Ethanol (6%; oral)	-	Two-bottle free-choice (water vs. ethanol)	Antagonist had no effect alone; tropisetron decreased morphine-induced (17.0 mg/kg; 10.0 mg/kg; 1.5 mg/kg) increases in ethanol intake, at the respective doses of 1.0 mg/kg, 10.0 mg/kg, and 10.0, 17.0 mg/kg	Hodge et al. (1995)
Morphine (0-17 mg/kg)	1.5, 17 mg/kg (s.c.; -20 min)	SD rats	Sweetened ethanol (10% ethanol, 3% glucose)	-	Two-bottle free-choice (water vs. ethanol)	Antagonist decreased ethanol solution intake at 0.1 and 1.0 mg/kg	Silvestre et al. (1998)
● Granisetron (0-1.0 mg/kg)	0.1, 1.0 mg/kg (s.c.; twice daily over 4 days)						
● Ondansetron (0-3.0 mg/kg)	(s.c.; 0.1 mg/kg over five days)	Long-Evans rats	Ethanol (8%; oral)	-	FR 5 lever press	No effect in any condition	Beardsley et al. (1994)
● Granisetron (0-1.0 mg/kg)	(s.c.; 0.3 mg/kg over five days)						
● SC 51296 (0-10 mg/kg)	(s.c.; 0.1 mg/kg over five days)						
● MDL 72222 (0-7 mg/kg)	3, 5, 7 mg/kg (i.p.; 3 times daily over 6 days)	Sardinian ethanol-preferring rats	Ethanol (10%; oral)	-	Two-bottle free-choice (water vs. ethanol)	Reduced ethanol consumption without affecting overall fluid intake (rats increased water intake)	Fadda et al. (1991)
● MDL 72222 (0-5 mg/kg)	5 mg/kg (s.c.; -30 min)	Sardinian ethanol-preferring rats	Ethanol (15%; oral)	-	FR5	Reduced responding for ethanol in first 30 min and ethanol and water over 4 h	McKinzie et al. (2000)
	1 mg/kg (s.c.; -30 min)					No effect on rats tested at same time each day; reduced responding for animals trained on variable time schedule (i.e. access to ethanol at variable times in the day)	

Table 2B (Continued)

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species	Self-administered drug (dose range and route)	Effective doses	Schedule of reinforcement	Effects	References
	● ICS 205930 (50, 100 μM)	All antagonist doses, except for 10 μM LY (intra-VTA; 0 min)	Wistar rats	Ethanol (200 mg%; intra-posterior, but not anterior, VTA)	–	FR1, active vs. inactive lever	All antagonists decreased active ethanol-lever pressing; no effects on lever-pressing when administered alone	Rodd-Henricks et al. (2003)
	● LY 278584 (0–100 μM)							
	● Zacopride (0–100 μM)							
	● ICS 205930 (200 μM)	200 μM (intra-VTA; 0 min)	Wistar rats	Ethanol (75–300 mg%; intra-posterior VTA)	–	FR1, active vs. inactive lever	Antagonist attenuated intra-VTA ethanol administration	Rodd et al. (2010, 2005b)
	● ICS 205930 (0–400 μM)			Acetaldehyde (6–90 μM)	–		Antagonist did not affect intra-VTA acetaldehyde administration	
	–	–	B6SJL/F1 mice (over-express 5-HT ₃ receptors in the forebrain)	Ethanol (10%; oral)	–	Two-bottle free-choice (water vs. ethanol)	Transgenic mice administer less ethanol than wildtype counterparts	Engel et al. (1998)
	● MDL 72222 (0–30 μg/kg, 1 mg/kg)	(s.c.; –60 min)	Long-Evans rats	Nicotine	0.03 mg/kg/infusion	FR5	Antagonists had no effect on nicotine-induced responding	Corrigall and Coen (1994)
	● ICS 205930 (0–30 μg/kg)	(s.c.; –60 min)						
	● Ondansetron (0–1.0 mg/kg)	(s.c.; –30 min)	Wistar rats	Heroin	0.03 mg/kg/infusion	FR5	Antagonists had no effect on heroin-induced responding	Higgins et al. (1993b)
	● MDL 72222 (0–3.0 mg/kg)	(s.c.; –30 min)						
	● Ondansetron (0–1.0 μg/kg)	1.0 μg/kg (i.p.; twice daily)	SD rats	Morphine	0.4 mg/ml	Two-bottle choice test (morphine/5% sucrose; water/5% sucrose) over a 21 day period	On day 21 the 1.0 μg/kg dose of ondansetron produced a significant decrease in morphine consumption, as did the 1.0 μg dose of tropisetron from days 17–21	Hui et al. (1993)
	● Tropisetron (0–1.0 μg/kg)	1.0 μg/kg (i.p.; twice daily)						
	● CPBG (0–100 μM)	0.10–100 μM (intra-VTA; 0 min)	Wistar and alcohol preferring P rats	–	–	FR1, active vs. inactive lever	P rats self infused lower concentrations (0.10 μM to highest dose tested) than did Wistar rats (1.0 μM to highest dose tested) ICS attenuated effects of CPBG without having effects on its own	Rodd et al. (2010)
	● ICS 205930 (0–200 μg/kg)	100, 200 μM (intra-VTA; 0 min)						
6	● SB 258510A (0–10 mg/kg)	3, 10 mg/kg (i.p.; –30 min)	Wistar rats	Cocaine	0.024 mg/kg/infusion	FR1; PR	Antagonist had no effect alone or on cocaine responding	Frantz et al. (2002)
				d-Amphetamine	0.024, 0.048 mg/kg/infusion	FR1; PR	Antagonist (3, 10 mg/kg and 10 mg/kg) decreased FR1 amphetamine-induced responding at both 0.024 and 0.048 mg/kg/infusion doses, respectively. The 3 mg/kg also increased the breaking point during the PR schedule	

● Agonist.

● Antagonist.

Table 2C

The effect of 5-HT receptor subtype ligands on place conditioning.

