

The serotonin 5-HT_{2C} receptor and the non-addictive nature of classic hallucinogens

by

Clinton E Canal¹ and Kevin S Murnane²

Journal of Psychopharmacology 1-17

DOI: 10.1177/0269881116677104

© The Author(s) 2016

original report: <https://pdfs.semanticscholar.org/39f4/85b6acf2bd17dace8cdc053ac0c164c1dbbe.pdf>

backup source: <http://www.psilosophy.info/resources/85b6acf2bd17dace8cdc053ac0c164c1dbbe.pdf>

¹ Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, Boston, USA

² Department of Pharmaceutical Sciences, Mercer University College of Pharmacy, Mercer University Health Sciences Center, Atlanta, USA

Corresponding author:

Clinton E. Canal, Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA, USA.

Email: c.canal@northeastern.edu

Table of Contents:

Abstract

Classic hallucinogens are serotonin 5-HT₂ receptor agonists

Results from preclinical studies and reports from experienced hallucinogen users show that classic hallucinogens have low addiction liability

Why are classic hallucinogens nonaddictive? Focus on serotonin

Considerations of 5-HT_{2A} receptor activation to addiction liability

Considerations of 5-HT_{2B} receptor activation to addiction liability

Considerations of 5-HT_{2C} receptor activation to addiction liability: Behavioral studies

Considerations of 5-HT_{2C} receptor activation to addiction liability: Neurochemistry studies

The NAc is a key site for 5-HT_{2C} receptor modulation of reward circuitry

5-HT_{2C} modulation of intrinsic plasticity via inhibition of NAc Kv1.x channels: A novel hypothesized mechanism for psychostimulant addiction treatment

Caveat emptor

Classic hallucinogens treat addiction

Testable hypotheses for unraveling the anti-addictive effects of classic hallucinogens

Acknowledgements

References

Abstract

Classic hallucinogens share pharmacology as serotonin 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptor agonists. Unique among most other Schedule 1 drugs, they are generally non-addictive and can be effective tools in the treatment of addiction. Mechanisms underlying these attributes are largely unknown. However, many preclinical studies show that 5-HT_{2C} agonists counteract the addictive effects of drugs from several classes, suggesting this pharmacological property of classic hallucinogens may be significant. Drawing from a comprehensive analysis of preclinical behavior, neuroanatomy, and neurochemistry studies, this review builds rationale for this hypothesis, and also proposes a testable, neurobiological framework. 5-HT_{2C} agonists work, in part, by modulating dopamine neuron activity in the ventral tegmental area - nucleus accumbens (NAc) reward pathway. We argue that activation of 5-HT_{2C} receptors on NAc shell, GABAergic, medium spiny neurons inhibits potassium Kv1.x channels, thereby enhancing inhibitory activity via intrinsic mechanisms. Together with experiments that show that addictive drugs, such as cocaine, potentiate Kv1.x channels, thereby suppressing NAc shell GABAergic activity, this hypothesis provides a mechanism by which classic hallucinogen-mediated stimulation of 5-HT_{2C} receptors could thwart addiction. It also provides a potential reason for the non-addictive nature of classic hallucinogens.

Keywords: Hallucinogens, 5-HT_{2C}, cocaine, Kv1, addiction

Classic hallucinogens are serotonin 5-HT₂ receptor agonists

Classic hallucinogens (CH) are powerful psychoactive substances that are categorized into two broad chemotype classes: indoleamines (including tryptamines and ergotamines) and phenylalkylamines (including phenethylamines and phenylisopropylamines; Halberstadt, 2015). Prototypical CH representative of each subclass include psilocybin, a tryptamine found in several genera of mushrooms (Stamets, 1996); lysergic acid diethylamide (LSD), an ergotamine originally derived from ergot fungi (Hofmann, 1970); mescaline, a phenethylamine found in peyote (Heffter, 1898) and other cacti; and 2,5-dimethoxy-4-bromoamphetamine (DOB), a phenylisopropylamine (substituted amphetamine) derived solely via synthetic schemes (Shulgin and Shulgin, 1991). Various analogues of these compounds have been synthesized and tested for bioactivity (Nichols *et al.*, 2015; Shulgin and Shulgin, 1991, 1997; Shulgin *et al.*, 2011), but for the focus of this paper, we confine classification of CH to those drugs that have been characterized extensively in both nonhuman animals and in humans (Bogenschutz and Johnson, 2016; Halberstadt, 2015). For example, we do not classify novel N-benzyl substituted phenethylamine hallucinogens as CH, because their receptor and behavioral pharmacology are not fully characterized or diverge from CH (Nichols *et al.*, 2008).