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species (strain)	Place conditioned drug or treatment	Effective doses (route and timing)	Compartment types	Apparatus or design bias	Conditioned place preference or aversion	References
1A	● 8-OH-DPAT (0-0.25 mg/kg)	0.1, 0.125, 0.25 mg/kg (s.c.; -15 min)	SD rats	SCH-23390	1.0 µl/h; i.v.; continuous throughout acquisition/expression	White wall, rough Plexiglas floor; black wall, smooth Plexiglas floor	Unbiased	CPP (SCH blocks CPP induced by 0.1 mg/kg 8-OH-DPAT, no effect alone; sulpiride does not block, no effect alone) CPP	Fletcher et al. (1993) and Shippenberg (1991)
	● 8-OH-DPAT (0.1, 0.5, 1.0 µg)	0.1 µg (intra-dorsal or intra-median raphe)		Sulpiride	-				
	● 8-OH-DPAT (0-1.0 mg/kg)	0.625, 0.125, 1.0 mg/kg (i.p.; -15 min)	Lister rats	Sulpiride	40 mg/kg; i.p.; -2 h	Black and white walls; wire mesh and wood flooring	Biased design	CPP (sulpiride blocks; no effect alone)	Papp and Willner (1991)
	● Buspirone (1.0, 3.0 mg/kg)	1, 3 mg/kg (s.c.; 0 min)	SD rats	-	-	White wall, wire mesh floor, pine bedding; Black wall, metal grid, cedar bedding; middle room, grey wall, wood floor	Apparatus bias	CPA (sulpiride does not block) CPP	Neisewander et al. (1990)
	● Gepirone (1.0, 3.0 mg/kg) ● Buspirone (0-2.0 mg/kg)	3 mg/kg (s.c.; 0 min) (i.p.; 0 min)	BKW mice	Cocaine	5 mg/kg; s.c.; 0 min	Striped wood wall and glass floor; metal wall and striped floor	Unbiased	No effect on cocaine-induced CPP	Ali and Kelly (1997)
	● Pindobind (2.5 mg/kg)	2.5 mg/kg (i.p.; -30 min)	Swiss Webster mice	Ethanol	2 g/kg	Steel holed floor; steel grid floor	Unbiased	CPP with ethanol + pindobind (no place conditioning on their own)	Risinger and Boyce (2002)
	● WAY 100635 (2 mg/kg)	2 mg/kg (i.p.; -20 min)	129Svj x C57BJ mice	Amphetamine	5.0 mg/kg; i.p.; 0 min	Black wall; white wall	-	WAY 100635 does not block amphetamine CPP (no effect reported for WAY alone)	Budygin et al. (2004)
	● F 13640 (0.63 mg/day)	0.63 mg/day (i.v.)	SD rats	Morphine	7.5 mg/kg; i.p.; -15 min	Three compartments - black dots, smooth floor; black stripes, medium rough floor; white, rough	Unbiased	F 13640 attenuated morphine-induced acquisition of CPP without having effects alone	Colpaert et al. (2006)
1B	● CP 94253 (0-10 mg/kg)	2.5, 10 mg/kg (i.p.; -30 min)	SD rats	● GR 127935 (0-10 mg/kg)	10 mg/kg; s.c., -40 min	Grey wall, loose mesh floor; black w/vertical white striped wall, tight mesh floor	Unbiased	CPA with 2.5, 10 mg/kg CP 94253, blocked by GR (no effect of GR alone when given during acquisition or expression)	Cervo et al. (2002)
		2.5 mg/kg (i.p.; -30 min)		Cocaine (0-10 mg/kg); GR 127935	Cocaine: 2.5 mg/kg, i.p., 0 min; GR: 10 mg/kg, s.c., -40 min			CP 94253 produced CPP in combination with subthreshold dose, 2.5 mg/kg, of cocaine; GR 127935 blocked this CPP	

Table 2C (Continued)

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species (strain)	Place conditioned drug or treatment	Effective doses (route and timing)	Compartment types	Apparatus or design bias	Conditioned place preference or aversion	References
	–	5-HT(1B) protein viral particles (bilateral intra-NAc resulting in VTA receptor expression; 2 μ l)	SD rats	Cocaine	5, 10, 20 mg/kg; i.p.; 0 min OR –45 min	Three compartments differing in lighting (low, medium, high), wall colour (black, white, grey), and floor texture (grid, rod, solid)	Unbiased	Rats with overexpressed VTA 5-HT(1B) receptors showed CPP when cocaine (5 mg/kg) was administered at $t=0$ but not at $t=-45$ min Control rats showed cocaine-induced (10, 20 mg/kg; $t=0$ only) CPP, while rats overexpressing 5-HT(1B) receptors showed a cocaine-induced (20 mg/kg; $t=-45$ min only) CPA	Barot et al. (2007) and Neumaier et al. (2002)
2B	● RS 127445	0.5 mg/kg (i.p.; –40 min)	5-HT(2B) receptor knockout mice, 129Sv/PAS	MDMA	10, 30 mg/kg; i.p.; –10 min	Two compartments with different patterns on walls and floors	Biased design; unbiased compartment (?)	MDMA-induced (10 mg/kg) CPP was seen in wildtype, but not knockout, mice; the higher dose produced CPP in both groups MDMA-induced reinstatement of CPP (following extinction) was prevented by pretreatment with the 5-HT(2B) receptor antagonist	Doly et al. (2009)
2C	● WAY 161503 (0–3 mg/kg)	(s.c.; –10 min)	SD rats	–	–	Bar floor; grate wire floor	Unbiased; biased	No effect	Mosher et al. (2005)
	● WAY 161503 (0–3 mg/kg)	3 mg/kg (s.c.; –10 min)	SD rats	WAY 161503 (0–3 mg/kg)	3 mg/kg (s.c.; –10 min) post-conditioning	Bar floor; grate wire floor	Unbiased design	Context-dependent CPA (with WAY 161503 administered in post-conditioning)	Mosher et al. (2006)
	● WAY 161503 (0–3 mg/kg)	(s.c.; –10 min)	SD rats	Nicotine	0.6 mg/kg (s.c.; 0 min)	Bar floor; grate wire floor	Biased design	No effect on nicotine-induced CPP No effect alone	Hayes et al. (2009c)
	● Ro 60-0175 (3 mg/kg)	3 mg/kg (?)	? rats	THC (0.3 mg/kg)	0.3 mg/kg (?)	Bar floor, white walls; grate floor, black walls	Biased apparatus (?); design (?)	Agonist blocked THC-induced CPP	Ji et al. (2006)
3	● 1-Phenylbiguanide (PBG; 0–30 mg/kg)	30 mg/kg (i.p.; 0 min)	Wistar rats	● Ondansetron (0–0.1 mg/kg)	0.01, 0.1 mg/kg (s.c.; –30 min)	White walls, rough perspex floor; Black walls, smooth perspex floor	Apparatus bias; unbiased design	CPA; attenuated by ondansetron (no effect alone)	Higgins et al. (1993a)
				● ICS 205-930 (0.1 mg/kg)	0.1 mg/kg (i.p.; –30 min)			CPA; attenuated by ICS 205-930 and Q-ICS 205-930 (no effects on their own)	

<ul style="list-style-type: none"> • m-Chlorophenylbiguanide (mCPBG; 0–10 mg/kg) • MDL 72222 (0–0.03 mg/kg) 	1, 10 mg/kg (i.p.; 0 min)	SD rats	<ul style="list-style-type: none"> • Q-ICS 205-930 (0.1 mg/kg) 	0.1 mg/kg (i.p.; –30 min)	–	–	–	CPA (though not dose-dependent as 0.3, 3.0 mg/kg had no effect)	Carboni et al. (1989) and Carboni et al. (1988)
	0.015, 0.03 mg/kg (s.c.)		Morphine (1 mg/kg)	1 mg/kg (s.c.)		Plexiglas boxes, white walls and grey walls	Biased design	MDL blocked morphine- and nicotine-induced CPP without effects alone; no effect on amphetamine-induced CPP	
	0.03 mg/kg		Nicotine (0.6 mg/kg)	0.6 mg/kg (s.c.)					
	–		Amphetamine (1 mg/kg)	1 mg/kg (s.c.)					
<ul style="list-style-type: none"> • ICS 205-930 (0–0.03 mg/kg) 	0.015 mg/kg (s.c.)		Morphine (1 mg/kg)	1 mg/kg (s.c.)				ICS blocked morphine- and nicotine-induced CPP without effects alone; no effect on amphetamine-induced CPP	
	0.03 mg/kg		Nicotine (0.6 mg/kg)	0.6 mg/kg (s.c.)					
	–		Amphetamine (1 mg/kg)	1 mg/kg (s.c.)					
<ul style="list-style-type: none"> • MDL 72222 (0–1 mg/kg) 	1 mg/kg (s.c.; –30 min)	Wistar rats	Morphine (0–3 mg/kg)	1, 1.5, 3 mg/kg (s.c.; 0 min) though only 1.5 mg/kg was used for interaction studies		White walls, rough perspex floor; Black walls, smooth perspex floor	Apparatus bias; unbiased design	MDL and ondansetron blocked morphine-induced CPP; no effects alone	Higgins et al. (1992)
<ul style="list-style-type: none"> • Ondansetron (0–1 mg/kg) • MDL 72222 (0–1 mg/kg) 	0.1 mg/kg (s.c.; –30 min)	Wistar rats	Cocaine (20 mg/kg)	20 mg/kg (i.p.; 0 min)		Black walls, smooth floor, drops of acetic acid; white walls, wire mesh floor, no acid	Unbiased design	MDL blocked acquisition, but not expression, of cocaine-induced CPP; no effects alone	Kankaanpaa et al. (2002)
	1 mg/kg (s.c.; –30 min)								
<ul style="list-style-type: none"> • MDL 72222 (0–1 mg/kg) 	0.1 mg/kg (i.p.)	ddY mice	Cocaine (0–4 mg/kg)	4 mg/kg (i.p.)		White wall, textured floor; black wall, smooth floor	Unbiased design	MDL and ICS (0.1 mg/kg) blocked cocaine-induced CPP; MDL (0.1 mg/kg) and ICS (1 mg/kg) blocked methamphetamine-induced CPP; no effects on their own	Suzuki et al. (1992)
<ul style="list-style-type: none"> • ICS 205-930 (0–1 mg/kg) • Tropicsetron (0–0.1 mg/kg) 	0.1, 1 mg/kg (i.p.)	SD rats	Methamphetamine (0–2 mg/kg)	2 mg/kg (i.p.)		Grey wall, loose mesh floor; black w/vertical white striped wall, tight mesh floor	Unbiased design	Antagonists had no effect on the acquisition or expression of cocaine-induced CPP; no effects on their own	Cervo et al. (1996)
	(s.c.; –60 min)		Cocaine (10 mg/kg)	10 mg/kg (i.p.; 0 min)					
<ul style="list-style-type: none"> • MDL 7222 (0–3 mg/kg) • Ondansetron (0–0.1 mg/kg) • MDL 7222 (0.03 mg/kg) 	(s.c.; –30 min)	SD rats	Naloxone (0.8 mg/kg)	0.8 mg/kg (s.c.; 0 min)		Plexiglas compartments; white wall; grey wall	Biased design	Antagonists block naloxone-, phencyclidine-, and picrotoxin-induced CPA; no effects alone	Acquas et al. (1990)
	(s.c.; –30 min)								
	0.03 mg/kg (s.c.; –45 min)								

Table 2C (Continued)

Receptor subtype	5-HT ligand (dose range)	Effective doses (route and timing)	Species (strain)	Place conditioned drug or treatment	Effective doses (route and timing)	Compartment types	Apparatus or design bias	Conditioned place preference or aversion	References
	● ICS 205-930 (0–0.03 mg/kg)	0.015, 0.03 mg/kg (s.c.; –45 min)		Phencyclidine (2.5 mg/kg) Picrotoxin (2.0 mg/kg)	2.5 mg/kg (s.c.; 0 min) 2.0 mg/kg (i.p.; 0 min)				
	● MDL 7222 (0–0.03 mg/kg)	0.015, 0.03 mg/kg (s.c.; –20 min)	SD rats	MDMA (6.3 mg/kg)	6.3 mg/kg (s.c.; –10 min)	Grey wall, parallel bar floor; black and white striped wall, perpendicular bar floor	Unbiased design	Antagonist blocks MDMA-induced CPP; no effect alone	Bilsky and Reid (1991)
	● Tropicsetron (1.0 mg/kg)	1.0 mg/kg (s.c.; –35 min)	Wistar rats	MDMA (0–1000 ng/rat)	1–1000 ng (i.c.v.; 0 min)	Black wall, grid floor; white wall, bar floor	Biased apparatus; biased design	Antagonist blocks MDMA-induced (10 ng) CPP	Braida et al. (2005)
	● Ondansetron (0–3 mg/kg)	0.1, 0.3 mg/kg (s.c.; –30 min)	ddY mice	Ketamine (0–10 mg/kg)	1–10 mg/kg (i.p.; 0 min)	White wall, textured floor; black wall, smooth floor	Unbiased design	Ondansetron blocks ketamine-induced (10 mg/kg) and dizocilpine-induced (0.2 mg/kg) CPP; no effect alone	Suzuki et al. (1999)
	● Tropicsetron (0–0.5 mg/kg)	(s.c.; –20 min)	Wistar rats	MK 801 (0–0.2 mg/kg) Ethanol (1.5 g/kg)	0.1, 0.2 mg/kg (i.p.; 0 min) 1.5 g/kg (i.p.; 0 min)	White wall, natural plank floor; brown wall, black Plexiglas floor	Unbiased design	Antagonist did not affect ethanol-induced CPA	Bienkowski et al. (1997)
6	● Ro 4368554 (5 mg/kg)	5 mg/kg (i.p.; –30 min)	SD rats	Cocaine	5, 20 mg/kg; i.p.; 0 min	Three compartments differing in lighting (low, medium, high), wall colour (black, white, grey), and floor texture (grid, rod, solid)	Unbiased	Rats with overexpressed NAc 5-HT(6) receptors showed no cocaine-induced CPP, while controls showed a robust CPP	Ferguson et al. (2008)
		5-HT(6) protein viral particles (bilateral intra-NAc; 2 µl)						The antagonist produced cocaine-induced (5 mg/kg) CPP, cocaine-only animals did not show CPP; the antagonist alone had no effect on place conditioning	

● Agonist.

● Antagonist.

Table 3
Comparison of 5-HT receptor subtype function across reward-related behaviours.

Receptor subtype	Intracranial self-stimulation	Self-administration	Place conditioning
1A	↑ Reward; May ↓ motor performance (when administered systemically) Antagonist has no effect alone Intra-raphé (median and dorsal) may ↑ reward	1A agonist and antagonist	No self-administration
		Cocaine	↓ Reward (at high doses); May ↑ reward (at low doses or in monkeys)
		Amphetamine	No effect when co-administered during intra-NAC amphetamine self-administration
		Ethanol	Non-specific effects
		Morphine/ heroin/ nicotine	No studies
1B	↓ Reward	1B agonist	Unreplicated, intermittent self-administration (Parsons et al., 1998)
		Cocaine	↑ Reward (following systemic and intra-ventricular administration)
		Amphetamine	↓ Reward (following intra-NAC activation)
		Ethanol	Non-specific effects; although increased VTA 5-HT _{1B} receptors = ↑ ethanol reward
		Morphine/ heroin/ nicotine	No studies
2A	Agonist decreased reward (without effects on cocaine-induced reward); antagonist does not affect reward or amphetamine-induced reward	Cocaine	Antagonist does not alter cocaine responding (though it may decrease cue-induced responding)
		MDMA Ethanol Morphine/ heroin/ nicotine	Antagonists ↓ reward Antagonists ↓ reward (of intra-VTA ethanol responding following intra-VTA 2A antagonist) No studies
2B	No studies	No studies	MDMA Amphetamine/ ethanol/ morphine/ heroin/ nicotine
			CPP (at low doses) CPA (at high doses)/antagonist had no effect 5-HT _{1A} receptor activation + subthreshold cocaine (5 mg/kg) = no place conditioning. 5-HT _{1A} receptor blockade did not attenuate amphetamine CPP
			Ethanol 5-HT _{1A} receptor blockade + subthreshold ethanol (2 g/kg) = CPP Attenuated morphine-induced CPP
			Morphine
			1B agonist and antagonist
			Cocaine
			5-HT _{1A} receptor activation + subthreshold cocaine (2.5 mg/kg) = CPP. Increased VTA 5-HT _{1B} receptors = ↑ cocaine reward
			No studies
			Amphetamine/ ethanol/ morphine/ heroin/ nicotine
			No studies
			Low dose did not produced CPP in KO mice; high dose does MDMA-induced reinstatement of CPP was prevented with antagonist No studies

Table 3 (Continued)