The fundamental, shared pharmacological property of all CH is high affinity and agonist activity at serotonin 5-HT₂ G protein-coupled receptor (GPCR) subtypes (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), with most binding to and stimulating 5-HT₂ receptors at low nanomolar concentrations. However, depending on the CH examined, activities at other GPCRs have been identified, particularly other 5-HT receptors, and, most notably, 5-HT₁ receptor subtypes (Nichols, 2004; Roth *et al.*, 2000). Many attempts have been made to uncover additional molecular targets of CH. For example, tryptamine hallucinogens display activity at the sigma-1 receptor, the serotonin transporter (SERT), and the vesicular monoamine transporter (Cozzi *et al.*, 2009; Fontanilla *et al.*, 2009), but high concentrations, reaching micromolar levels, are required to elicit activity, which calls into question their contribution to psychoactive effects. Also, it was reported recently that certain substituted amphetamine hallucinogens, including 2,5-dimethoxy-4-iodoamphetamine (DOI) and DOB, bind with appreciable affinity at adrenergic GPCRs (Ray, 2010). However, using traditional radioligand competition binding assays, we did not replicate the observed effects at alpha-adrenergic receptors. We obtained micromolar affinity (K_i) values of (\pm)-DOI at each of the α -adrenergic receptor subtypes we screened (α 1a, α 1b, α 2a, α 2b, and α 2c; unpublished observations; data available upon request).

Most germane to the psychoactive effects of CH is that they are blocked by 5-HT₂ antagonists in both rodents (Fantegrossi *et al.*, 2005) and humans (Komater *et al.*, 2013; Vollenweider *et al.*, 1998). It should be noted, however, that there are exceptions wherein 5-HT₂ antagonism is insufficient to eliminate the discriminative

stimulus properties of CH (e.g., psilocybin and LSD) in rodents (Benneyworth *et al.*, 2005; Winter *et al.*, 2007). Clearly, pharmacodynamics and pharmacokinetics across species play an important role, and may underlie observed discrepancies (Canal *et al.*, 2013). Nevertheless, adding to support that 5-HT₂ receptors are the predominant mediators of CH psychoactive effects are the observations that 5-HT_{2A} knockout mice do not exhibit behaviors, such as the head-twitch response (HTR; Gonzalez-Maeso *et al.*, 2007; Hanks and Gonzalez-Maeso, 2013), typically elicited by CH. Also, the DOI-elicited HTR is reduced in 5-HT_{2C} receptor knockout mice (Canal *et al.*, 2010). Collectively, it can be said with confidence that 5-HT₂ receptors predominantly mediate the psychoactive effects of CH. Here, we focus on interrogating 5-HT_{2A}, 5-HT_{2B}, and/or 5-HT_{2C} receptors as the elemental GPCRs that underlie their non-addictive nature.

Results from preclinical studies and reports from experienced hallucinogen users show that classic hallucinogens have low addiction liability

One of the fascinating aspects of CH, long recognized by experienced hallucinogen users and only recently gaining traction by the broader scientific community, is that compared with most other psychoactive drugs scheduled by federal governments in the most restrictive classes (e.g., heroin in Schedule 1 and cocaine in Schedule 2), they are relatively non-addictive (Bogenschutz and Johnson, 2016). As a caveat, we understand that there can be controversy defining what are and what are not addictive substances, including defining CH as addictive or not (Nutt *et al.*, 2010; Stone *et al.*, 2006). Considering the DSM-5 criteria for a diagnosis of a substance-use disorder (American Psychiatric Association, 2013), we narrowly define addictive drugs as those that induce craving or an impulse to re-dose after psychoactive effects have peaked or have begun to subside. Note, this feeling and impulse is also described in the literature as "wanting" or "increased incentive salience." Experienced drug users report that CH do not produce drug craving, which is typically elicited by other psychoactives of distinct chemical classes (e.g., methamphetamine, MDPV, nicotine, alcohol, cocaine, heroin; see erowid.org). Also, although tolerance to most CH, excluding short-acting *N,N*-dimethyltryptamine (DMT; Strassman *et al.*, 1996), is evident with repeated, continuous exposure, withdrawal symptoms are generally non-existent once effects subside, distinguishing CH from most other drugs of abuse, including closely related serotonin-releasing empathogens such as 3,4-methylenedioxymethamphetamine (MDMA) that also have activity at dopamine transporters (Ball and Slane, 2014; Meyer, 2013).

The relatively non-addictive characteristics of CH described by human users are recapitulated in well-controlled, preclinical animal studies, which provide reliable and conclusive evidence. Such animal studies typically employ intravenous self-administration, in which an operant response by the animal (e.g., pressing a lever) is reinforced by the delivery of a dose of drug. While intramuscular (Goldberg *et al.*, 1976), inhalation (Carroll *et al.*, 1990a), and oral (Gomez *et al.*, 2002) routes of administration also maintain drug-taking behavior, intravenous drug delivery is the most employed route of administration in self-administration studies, as intravenous delivery causes a rapid onset of action, facilitating learning of the association between the operant response and the psychoactive effects of the drug. Animal self-administration experiments demonstrate a very strong correlation between drugs that produce dependence in humans and those that are voluntarily consumed by laboratory animals (Brady *et al.*, 1984; Griffiths, 1980; Griffiths *et al.*, 1978, 1980).

One of the earliest studies on the reinforcing effects of drugs using the intravenous self-administration procedure in rhesus monkeys found that no animal initiated self-injection of mescaline either spontaneously or after one month of programmed administration, and this was apparent at doses that produced physiological and psychoactive effects such as salivation, mydriasis, pilo-erection, and apparent apprehension (Deneau *et al.*, 1969). The lack of mescaline self-administration stood in contrast to positive findings of self-administration of morphine, codeine, cocaine, amphetamine, pentobarbital, ethanol, and caffeine. A subsequent study with rhesus monkeys using 2,5-dimethoxy-4-methylamphetamine (DOM; Yanagita, 1986) provided similar results as the mescaline study. These findings have withstood the test of time, as the primary literature is virtually devoid of any accounts of self-administration of CH, suggesting that there are very limited conditions under which laboratory animals voluntarily consume CH. In one example, extreme environmental conditions were required to elicit self-administration of DMT in monkeys (Siegel and Jarvik, 1980). In this study, under baseline conditions, monkeys sampled DMT but did not engage in significant or persistent self-administration. However, following several days of sensory deprivation (i.e., the absence of light and sound), two of the three

monkeys consistently self-administered DMT for up to 20 days (which was the *a priori* imposed endpoint of the experiment). These observations were conceptualized as the DMT engendering an internal or mental perceptual window with concomitant positive reinforcing effects in the context of sensory deprivation. In a second example, various hallucinogens were substituted in monkeys that were maintained on a baseline of (\pm)-MDMA self-administration. Although none of the subjects consistently self-administered any of the hallucinogens tested, all of the subjects transiently and sporadically self-administered psilocybin, mescaline, and DMT at response rates that were comparable to MDMA and up to the maximum number of infusions that were available (Fantegrossi *et al.*, 2004a). These effects, however, were transient and sporadic, and clearly unlike those seen across a broad range of other psychoactive drugs. In our studies, we observed very weak reinforcing effects of psilocybin in rhesus macaque monkeys. Once responding during saline administration was procedurally manipulated to an extraordinarily low level (approximately 0.01 responses per second), some positive reinforcing effects were apparent with psilocybin (unpublished observations; data available upon request), but yet again, these effects massively pale in comparison to other drugs of abuse (Murnane *et al.*, 2013b). Based on these studies, it is clear that conditions have not yet been found, despite decades of efforts, wherein CH are readily self-administered by laboratory animals. Given the very strong correlation between drugs that produce dependence in humans and those that are voluntarily consumed by laboratory animals (Brady *et al.*, 1984; Griffiths, 1980; Griffiths *et al.*, 1978, 1980), this is among the strongest evidence for the non-addictive nature of CH.

Despite the relative absence of addictive properties, observed in well-controlled preclinical studies and reported by human users, CH can dose-dependently elevate mood and produce a strong sense of well-being, depending on mental set and environmental setting (Studerus *et al.*, 2012). In fact, many people who have taken CH report that their experiences were of the most influential and positive of their lives (Griffiths *et al.*, 2011). These positive psychological effects of CH, nonetheless, do not qualify them as without risk, especially when taken without precaution, careful planning, and supervision. CH produce profound alterations in cognition and sensory perception and can produce emotional lability, fear, anxiety, and/or panic, among other adverse psychological and physiological effects. Nonetheless, if CH can elevate mood and produce a sense of well-being, why are they non-addictive?

Why are classic hallucinogens nonaddictive? Focus on serotonin

There are several biological possibilities to explore why CH are relatively non-addictive. For example, the long durations of action of many CH and their capacity to induce 5-HT_{2A} receptor desensitization (Leysen *et al.*, 1989), which causes rapid, prolonged, and profound tolerance to their psychoactive effects (i.e., tachyphalaxis), may be factors. In support of these possibilities, it is well known that long pharmacokinetic profiles, including long durations of action, can minimize abuse liability (Abreu *et al.*, 2001; Fantegrossi *et al.*, 2004b; Marsch *et al.*, 2001; Nelson *et al.*, 2006; Volkow *et al.*, 2000; Woolverton and Wang, 2004). The psychedelic effects of LSD, which persist for approximately 8-12 hours, are greatly attenuated with repeated dosing; a few days of abstinence are required before subjective effects return to pre-exposure levels (Belleville *et al.*, 1956). Thus, spacing intake of LSD is necessary, which prevents the binge-like patterns of drug consumption often seen with highly addictive substances (Aarde *et al.*, 2015; Roberts *et al.*, 2007). However, effects of DMT are inconsistent with this explanation. The hallucinogenic effects of DMT commence within two minutes of intravenous administration, and subside by 30 minutes (Strassman and Qualls, 1994). Moreover, the psychedelic effects of DMT persist with repeated administration in a single drug-taking session (Strassman, 1996). This may generalize across some tryptamines, as a recent study shows profound tolerance in mice to two phenethylamines (DOI and 2C-T-7), but a lack of tolerance to two tryptamines (DPT and DIPT; Smith *et al.*, 2014). Despite their different durations of action and capacities to induce tolerance, none of the CH mentioned above are known to produce drug craving in human users. Comparatively, re-intoxication from addictive psychoactives can be achieved quickly after their effects subside, despite long durations of action (e.g., MDMA) combined with target desensitization and/or internalization and tolerance. For example, cannabinoid CB1 receptor downregulation is evident with prolonged cannabis use (Ceccarini *et al.*, 2015), but the subjective high from cannabis persists, even with tolerance and daily use. To maintain scope, this review focuses on serotonin receptor targets of CH that likely underlie their non-addictive properties.