Receptor subtype	Intracranial self-stimulation	Self-administration	Place conditioning	
2C	↓ Reward; No effect following intra-VTA, intra-NAC shell/core, or intra-prefrontal cortex activation However, systemic and intra-NAC core/shell and prefrontal cortex (but not VTA) agonists decrease cocaine-induced reward; systemic antagonist increases cocaine-induced reward	2C agonist and antagonist Cocaine Ethanol Amphetamine/ morphine/ heroin/ nicotine	No self-administration Agonist reward ↓ Antagonist ↑ reward ↓ Reward; Except ↑ Reward (for low-ethanol responding rats) No studies 2C agonist Nicotine THC Cocaine/ amphetamine/ ethanol/ morphine/ heroin	Context-dependent CPA only (when 2C agonist is administered in expression period only) Does not block nicotine-induced CPP Blocked THC-induced CPP No studies
3	No effects of antagonist alone; Though it may attenuate cocaine- and morphine-induced increases in reward; Antagonist does not affect nicotine-induced increases in reward	Antagonist Cocaine Ethanol Nicotine Heroin/morphine	No self-administration Antagonist has generally no effect; Intra-VTA antagonist administration and repeated systemic administration may ↓ reward measures Antagonist has generally no effect; Intra-VTA antagonist administration and timing of systemic administration may ↓ reward Antagonist had no effect Antagonist has generally no effect; Though repeated administration may ↓ reward	CPA/no effect Antagonist can block drug-induced CPP (depending on drug and dose); Although did not block amphetamine-induced CPP Antagonist had no effect on ethanol-induced CPA (Bienkowski et al., 1997) Antagonist attenuated nicotine-induced CPP Antagonist attenuated morphine CPP and naloxone CPA Antagonist attenuated phencyclidine and picrotoxin CPA and ketamine CPP
4	Antagonist has no effect		No studies	No studies
5	No studies		No studies	No studies
6	No studies	6 antagonist Cocaine Amphetamine	No effect No effect of antagonist Antagonist may ↑ reward	No effect Antagonist may ↑ reward Increased NAc 5-HT ₆ receptors showed no cocaine reward
7	No studies		No studies	No studies

Note: Effects outlined in the table assume receptor subtype agonist/stimulation, unless otherwise indicated. Abbr: CPP, conditioned place preference; CPA, conditioned place aversion; NAC, nucleus accumbens; VTA, ventral tegmental area.

doses of ethanol (Risinger and Boyce, 2002) – although these studies are difficult to compare given their differential use of species (alcohol preferring Wistar rats vs. Swiss Webster mice) and ligands (WAY 100635 vs. pindobind), respectively. Few studies have been performed with other drugs of abuse, but it is interesting to note that the direct activation of NAc 5-HT_{1A} receptors does not appear to affect intra-NAc amphetamine self-administration (Fletcher et al., 2002a) and that the systemically administered selective 5-HT_{1A} receptor ligand F 13640 attenuates morphine-induced CPP (Colpaert et al., 2006).

In humans, no studies investigating the effects of selective 5-HT_{1A} receptor ligands in reward-related behaviours have been published (although, see Kranz et al., 2010 for an overview of recent related abstracts). However, 5-HT_{1A} receptor function has been implicated in numerous neuropsychiatric disorders with associated alterations in reward-related processing. For instance, decreased receptor levels and/or function have been implicated in various anxiety disorders (Akimova et al., 2009; Lanzenberger et al., 2007) as well as in depression (Drevets et al., 2000) and schizophrenia (Meltzer and Sumiyoshi, 2008).

Taken together, although studies to date generally support a reward enhancing effect for 5-HT_{1A} receptor agonists at low doses (and the opposite effect for higher doses), more work is needed to investigate the pre- vs. post-synaptic receptor activation hypothesis. In addition, the use of newly developed highly selective ligands for the 5-HT_{1A} receptor (e.g. Fiorino et al., 2010) will be able to clarify if these apparently biphasic effects are due, in any part, to activities at 5-HT₇ receptors – particularly given that 5-HT_{1A} receptors are inhibitory G-protein coupled receptors while 5-HT₇ receptors are stimulatory (Table 1). Finally, it is currently unclear whether the effects on cocaine reward can be extended to other drugs of abuse such as morphine, MDMA or nicotine given the lack of studies; more studies investigating the effects of site-specific ligand injections (e.g. into the orbitofrontal or anterior cingulate cortices where these receptors are of high density; Hall et al., 1997) are needed to confirm the broader role of the raphe nuclei 5-HT_{1A} receptors in reward-related behaviours (e.g. Ahn et al., 2005; Fletcher et al., 1993, 1995).

4.2. Serotonin 1B and related receptors

Serotonin 1B (5-HT_{1B}) receptors were ideal candidates for investigating a potential serotonergic involvement in reward processing. They are found throughout reward-related brain areas (e.g. VTA, NAc, prefrontal cortex, among others; see Bruinvels et al., 1993; Sari et al., 1999 for rat brain localization and Sari, 2004 for a broad review of receptor function), and the selective agonists, CP 94253 and CP 93129, and the 5-HT_{1B/1D} receptor antagonist GR 127935, have been commercially available for about two decades. In addition, 5-HT_{1B} receptor activation appears to dose-dependently increase dopamine release in the mesocorticolimbic system (as noted by microdialysis studies in rodents) – which is strongly associated with reward-related processing (Iyer and Bradberry, 1996; Yan and Yan, 2001; Yan et al., 2004).

It is worth noting that while this receptor was initially claimed to only exist in rodents (Pedigo et al., 1981), subsequent molecular and pharmacological investigations discovered human and primate homologues (Sari, 2004), as well as other highly related receptors (i.e. 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}; see Table 1 for additional information). While selective 5-HT_{1D} and 5-HT_{1F} receptor ligands have been developed (Choi et al., 2008) – largely to explore their potential clinical role in reducing migraines (Goadsby and Classey, 2003) – they have not yet been investigated in reward-related models of behaviour and so will not be discussed here. In addition, 5-HT_{1E} receptor function is largely unknown, owing to its absence

in rodents and a lack of selective pharmacological tools, and so will also not be covered here (Klein and Teitler, 2009).

In general, 5-HT_{1B} receptor activation decreases measures of reward as indicated by increases in ICSS stimulation thresholds (Hayes et al., 2009b; as well as Harrison et al.'s, 1999 work involving the use of non-selective ligands), the induction of a conditioned place aversion (CPA) (Cervo et al., 2002), and the attenuation of amphetamine-maintained self-administration following the activation of 5-HT_{1B} receptors in the NAc (Fletcher et al., 2002a). Like its closely related family member, the 5-HT_{1A} receptor, the 5-HT_{1B} receptor does not appear to be tonically active given that functional antagonism appears to have no effect on reward-related behaviours (e.g. Hayes et al., 2009b; Risinger et al., 1999; Tomkins and O'Neill, 2000) – although see the work of Crabbe et al. (1996) and Rocha et al. (1997) for increased drug self-administration in 5-HT_{1B} receptor knock-out mice and David et al. (2004) for increased intra-VTA cocaine self-administration following the administration of the 5-HT_{1B/1D} receptor antagonist GR 127935 (although these effects could also be explained, respectively, by developmental compensatory changes in knockout mice and GR 127935's actions as a partial agonist; Pauwels et al., 1997).

Regarding ethanol, 5-HT_{1B} receptor stimulation typically leads to non-specific decreases in consumption (e.g. Maurel et al., 1999; as noted by the non-selective disruption of operant responding for both ethanol- and water-associated levers), however, one study showed specific increases in ethanol preference following increased receptor expression in the VTA (Hoplight et al., 2006). Additionally, a potential role in ethanol reward (particularly in addictive states) cannot be ruled out as lower receptor densities in reward-related brain regions of alcohol preferring rats have been noted (McBride et al., 1997; McBride et al., 1993). While constitutive or tonic activity of this receptor is not thought to be involved (given that antagonists and partial agonists largely have no effect alone), the mechanism of action (including how ethanol interacts, if at all, with the 5-HT_{1B} receptor) is still unclear. Nonetheless, recent data suggest that 5-HT_{1B} receptors located post-synaptically on medium spiny projection neurons of the NAc shell are involved in both the preference for higher concentrations of ethanol as well as for increased amounts of consumption (Furay et al., 2010). As noted above, the enhancement of drug-induced reward following the stimulation of 5-HT_{1B} receptors is generally considered to be due to the disinhibition of dopaminergic cells in the VTA. Nevertheless, stimulation of these 5-HT_{1B} receptors alone appears to result in aversion, although the reason for this remains unclear.

One of the best explored functions of brain 5-HT_{1B} receptor stimulation is its ability to increase the effects of cocaine. Although not studied in the context of self-stimulation (but see Harrison et al., 1999, who showed that the mixed 5-HT_{1A/1B} receptor agonist RU 24969 decreased cocaine-related changes to reward), self-administration (e.g. Parsons et al., 1998; Przegalinski et al., 2007) and place conditioning (e.g. Cervo et al., 2002) experiments have shown that receptor stimulation enhances the reinforcing effects of cocaine. That this is a 5-HT_{1B} receptor-mediated effect was further supported by the observation that virally-mediated receptor increases in the VTA resulted in increased cocaine reward (Barot et al., 2007; Neumaier et al., 2002) – and increased aversion at higher doses of cocaine, similar to effects seen by increasing the dose of cocaine. Interestingly, while Pentkowski et al. (2009) further confirmed the role of these receptors in cocaine-related reward, they also showed that receptor stimulation attenuated or blocked reinstatement of cue-induced cocaine-seeking behaviour. While the mechanism of action is still unclear, it is interesting to note that some authors have found increased 5-HT_{1B} mRNA expression throughout the mesocorticolimbic circuit in animals chronically exposed to cocaine (Hoplight et al., 2007), which could contribute to the sensitization effects of cocaine seen in these animals. Some

authors have also suggested that these data are most consistent with the presence of 5-HT_{1B} receptors on GABAergic medium spiny neurons of the NAc projecting to the VTA (Barot et al., 2007).

Beyond the preclinical evidence suggesting that 5-HT_{1B} receptors may be beneficial targets in alleviating cocaine addiction, no studies investigating the selective activation/attenuation of these receptors have been done in humans. One study, however, has found that recently abstinent alcoholics have increased 5-HT_{1B} receptor expression in the ventral striatum (Hu et al., 2010) – consistent with results from some laboratory animal studies (Hoplight et al., 2006) while seemingly conflicting with others (e.g. Lappalainen et al., 1998; McBride et al., 1993). 5-HT_{1B} receptors have also been implicated in major depression (which is associated with alterations in reward processing, for example as reflected by the presence of anhedonia) and the effects of antidepressant activity (Ruf and Bhagwagar, 2009; Watson and Dawson, 2007) – suggesting that receptor down regulation or functional antagonism may be required for antidepressant effects – although results from clinical trials are pending. Along these lines, it is also interesting to note that some selective serotonin reuptake inhibitors appear to attenuate both reward- and aversion-related processing in healthy subjects, as indicated by a recent neuroimaging study (McCabe et al., 2010).

Taken together, these studies generally support a reward decreasing effect for 5-HT_{1B} receptor agonists alone, and an enhancing effect in the presence of cocaine (while effects on other drugs of abuse such as MDMA, morphine, and nicotine have not been assessed). It is important, however, to point out that one study (Parsons et al., 1998) showed that the agonist CP 94253 (0.1 mg/infusion) was able to maintain self-administration behaviour for under 90 min in some rats, raising the possibility (as with the 5-HT_{1A} receptor) that differential pre- and post-synaptic effects may be involved. Although 5HT_{1B} receptors act as autoreceptors (Engel et al., 1986; Gothert et al., 1987) or heteroreceptors on cells containing acetylcholine (Cassel et al., 1995), glutamate (Boeijinga and Boddeke, 1996) or GABA (Sari et al., 1999) it is difficult to draw any conclusions from this CP 94253 study because higher and lower doses did not maintain self-administration and this phenomenon has not been replicated in the literature. Additionally, to date, no other experiments have reported clear biphasic effects. Future studies are needed to determine why 5-HT_{1B} receptor stimulation may increase mesocorticolimbic dopamine release (potentially consistent with its effects on cocaine reward), while generally decreasing other reward-related behaviours. As noted above, while dopamine may be involved, the effects of other neurotransmitters cannot yet be ruled out as the precise mechanisms involved (specifically regarding 5-HT_{1B} receptors and in reward processing in general) are incompletely understood.

4.3. Serotonin 2A receptors

As the main interest of the 5-HT_{2A} receptor in psychiatry has focused on its potential role in schizophrenia – for example, in mediating hallucinations and related psychotic symptoms (Geyer, 1998; Vollenweider et al., 1998) – few studies have investigated its potential role in reward-related behaviours. However, investigating this receptor's potential impact in reward makes sense given that reward-related processing is often dysfunctional in schizophrenia (Ziauddeen and Murray, 2010), that 5-HT_{2A} receptor antagonism is thought to contribute to the efficacy of atypical antipsychotics (Lieberman et al., 1998), and that the effects of some abused drugs such as MDMA and lysergic acid diethylamide are believed to be partly 5-HT_{2A} receptor mediated (Liechti et al., 2000; Winter, 2009). In addition, a study in humans showed that 5-HT_{2A} receptors may have increased binding potential (a combined measure of affinity and receptor density) in remitted, formerly

depressed, individuals (Bhagwagar et al., 2006) – though these results were considered preliminary and it is currently unclear if and how increased 5-HT_{2A} receptor density and/or function is involved in the pathophysiology of depression.

Studies in rodents using 5-HT_{2A} receptor antagonists have failed to demonstrate reward-related changes in ICSS (Benaliouad et al., 2007; Moser et al., 1996) and cocaine self-administration (Fantegrossi et al., 2002; Filip, 2005) behaviours. However, antagonism was shown to attenuate the self-administration of MDMA (Fantegrossi et al., 2002) and intra-VTA ethanol (Ding et al., 2009). Although it has been suggested that some of these effects (especially regarding intra-VTA ethanol) may be related to the fact that the activation of VTA 5-HT_{2A} receptors results in increased dopamine release (Pessia et al., 1994), more research is necessary to confirm this and to expand upon our current limited knowledge. For example, future studies investigating the role of this receptor in place conditioning (there are currently none to our knowledge) may contribute to a better understanding of its potential role in the conditioned effects of drugs of abuse.

4.4. Serotonin 2B receptors

Despite its distribution throughout the brain (Duxon et al., 1997), 5-HT_{2B} receptor function is largely unknown as are its effects (if any) on reward-related behaviours. Only one study to date has examined the role of this receptor in this context, finding that 5-HT_{2B} receptor knockout mice do not exhibit CPP to a low (but not high) dose of MDMA (Doly et al., 2009). In wildtype mice, receptor antagonism prevented the normal MDMA-induced reinstatement of CPP (following extinction). These effects have been attributed to the role that this receptor is known to play in regulating serotonin and dopamine release and/or its ability to regulate serotonin transporter function (Doly et al., 2009; Launay et al., 2006). Specifically, Doly et al. (2009) showed that 5-HT_{2B} receptor knockout mice do not display normal dopamine D1 receptor-dependent phosphorylation of extracellular signal-regulated kinase, or ERK, in the NAc (a key factor in the long-term effects of drugs of abuse). Additionally, Launay et al. (2006) showed that 5-HT_{2B} receptors within the raphe nuclei are important regulators of 5-HT transport through their effects on the phosphorylation of serotonin transporters (where the constitutive activity of 5-HT_{2B} receptors allows for transport and their stimulation results in the attenuation of 5-HT transport). This finding also identified an additional mechanism by which some antidepressants may work, especially given that some antidepressants (e.g. fluoxetine) have shown to be active 5-HT_{2B} receptor agonists (Li et al., 2008). Recent and ongoing advancements in the development of selective 5-HT_{2B} receptor ligands will allow for a more thorough characterization of this receptor.