The reinforcing and addictive effects of psychoactive drugs are primarily attributed to drug-induced changes in central dopamine function. Pointedly, the transition to addiction is mediated by increases in firing of ventral

tegmental area (VTA) dopamine neurons projecting to the nucleus accumbens (NAc), which increases dopamine release in the NAc (Cline *et al.*, 1992; Kuhar *et al.*, 1999; Pascoli *et al.*, 2015; Ritz *et al.*, 1989; Robison and Nestler, 2011); all addictive drugs increase dopamine release in the NAc. Serotonin, on the other hand, plays an important modulatory role in the behavioral effects of many psychoactive drugs. Serotonin neurons originate in the raphe nuclei in the brainstem, and send strong projections to the VTA, prefrontal cortex (PFC), amygdala, hippocampus, dorsal striatum, and NAc (Halliday and Tork, 1989). Serotonergic projections innervate cell bodies and terminals of dopamine neurons (Beart and McDonald, 1982; Geyer *et al.*, 1976; Nedergaard *et al.*, 1988; Parent *et al.*, 1981), often making direct synaptic contact (Herve *et al.*, 1987; Nedergaard *et al.*, 1988), and serotonin provides tonic and phasic control of dopaminergic systems within the limbic pathway (Alex and Pehek, 2007).

Converging results from many studies demonstrate that enhancing central serotonin release attenuates addictive behaviors (Muller and Homberg, 2015). For example, selective stimulation of serotonergic dorsal raphe nucleus afferents to the NAc, using designer receptors exclusively activated by designer drugs (DREADDs), abolishes cocaine-elicited conditioned place preference (You *et al.*, 2016). Furthermore, there is a negative relationship between the potencies of several cocaine- and amphetamine-like analogs in self-administration studies and their binding potencies as SERT inhibitors (Ritz and Kuhar, 1989; Ritz *et al.*, 1989). For example, rhesus monkeys self-administer more infusions of PAL-353, which has high selectivity for releasing dopamine versus serotonin, than PAL-313, which non-selectively releases dopamine and serotonin (Wee *et al.*, 2005). Similarly, rhesus monkeys do not self-administer PAL-287, which is relatively nonselective at releasing dopamine and serotonin, across a range of doses (Rothman *et al.*, 2005). Adding to the evidence, systemic administration of selective SERT inhibitors, which selectively increase extracellular levels of serotonin, decrease cocaine self-administration in rodents (Carroll *et al.*, 1990b; Richardson and Roberts, 1991) and nonhuman primates (Kleven and Woolverton, 1993). In nonhuman primates, SERT inhibitors, such as citalopram, fluoxetine, and alaproclate, attenuate the behavioral-stimulant effects of cocaine, cocaine self-administration, cocaine-induced increases in extracellular dopamine, and cocaine-induced activation of the PFC (Czoty *et al.*, 2002; Howell and Byrd, 1995; Howell *et al.*, 2002; Spealman, 1993). Additional studies show that SERT inhibitors attenuate drug-induced increases in dopamine levels in rodents and nonhuman primates (Czoty *et al.*, 2002; Di Matteo *et al.*, 2008) and cue-induced reinstatement of extinguished cocaine-maintained lever-pressing behavior in rats (Baker *et al.*, 2001; Burmeister *et al.*, 2003). Furthermore, an early study shows that serotonin infused directly into the NAc attenuates locomotor activity stimulated by direct infusions of dopamine into the NAc (Jones *et al.*, 1981). These studies demonstrate convincingly that serotonin opposes the effects of dopamine and attenuates the abuse-related and addictive effects of psychoactive drugs (for reviews, see Howell and Murnane, 2008; Murnane and Howell, 2011).

While it is well documented that serotonin attenuates the reinforcing effects of a variety of psychoactive drugs through suppression of dopamine neurotransmission, it is important to consider that there are 16 distinct serotonin receptors (not including splice variants or RNA-edited 5-HT_{2C} receptors) that are grouped into seven families: 5-HT₁-5-HT₇ receptors (Boess and Martin, 1994; Green, 2006; Hoyer *et al.*, 1994, 2002). Unique serotonin receptors can facilitate, inhibit, or have no effect on dopamine neurotransmission and on the reinforcing properties of a variety of psychoactive drugs. With particular relevance to the anti-addictive properties of CH, there are a number of reported observations of opposing effects between the 5-HT_{2C} and 5-HT_{2A} receptor subtypes, with 5-HT_{2A} receptors facilitating and 5-HT_{2C} receptors suppressing dopamine neurotransmission (Bubar and Cunningham, 2008; De Deurwaerdere and Spampinato, 1999; Filip *et al.*, 2004, 2006; Fletcher *et al.*, 2002; McMahon and Cunningham, 2001; McMahon *et al.*, 2001). The divergent effects of 5-HT_{2A} and 5-HT_{2C} on dopamine neurotransmission are at first consideration peculiar, since 5-HT₂ receptor subtypes couple to the same G-proteins (e.g., G_{α_{q/11/12/13}}) and activate the same intracellular signaling pathways (e.g., phospholipase C [PLC], mitogen-activated protein kinase, β-arrestin), with a few notable exceptions (Berg *et al.*, 1994, 2001; Chagraoui *et al.*, 2016; Knauer *et al.*, 2009; Sanders-Bush *et al.*, 2003). However, the differences observed may also be due to differences in the relative expression of 5-HT_{2A} and 5-HT_{2C} receptors across cell types and microcircuits that control unique aspects of neural function, a point discussed in greater detail in the 5-HT_{2C} sections below. Nonetheless, the differences between 5-HT_{2A} and 5-HT_{2C} modulation of dopamine neurotransmission provide a clear hypothesis for why CH, which do not provide a large spread between 5-HT_{2C} and 5-HT_{2A} receptor activation, do not induce craving. We argue that activation of 5-HT_{2C} receptors tempers the addictive liability of CH.

Considerations of 5-HT_{2A} receptor activation to addiction liability

There is a substantial body of evidence that the 5-HT_{2A} receptor facilitates dopamine neurotransmission. For example, systemic administration of DOI increases the firing rates of dopamine neurons in the VTA and induces dopamine release in the PFC, effects that are attenuated by selective antagonism of the 5-HT_{2A} receptor (Bortolozzi *et al.*, 2005; Pehek *et al.*, 2006) or genetic deletion of the 5-HT_{2A} receptor (Di Matteo *et al.*, 2000; Huang *et al.*, 2011). The preponderance of evidence for 5-HT_{2A} receptor facilitation of dopamine neurotransmission emanates from studies of the mesocortical system because of the widespread interest in serotonin modulation of this system in schizophrenia. Nevertheless, some studies examined 5-HT_{2A} receptor modulation of dopamine neurotransmission within the NAc, which is a key region in the mesolimbic dopamine pathway critical for addiction (Haber and Knutson, 2010; Russo and Nestler, 2013; Sesack and Grace, 2010). In this regard, direct administration of DOI into the posterior NAc significantly increases dopamine levels locally within the NAc, effects that are blocked by 5-HT_{2A} antagonists (Bowers *et al.*, 2000; Yan, 2000). However, we recently showed that systemic administration of DOI in rhesus monkeys engenders only meager (~10% increase above baseline) elevations in dopamine levels in the NAc (unpublished observations; data available upon request), and similarly, previous studies in rats show that systemic DOI does not affect dopamine release in the NAc (Di Matteo *et al.*, 2000). This suggests that DOI acting on additional neural systems or microcircuits suppresses the increase in dopamine neurotransmission in the NAc.

That 5-HT_{2A} receptors may contribute to drug seeking is further supported by studies employing neuroimaging, behavioral pharmacology, and genetic tools. A recent primate neuroimaging study shows that several months of cocaine self-administration increases the availability of 5-HT_{2A} receptors in the PFC, suggesting that increased 5-HT_{2A} receptor availability facilitates drug-taking behavior (Sawyer *et al.*, 2012). This is supported by observations that 5-HT_{2A} knockout mice self-administer MDMA to a lesser degree than wild-type mice, and that the selective 5-HT_{2A} inverse agonist, eplivanserin, blocks cue-induced reinstatement of MDMA seeking (Orejarena *et al.*, 2011). Other studies report that 5-HT_{2A} receptor antagonists attenuate the stimulatory effects of cocaine, amphetamine, MDMA, and methamphetamine on dopamine neurotransmission as well as their locomotor stimulant and interoceptive effects (Auclair *et al.*, 2004; Broderick *et al.*, 2004). Intra-VTA microinjections of 5-HT_{2A} receptor antagonists attenuate cocaine- and amphetamine-induced increases in motor activity in mice (Auclair *et al.*, 2004) and rats (McMahon *et al.*, 2001), and we showed recently that selective 5-HT_{2A} receptor antagonism attenuates the dopamine releasing and behavioral effects of amphetamine in primates (Murnane *et al.*, 2013a). Systemic administration of 5-HT_{2A} receptor antagonists (including SR 46349B, M100907, and MDL 11,939), in contrast to the effects of agonists, do not alter firing rates of dopamine neurons in the VTA or dopamine release in the NAc or PFC of rodents (Bonaccorso *et al.*, 2002; Di Giovanni *et al.*, 1999; Gobert *et al.*, 2000; Pehek *et al.*, 2006; Porrás *et al.*, 2002). Therefore, although the 5-HT_{2A} receptor does not appear to exert a tonic influence on dopamine neuronal firing or release, agonist stimulation of this receptor enhances dopaminergic activity (Bubar and Cunningham, 2008). Though, net effects may depend on specific cell types and circuits examined.