4.5. Serotonin 2C receptors

Like the 5-HT₁ and 5-HT_{2A} receptors, 5-HT_{2C} receptors are expressed throughout the mesocorticolimbic system (Bubar and Cunningham, 2007; Clemett et al., 2000) and are believed to be effective targets for some antidepressants (Chanrion et al., 2008; Dremencov et al., 2009) and atypical antipsychotics (Rauser et al., 2001; Reynolds et al., 2005). While many earlier studies made great strides in characterizing 5-HT₂ receptor function in reward-related behaviours, they did so by using ligands which were not selective for this receptor subtype, such as DOI, TFMPP, and mCPP (for examples, see Grottick et al., 1997; Rocha et al., 1993; Wilson et al., 1998) – often leading to conflicting and confusing results.

The development of selective agonists such as Ro 60-0175 and WAY 161503, and antagonists such as SB 242084 – along with the use of vastly improved reward-related measures – have led to a much clearer understanding of this receptor in reward-related

behaviours. In general, the available evidence suggests that 5-HT_{2C} receptor activation decreases reward-related measures while antagonism increases these measures under some circumstances. In particular, Hayes et al. (2009a) and Mosher et al. (2005, 2006) have shown that 5-HT_{2C} receptor activation may increase ICSS frequency-thresholds (indicating a decrease in reward) and induce a context-dependent CPA. However, 5-HT_{2C} receptors in the NAc shell/core, VTA, or medial prefrontal cortex do not appear to be involved (Hayes et al., 2009a; Katsidoni et al., 2010). 5-HT_{2C} receptor activation has also been shown to decrease cocaine (particularly in the NAc shell/core and medial prefrontal cortex, but not the VTA) and ethanol self-administration (Fletcher et al., 2004; Katsidoni et al., 2010; Tomkins et al., 2002). However, these effects are not likely due to general decreases in reward-related processing, as the selective 5-HT_{2C} receptor agonist WAY 161503 attenuated nicotine-induced locomotor activity without affecting CPP (Hayes et al., 2009c); although there are no studies using nicotine-induced self-administration or self-stimulation to assess the specificity of these effects across reward-related behaviours.

Alternately, functional 5-HT_{2C} receptor antagonism has been shown to increase cocaine and ethanol self-administration (Fletcher et al., 2002b; Rocha et al., 2002; Tomkins et al., 2002), and to produce trends toward reward-enhancing (although non-significant) effects in ICSS and spontaneous locomotor activity (Hayes et al., 2009a; Mosher et al., 2005). Although minor, these effects are in line with the fact that SB 242084 can increase the putatively reward-related firing rates of VTA dopamine cells and subsequent release of dopamine in the NAc (Di Giovanni et al., 2000; Di Matteo et al., 1999). These effects are also in line with data showing that the constitutive activity of this receptor, along with its ability to produce numerous protein variations due to RNA editing (which appears to be uncommon among G-protein coupled receptors, and which may be linked to the level of constitutive activity), may be involved in reward-related processing (Dracheva et al., 2009; Leggio et al., 2009). Given these and other data, the constitutive activity of the 5-HT_{2C} (along with the 5-HT_{2A}) receptor should be given increased focus in future studies (Aloyo et al., 2009). In particular, the use of inverse agonists (with direct comparison to putative agonists and antagonists) should be further investigated in both animals and humans, especially given that they may have clinical relevance in schizophrenia and major depressive disorder (Berg et al., 2008b).

Taken together, these data suggest that 5-HT_{2C} receptors generally play an inhibitory role in the regulation of reward-related behaviours, and that their constitutive activity may be essential to understanding their broader function in this context. Although the activation of these receptors in the NAc shell may not be involved in basal reward-related processing (Hayes et al., 2009a; Navailles et al., 2008), both NAc and VTA 5-HT_{2C} receptors may be involved in cocaine-induced reward (Fletcher et al., 2004; Navailles et al., 2008). Future research should investigate this receptor's potential role in drug-induced changes in reward (beyond alcohol and cocaine) and should further investigate the likely primary locations pertaining to these effects – as these receptors are found abundantly on non-dopaminergic cells throughout the reward-related circuitry of the brain (Bubar and Cunningham, 2007; Di Giovanni et al., 2001; Serrats et al., 2005).

4.6. Serotonin 3 receptors

The 5-HT₃ receptors have, much like the 5-HT_{1A} receptor subtypes, been of great interest to researchers due to the fact that highly selective ligands (particularly antagonists) have been available for decades. In addition, they represent the only ionotropic serotonin receptor subtype, suggesting that their actions centrally may be faster, and more functionally selective, than those of the

G-protein coupled subtypes (for additional information on the molecular biology of these receptors see Hannon and Hoyer, 2008). Despite extensive research into their potential roles in neuropsychiatric disorders and reward-related behaviours, antagonism of these receptors is still of greatest use clinically against emesis and disorders with visceral pain (Costall and Naylor, 2004; Greenshaw, 1993a). Nonetheless, there is some evidence for their use in combating the effects of drugs of abuse.

5-HT₃ receptor antagonism alone appears to have no effect on reward-related behaviours, as indicated by studies of self-stimulation, self-administration, and place conditioning (e.g. Greenshaw, 1993a,b; Peltier and Schenk, 1991; Carboni et al., 1989). However, it may attenuate the effects of cocaine (e.g. Davidson et al., 2002; Kankaanpaa et al., 2002; Kelley and Hodge, 2003) and morphine (e.g. Carboni et al., 1989; Hui et al., 1993; Rompre et al., 1995) across these behaviours, particularly following repeated administration. Interestingly, it does not appear to affect the actions of another potent psychostimulant amphetamine, as suggested by studies looking at amphetamine-induced (Carboni et al., 1989; Montgomery et al., 1993) or nicotine-induced (Ivanova and Greenshaw, 1997) CPP and increases in ICSS responding. Also, the effects of 5-HT₃ antagonists on nicotine-related reward cannot be generalized across reward paradigms, as receptor antagonism has been shown to attenuate nicotine-induced CPP (Carboni et al., 1989, 1988) without affecting self-administration (Corrigall and Coen, 1994) or self-stimulation (Ivanova and Greenshaw, 1997) behaviour – suggesting that the 5-HT₃ receptor plays a drug-specific, and perhaps even a context-specific, role in reward-related processing. This point seems best elucidated by the work combining 5-HT₃ receptor antagonism and ethanol-induced reward.

Although the effect of receptor antagonism on ethanol reward has not been reported in ICSS, and has been suggested in one study to not affect ethanol-induced CPA (Bienkowski et al., 1997), numerous studies have investigated these effects in self-administration behaviour. While many experiments have revealed no effects on ethanol self-administration (e.g. Beardsley et al., 1994; Meert, 1993; Wilson et al., 1998), others have shown decreased ethanol intake and preference following systemic administration of 5-HT₃ receptor antagonists (e.g. Hodge et al., 1993, 1995; Knapp and Pohorecky, 1992; Silvestre et al., 1998). The large variability of results across studies may be partly explained by the wide variation in parameters used, including differences in animal strain, individual preference for ethanol, ethanol dose, and drug pretreatment and self-administration parameters (e.g. oral administration is the preferred method of self-administration used by experimenters, as it is the simplest and most natural approach, however, other factors such as individual differences in response and metabolism make results from this approach more difficult to assess). As such, a few studies involving ethanol-preferring rats and the use of microinjections into selective brain areas have been particularly useful in determining the role of these receptors in ethanol reinforcement.