The use of reinstatement procedures provides an important complement to drug self-administration, as it is the most widely accepted model of drug relapse. As drug relapse is critically influenced by craving and withdrawal, reinstatement experiments have particular relevance for understanding the non-addictive nature of CH. Such studies show that 5-HT_{2A} receptor antagonism prevents reinstatement of drug-seeking behavior. For example, the 5-HT₂ receptor antagonist ketanserin attenuates cue-induced reinstatement of extinguished cocaine self-administration in rats (Burmeister *et al.*, 2004), and the selective 5-HT_{2A} receptor antagonist M100907 attenuates both drug- and cue-induced reinstatement of extinguished cocaine self-administration in rats (Fletcher *et al.*, 2002; Nic Dhonnchadha *et al.*, 2009). Consistent with these findings, we have shown that 5-HT_{2A} receptor antagonism attenuates cue- as well as drug-induced reinstatement of extinguished behavior that was previously maintained by cocaine in rhesus monkeys (Murnane *et al.*, 2013b).

These studies suggest that selective activation of 5-HT_{2A} receptors may induce craving and/or relapse. Nevertheless, it will be critical to assess empirically the addictive or anti-addictive potential of highly selective 5-HT_{2A} agonists. A recent report shows that an analogue from the phenethylamine class of CH, (4-bromo-3,6-dimethoxybenzocyclobuten-1-yl) methylamine (TCB-2) that has high 5-HT_{2A} agonist potency (McLean *et al.*, 2006) reduces intracranial self-stimulation (ICSS), but does not attenuate the potentiating effects of cocaine on

ICSS (Katsidoni *et al.*, 2011). Its activity at 5-HT_{2B} and 5-HT_{2C} receptors, however, has not been reported to our knowledge. Finally, CH may be biased agonists (Gonzalez-Maeso and Sealfon, 2009; McLean *et al.*, 2006; Wacker *et al.*, 2013) that stabilize 5-HT_{2A} receptor active conformations that block craving. Certainly, additional studies are warranted.

Considerations of 5-HT_{2B} receptor activation to addiction liability

Owing to their low expression in the central nervous system (Bonhaus *et al.*, 1995; Duxon *et al.*, 1997; Kursar *et al.*, 1994; Loric *et al.*, 1992), much less attention has been given to the potential role of 5-HT_{2B} receptors to the effects of psychoactive substances. Moreover, as prolonged activation of 5-HT_{2B} receptors on heart valve leaflets is linked to valvular heart disease (Hutcheson *et al.*, 2012; Roth, 2007; Rothman and Baumann, 2009), an impetus to develop highly-selective 5-HT_{2B} agonists has been lacking. Indeed, there is not a highly selective 5-HT_{2B} agonist probe that is a widely accepted tool of the scientific community. Thus, there are somewhat limited data regarding the contribution of 5-HT_{2B} receptor activation to psychoactive substances. Much of what is known, however, emanated predominantly from the Maroteaux laboratory. Converging data from 5-HT_{2B} receptor knockout mice and from use of 5-HT_{2B} ligands show that central 5-HT_{2B} receptors contribute to the psychomotor effects of MDMA (Doly *et al.*, 2008), the anorexiant effects of dexfenfluramine (Banas *et al.*, 2011), and the antidepressant effects of selective serotonin reuptake inhibitors (Diaz *et al.*, 2012; Hertz *et al.*, 2015). Another recent study shows that LY266097, a selective 5-HT_{2B} antagonist, reduces basal and amphetamine-stimulated dopamine release in the NAc, and also decreases amphetamine-elicited hyperlocomotion (Auclair *et al.*, 2010), although others report that selective 5-HT_{2B} antagonists, including SB 204741, do not affect cocaine-elicited hyperlocomotion or the discriminative stimulus effects of cocaine (Filip *et al.*, 2004, 2006). In addition to the different neuropharmacological effects of amphetamine versus cocaine, the potential discrepancies in these studies could relate to the use of different 5-HT_{2B} antagonist ligands, and consequently target selectivity or off-target liability.

Finally, Roth's group reported that the designer empathogen 1-(benzofuran-6-yl)propan-2-amine (6-APB), an MDMA analogue, binds with >100-fold selectivity to the 5-HT_{2B} receptor compared to 5-HT_{2A} or 5-HT_{2C} receptors, and furthermore, 6-APB is a 5-HT_{2B} receptor agonist (Iversen *et al.*, 2013). Interestingly, 6-APB has higher affinity at 5-HT_{2B} than any other target tested, including the dopamine transporter, a primary target of addictive psychostimulants (e.g., cocaine and methamphetamine). Anecdotal reports note that 6-APB produces subjective effects similar to MDMA, but according to some, it does not produce drug craving and has a low propensity to cause physical dependence (see bluelight.org and erowid.org). However, controlled tests of its addictive potential have not been reported. Additional studies assessing the contribution of 5-HT_{2B} receptor activation to the low addiction liability of CH are warranted.

Considerations of 5-HT_{2C} receptor activation to addiction liability: Behavioral studies

Numerous lines of evidence from multiple laboratories show that 5-HT_{2C} receptor activation attenuates self-administration of addictive substances and also attenuates ICSS of the brain's primary reward circuitry, and there are a number of excellent recent reviews on the topic of 5-HT_{2C} receptor agonists for addiction and mechanisms underlying their effects (De Deurwaerdere *et al.*, 2013; Devroye *et al.*, 2013; Di Giovanni *et al.*, 2006; Higgins and Fletcher, 2015; Howell and Cunningham, 2015; Muller and Homberg, 2015). Selective agonists of the 5-HT_{2C} receptor have generally been found to recapitulate the attenuating effects of indirect serotonin agonists on behavioral models of addiction, suggesting 5-HT_{2C} receptor activation is a key molecular mechanism by which serotonin exerts its anti-addictive effects. For example, the rate-suppressing effects of both the indirect serotonin receptor agonist fenfluramine and the 5-HT_{2C} receptor agonist Ro 60-0175 in an ICSS procedure are blocked by pretreatment with the 5-HT_{2C} receptor selective antagonist SB 242084 (Bauer *et al.*, 2015). Likewise, Ro 60-0175 blocks cocaine-seeking behavior in rats, an effect completely reversed by SB 242084 (Burbassi and Cervo, 2008). Acute VTA or systemic administration of a variety of relatively selective 5-HT_{2C} receptor agonists in rodents suppress the locomotor stimulant effects of cocaine (Craigie and Unterwald, 2013; Filip *et al.*, 2004; Fletcher *et al.*, 2004; Grottick *et al.*, 2000), the discriminative stimulus effects of cocaine (Callahan and Cunningham, 1995; Cunningham *et al.*, 2011; Fletcher *et al.*, 2008; Frankel

and Cunningham, 2004), cocaine self-administration (Cunningham *et al.*, 2011; Fletcher *et al.*, 2008; Grottick *et al.*, 2000), and reinstatement of cocaine seeking induced by exposure to cocaine and cocaine-associated cues (Burbassi and Cervo, 2008; Cunningham *et al.*, 2011; Fletcher *et al.*, 2008; Grottick *et al.*, 2000; Neisewander and Acosta, 2007). These findings have been extended to other classes of psychoactive drugs, including alcohol, cannabis, and nicotine (Higgins and Fletcher, 2015; Ji *et al.*, 2006; Marcinkiewicz, 2015; Quarta *et al.*, 2007; Zaniowska *et al.*, 2007).

In primates, recent studies show that Ro 60-0175 reduces psychostimulant effects of cocaine, cocaine self-administration, and cocaine-induced reinstatement (Manvich *et al.*, 2012b; RuediBettchen *et al.*, 2015). These effects do not appear to result from general suppression of operant responding, as the same dose of Ro 60-0175 has no effect on operant responding maintained by negative reinforcement (Manvich *et al.*, 2012b). Similarly, the highly-selective 5-HT_{2C} receptor agonist lorcaserin attenuates the discriminative stimulus effects of cocaine and suppresses cocaine self-administration following acute or 14-day treatment in rhesus monkeys (Collins *et al.*, 2016). Clinical trials assessing lorcaserin's ability to reduce cocaine self-administration are now underway (e.g., ClinicalTrials.gov Identifier: NCT02537873).

The hypothesis that 5-HT_{2C} receptors inhibit a variety of abuse-related effects of drugs is substantiated by the reliable finding that antagonists facilitate such effects. In rodents, systemic administration of 5-HT_{2C} receptor antagonists enhance the locomotor stimulant effects of cocaine (Fletcher *et al.*, 2002, 2006), the discriminative stimulus effects of cocaine (Filip *et al.*, 2006), cocaine self-administration (Fletcher *et al.*, 2002), and cocaine-induced reinstatement (Fletcher *et al.*, 2002). Consistent findings are reported in primates, as SB 242084 increases rates of responding maintained under a fixed-interval schedule of stimulus termination, increases cocaine-primed reinstatement of cocaine self-administration, and, critically, maintains self-administration when substituted for cocaine (Manvich *et al.*, 2012a). Other studies also suggest that 5-HT_{2C} antagonists themselves may be addictive substances (Di Giovanni *et al.*, 1999; Di Matteo *et al.*, 1999). Finally, 5-HT_{2C} receptor knockout mice exhibit increased sensitivity to the effects of cocaine (Rocha *et al.*, 2002). Collectively, the literature is replete with evidence that activation of 5-HT_{2C} receptors inhibits addictive effects of a variety of drugs. As CH activate 5-HT_{2C} receptors, we surmise this property is an essential facet that renders CH non-addictive.