For instance, McKinzie et al. (2000) used ethanol-preferring rats to reveal the importance of timing, showing that variable self-administration time schedules may be key to the permissive role of the 5-HT₃ receptor in ethanol reward (as only animals tested on a variable time schedule showed reduced responding) – an idea alluded to in an earlier study by Knapp and Pohorecky (1992). While the mechanism related to the increased sensitivity of ethanol in these rats (and ethanol self-administration in general) is not yet clear, it is interesting to note that ethanol appears to interact with 5-HT₃ receptors resulting in the stabilization of the open-channel state (Feinberg-Zadek and Davies, 2010) and the enhancement of ionic currents (Lovinger and White, 1991). Also, somewhat paradoxically, ethanol-preferring rats have been shown to have lower levels of 5-HT₃ receptor binding in the frontal cortex, hippocam-

pus, and amygdala in some (Ciccocioppo et al., 1998; Hensler et al., 2004), but not all (Chen and Lawrence, 2000), studies.

Additionally, microinjection studies have identified that 5-HT₃ receptors in the posterior (but not anterior) VTA appear to be important in mediating the rewarding effects of ethanol (Rodd-Henricks et al., 2003; Rodd et al., 2005b), although other brain areas cannot yet be ruled out. Specifically, Rodd et al. (2007, 2010) underscored the role of these receptors in ethanol-induced reward by showing that both Wistar rats and selectively bred ethanol-preferring P rats will self-administer the selective 5-HT₃ receptor agonists CPBG and ICS 205-930 directly into the posterior (but not anterior) VTA and that the P rats are more sensitive to these effects. In addition, they showed that repeated administration with a 5-HT₃ receptor antagonist (i.e. ICS 205-930) can alter the circuitry of the posterior VTA (Rodd et al., 2010). These results are consistent with the CPAs induced in another study following the administration of 5-HT₃ receptor agonists (Higgins et al., 1993a). For additional information on 5-HT₃ receptors as potential pharmacotherapeutic targets in drug abuse, see Engleman et al. (2008).

These results strongly suggest that these receptors are important in the reinforcing properties of many drugs of abuse (particularly alcohol). At least for alcohol, it appears that 5-HT₃ receptor-regulation of dopamine cells in the posterior VTA is very important for its rewarding properties (Campbell et al., 1996, 1995). However, these mechanisms need to be confirmed regarding the results seen with cocaine- and morphine-induced reinforcement. Nonetheless, given the putative role of these receptors in regulating many neurotransmitters throughout the brain, the development of newer, centrally active, agonists (see Butini et al., 2009 for some examples) should be used to investigate its potential role in reward-related behaviours.

4.7. Serotonin 4, 5, 6, 7 receptors

The 5-HT₅ receptor has not been studied regarding reward-related behaviour (and its physiological brain function, if any, is currently unknown) and will not be discussed further here. For additional information, the reader is referred to reviews by Thomas (2006) and Nelson (2004).

The 5-HT_{4,6,7} receptors are all found in the brain and appear to have a stimulatory function mediated by their coupling to the G_s proteins – making them potential candidates in the involvement of reward-related processing. 5-HT₄ receptors are of particular interest because their brain expression appears to be largely limited to the striatum (particularly within the NAc shell) and substantia nigra where they are likely located on GABAergic projection cells and GABAergic and cholinergic interneurons (Patel et al., 1995). Nonetheless, most research currently focuses on targeting peripheral receptors as these are known to affect cardiac and gastrointestinal function (e.g. De Maeyer et al., 2006); although the development of some newer ligands are being used to investigate this receptor's potential role in psychiatric disorders (for an in-depth discussion of recent developments and related research, see Modica et al., 2010). Interestingly, only one study has investigated the role of a 5-HT₄ receptor antagonist in reward-related behaviour, finding it had no effect on any ICSS measures (Reavill et al., 1998).

The key localization of 5-HT₆ receptors in many reward-related brain regions such as the NAc, caudate-putamen, and frontal cortex (Gerard et al., 1997; Ward et al., 1995) has made this receptor an interesting candidate for mediating reward-related behaviours. Nonetheless, only two studies to date have investigated their effects in this context. Frantz et al. (2002) showed that receptor antagonism decreased amphetamine-, but not cocaine-, maintained responding (i.e. on both fixed and progressive ratio schedules of self-administration). This, in conjunction with their finding

that 5-HT₆ receptor antagonism also potentiated amphetamine-induced increases in frontal cortex dopamine release, suggests that these central receptors may play a key role in amphetamine-induced reward. Interestingly, Ferguson et al. (2008) found that rats over-expressing 5-HT₆ receptors in the NAc (thought to be a functional agonism) did not show a cocaine-induced CPP, while pharmacological antagonism (in the absence of over-expressed receptors) produced a CPP in combination with an otherwise subthreshold dose of cocaine. In contrast to the cocaine-related results from Frantz et al. (2002), these results suggest that 5-HT₆ receptors (particularly those in the NAc) may play a role in both amphetamine- and cocaine-induced reinforcement. However, more work is needed to determine the precise role of these receptors in reward-related behaviours and the increasing development and availability of selective 5-HT₆ receptor ligands (Glennon et al., 2010) may help to make this target more appealing to investigators.

While no direct reward-related studies have been conducted regarding the 5-HT₇ receptor, its potential role in some neuropsychiatric disorders, such as depression (Kulkarni and Dhir, 2009), schizophrenia (Suckling et al., 2007), and anxiety (Wesolowska et al., 2006a,b), has been investigated using animal models. The strongest evidence to date suggests that these receptors may be involved in regulating depressive symptoms and receptor antagonism may play a role in the actions of some antidepressant drugs. For example, the 5-HT₇ receptor antagonist SB 269970 has been shown to have antidepressant-like effects (alone and in combination with subthreshold doses of antidepressants such as imipramine) in some animal models of depressive behaviour, including the tail suspension and forced swim tests; interestingly, it was shown to increase levels of 5-HT, dopamine and norepinephrine in the prefrontal cortex of rats (Bonaventure et al., 2007; Wesolowska and Kowalska, 2008). For a review of these and related studies, see Hedlund (2009).

Taken together, results from these few studies underscore the possibility that these receptors are involved in reward-related behaviour and, as such, may also be involved in mediating the dysregulation of reward-related processing seen in many neuropsychiatric disorders. The recent and ongoing development of pharmacologically selective receptor ligands will undoubtedly be essential to advance knowledge in this area.

4.8. What can be concluded about 5-HT and reward in general?

The results from this review indicate clearly that any studies outlining or suggesting a general role for 5-HT in reward should be regarded with extreme caution. It can be concluded that serotonin certainly does not have a single uniform role in mediating reward-related behaviours. In fact, while we have focused on the role of 5-HT in reward-related behaviours, it is highly likely that many (and perhaps even all) of the results in the reported studies can be interpreted in a different, but related, light. Specifically, 5-HT also plays a key role in aversion which is the (psychologically) operationally defined opposite of reward. For instance, acute tryptophan depletion (ATD) in humans (which decreases central levels of 5-HT) abolishes punishment/aversion-related response inhibition seen under normal conditions (without affecting global motor performance) – suggesting a role for 5-HT in the prediction of aversive outcomes (Crockett et al., 2009). Similarly, in non-human animals, ATD can result in increased measures of anxiety- and depression-like behaviours (consistent with increases in aversion-related processing) (Jans et al., 2010), although not all studies have noted such general effects of ATD (Jans and Blokland, 2008). Finally, it is prudent to note that other authors have also come to the conclusion that the diverse findings regarding 5-HT across processes (e.g. emotional processing, behavioural inhibition, aversion-related

behaviours) may be largely related to its actions at multiple receptor subtypes (Cools et al., 2008).

Given these results, it may be more accurate to speak of 5-HT in the broader context of valuation as opposed to having a general role in either reward or aversion. Although beyond the scope of the current review, we are aware that this approach raises the ongoing issue of more precisely defining exactly what the terms 'reward' and 'aversion' refer to at the biological level – especially given that they likely reflect a number of related and/or overlapping processes, which may be reflected to varying degrees across reward-related behaviours (e.g. pleasure/hedonia/liking, wanting/incentive salience, seeking, instrumental learning, behavioural activation) (Berridge and Robinson, 2003; Ikemoto and Panksepp, 1999; Salamone, 2006; Salamone et al., 2005; Schultz, 2006). Nonetheless, the complexity of 5-HT function in these behaviours suggests that its role selectively in either reward or aversion should, perhaps, only be considered with respect to the specific contents (e.g. receptor subtypes/function, localization) and contexts (e.g. type of reward-related behaviour and/or mechanism of drug of abuse under investigation) under investigation – something that we have attempted to accomplish in this review.

4.9. Conclusions

As outlined here, there is a vast collection of evidence indicating that the serotonergic system is imperative in the regulation of reward-related processing and associated behaviours. It is important to consider the potential role of each receptor subtype in this regard, as they can have very different localization patterns, functions, neurotransmitter interactions etc. In addition to underscoring the importance of content in these experiments (e.g. which receptor subtype is under investigation), it is undoubtedly important to consider the context under which these experiments are performed (e.g. does the animal model under investigation have a strong reward-related measure? are there measures of motor performance? how do these results compare to those from other models?). However, as noted in the introduction, serotonin is a multi-faceted neurotransmitter whose actions are not restricted to reward-related behaviours. As such, future studies must not only consider its role in the increasingly clarified subcomponents of reward, such as its hedonic or motivational components (Berridge et al., 2009), but must also consider its impact on processes other than reward (which may help explain some of the discrepancies seen across the presently noted studies), for instance in emotional regulation and behavioural inhibition (Cools et al., 2008; Kalueff et al., 2010).

Taken together, the results from the present review (as summarized in Table 3) are as follows. 5-HT_{1A} receptor stimulation alone (particularly in the raphe nuclei) leads to increases in reward, although neither agonists nor antagonists are self-administered. However, high doses of 5-HT_{1A} receptor agonists, especially when administered systemically, may decrease reward (and/or be aversive), and this may be due to a preferential activation of post-synaptic, over pre-synaptic, receptors at higher drug concentrations. Interestingly, current evidence suggests that 5-HT_{1A} receptor stimulation attenuates cocaine-induced and morphine-induced (but not amphetamine-induced) reward, while 5-HT_{1A} receptor antagonism enhances the rewarding effects of ethanol under some conditions (i.e. CPP), but not in others (i.e. self-administration). 5-HT_{1B} receptor stimulation alone leads generally to decreases in reward (note that they are not reliably self-administered). However, 5-HT_{1B} receptor stimulation (particularly in the VTA) enhances the reward-related effects of cocaine (as noted in self-administration and place conditioning studies) and ethanol (as noted in self-administration). 5-HT_{2A} receptor stim-

ulation may decrease reward (as indicated by one ICSS study); antagonism may decrease MDMA- and ethanol-induced reward (although neither stimulation nor antagonism had an effect on cocaine-related reward). Too few studies on 5-HT_{2B} receptors in reward have been conducted, however, receptor antagonism may prevent MDMA-induced reinstatement of CPP. 5-HT_{2C} receptor stimulation alone (though likely not those in the NAc shell/core, VTA, or medial prefrontal cortex) decreases measures of reward; it also decreases cocaine- (interestingly, particularly involving those receptors located in the NAc and medial prefrontal cortex but not in the VTA), ethanol-, and THC-induced reward. Its constitutive activity may be involved in its mechanism of action, as functional antagonism of this receptor enhances cocaine- and ethanol-induced reward. There is not enough evidence to comment on the role of 5-HT₃ receptor stimulation, although one study suggests that it may produce decreases in reward (and/or increased aversion). Alternately, 5-HT₃ receptor antagonists have been extensively studied, and while they typically have no effect alone, they can (particularly following repeated administration) decrease the reward-related effects of cocaine (in all paradigms), morphine (in all paradigms), ethanol (only in self-administration under certain conditions), nicotine (in place conditioning only), and the NMDA receptor antagonist ketamine (in place conditioning); they also attenuated the CPAs induced by the NMDA receptor antagonist phencyclidine and the GABA_A receptor antagonist picrotoxin. No conclusions can be made about 5-HT₆ receptor stimulation, but antagonism appears to increase the rewarding effects of amphetamine (in self-stimulation) and cocaine (in place conditioning but not self-stimulation) – although more studies must be undertaken before any clear role can be seen. Finally, given the lack of studies, no conclusions can be made about 5-HT_{4,5,7} receptors in reward.

In a nutshell, the results from this review were able to highlight some general conclusions and point out some gaps regarding our current knowledge of the role of the serotonergic system in reward-related behaviours.

Some general conclusions include:

1. All 5-HT receptor subtypes that have been studied in reasonable detail appear to be involved in regulating some aspects of reward-related behaviours.
2. Each receptor subtype (even those with similar mechanisms of action) may affect reward-related behaviours in many different ways through numerous potential mechanisms (especially given that they may be found on multiple cell types, and across many brain regions, which may have opposing overall effects on reward) – in short, results from studies using mixed ligands and/or systemic injections (without a clear hypothesis) will be exceedingly difficult to interpret.
3. Some receptor subtypes possess unique characteristics, which may play unique roles in reward-related processing. For instance, there is good evidence that 5-HT_{2C} receptors exhibit tonic control over at least some aspects of reward-related processing, as indicated by the fact that receptor antagonism has behavioural effects under certain conditions (but see #3 below).
4. Evidence indicates that some receptors are important in the direct effects of some drugs of abuse given that 5-HT receptor antagonism attenuates their reinforcing effects. These include receptor subtypes such as 5-HT_{1A} (in the aversive effects of ethanol and the reinforcing effects of morphine), 5-HT_{2C} (in the reinforcing properties of cocaine; although it is unclear whether these results are related to its constitutive properties), 5-HT₃ (in the reinforcing properties of cocaine and heroin), and 5-HT₆ (in the aversive properties of cocaine).

Current gaps in our knowledge worth exploring:

1. As underscored by Fink and Gothert (2007), 5-HT receptor subtypes regulate at least every major neurotransmitter within the brain, yet there are relatively few reward-related studies which have investigated these complex interactions (e.g. Acquas et al., 1990; Hayes et al., 2010). Future research would benefit from clear hypotheses about the interaction between select 5-HT receptor subtypes and other neurotransmitters (e.g. GABA, glutamate, acetylcholine) in this regard.
2. The use of recently developed highly selective receptor ligands, particularly for those receptors whose role is especially unclear such as the 5-HT_{2A,2B,4,6,7} subtypes, should be utilized in reward-related models to better clarify each subtype's role.
3. It is not clear whether, and in what way, the constitutive activity of the 5-HT_{2C} receptor and/or the extensive editing of its RNA, plays a role in its reward-regulating properties. Other subtypes with unique characteristics (e.g. the differential roles of pre- and post-synaptic 5-HT_{1A} receptors; the ionotropic nature of the 5-HT₃ receptor) offer similarly unsolved issues to consider.
4. Although the use of models with reward-selective measures is essential, it is important to note that 5-HT is important in many other behaviours involving reward-related processing, such as feeding and sexual activity. Future studies may benefit from a comparison of 5-HT receptor subtype function across such related behaviours.
5. Numerous 5-HT receptor subtypes have been implicated in the pathophysiology and/or treatment of many neuropsychiatric disorders that involve the dysregulation of reward-related processing, although the precise mechanisms involved are still unclear. For example, many receptor subtypes have been implicated in major depression and, as such, novel antidepressants are currently being created and tested with this in mind (Millan, 2009).
6. Future studies would benefit greatly from the use of a translational approach, whereby non-human animal studies are designed in parallel, in a complimentary fashion, with those in humans. In addition, the use of selective (radio)ligands for use in PET or pharmacological fMRI will greatly enhance our understanding of reward-related processing in humans.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neubiorev.2011.03.005](https://doi.org/10.1016/j.neubiorev.2011.03.005).

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