Considerations of 5-HT_{2C} receptor activation to addiction liability: Neurochemistry studies

The most supported mechanism for the anti-addiction effects of 5-HT_{2C} activation is inhibition of mesolimbic dopamine neurons, which decreases psychostimulant-elicited dopamine release in the NAc (Alex and Pehek, 2007; Bubar *et al.*, 2011; Collins *et al.*, 2016; Di Giovanni *et al.*, 2000; Di Matteo *et al.*, 2000; Fletcher *et al.*, 2008; Harvey-Lewis *et al.*, 2016; Howell and Cunningham, 2015; Manvich *et al.*, 2012b; Navailles *et al.*, 2008; Rocha *et al.*, 2002). Evidence suggests these effects are caused by 5-HT_{2C} receptor-mediated activation of GABA neurons in the VTA, which directly inhibit VTA dopamine neuron activity (Bubar and Cunningham, 2007; Bubar *et al.*, 2011; Di Giovanni *et al.*, 2001; Howell and Cunningham, 2015). Conversely, inactivation of 5-HT_{2C} receptors by antagonists or inverse agonists increases firing rates of VTA dopamine neurons, increasing dopamine levels in the NAc (Di Giovanni *et al.*, 1999; Di Matteo *et al.*, 2004). Identifying the specific neural circuitry examined in such studies, however, is important, as these observations ostensibly conflict with the conclusions from a new report about 5-HT_{2C} receptor modulation of dopamine neurotransmission (Xu *et al.*, 2016). Specifically, using slice electrophysiology, the authors report that 5-HT_{2C} receptors expressed on dopamine neurons stimulate a significant number of them. Collectively, the data suggest that the emergent effects of 5-HT_{2C} activation on dopamine neurotransmission depend on the relative activation of 5-HT_{2C} receptors on different cell types; for example, GABA neurons innervating dopamine neurons (resulting in dopamine neuron inhibition) relative to 5-HT_{2C} receptors expressed directly on dopamine neurons (resulting in dopamine neuron activation). In support of this, in mice that express 5-HT_{2C} receptors only on dopamine VTA neurons, 5-HT_{2C} activation enhances dopamine neuron activity to a greater degree than in wild-type mice, suggesting that 5-HT_{2C} receptors on other cell types have an inhibitory effect on dopamine neurotransmission (Xu *et al.*, 2016).

Other findings corroborate the view that 5-HT_{2C} receptor activation impacts reward circuitry via multiple

mechanisms. Recent studies point to direct modulatory effects of 5-HT_{2C} receptor activation on dopamine signaling in the NAc as contributors to their anti-addiction properties, and these effects may have as much relevance for addiction treatment as the effects of 5-HT_{2C} receptors in the VTA. For example, 5-HT_{2C} receptors expressed in the NAc inhibit postsynaptic dopamine signaling by inhibiting phosphorylation of DARPP-32, independent of dopamine release (Cathala *et al.*, 2015; Devroye *et al.*, 2015). 5-HT_{2C} receptor knockout mice also provide evidence for 5-HT_{2C} negative modulation of dopamine neurotransmission in reward circuitry. 5-HT_{2C} knockout mice are more sensitive to the psychostimulant effects of amphetamine, cocaine, and GBR 12909 (another dopamine reuptake blocker) and also exhibit increased cocaine-stimulated release of dopamine in their NAc (Abdallah *et al.*, 2009; Rocha *et al.*, 2002). Interestingly, the enhanced effects of cocaine on dopamine release in the NAc in 5-HT_{2C} knockout mice are not observed in the dorsal striatum (Rocha *et al.*, 2002). Similarly, amphetamine's effects on dopamine release in the dorsal striatum are not potentiated in 5-HT_{2C} knockout mice (Abdallah *et al.*, 2009). This neural system-specific effect is recapitulated using 5-HT_{2C}-selective ligands. For example, 5-HT_{2C} agonists administered systemically attenuate cocaine-stimulated dopamine release in the NAc, but not the dorsal striatum in wild-type mice (Di Giovanni *et al.*, 2000) or in nonhuman primates (Manvich *et al.*, 2012b). Also, systemic treatment with 5-HT_{2C} agonists alone reduces dopamine in the NAc, but not the dorsal striatum (Di Giovanni *et al.*, 2000; Marquis *et al.*, 2007), and the converse effects are observed after treatment with 5-HT_{2C} antagonists or inverse agonists; that is, they increase dopamine release in the NAc, but again, they have minimal effects on dopamine release in the dorsal striatum (Di Matteo *et al.*, 1999). These data are confluent with the distribution of 5-HT_{2C} receptors across neural systems, as 5-HT_{2C} receptors are densely expressed in the NAc but not the dorsal striatum (Figure 1). These observations suggest that post-synaptic 5-HT_{2C} receptors in the NAc may contribute strongly to the effects of selective 5-HT_{2C} agonists, administered systemically, on dopamine release in reward circuitry, a hypothesis we build in the following sections. Overall, the data provide a mechanistic rationale for the efficacy of CH, as 5-HT_{2C} agonists, to temper the rewarding effects of addictive drugs. As a recent optogenetic study showed exquisitely that dopamine cell firing in the medial forebrain bundle, including the VTA - NAc tract, is sufficient to cause a transition to addiction (Pascoli *et al.*, 2015), it is clear that 5-HT_{2C} agonists have promise as tools in the treatment of addiction.

The NAc is a key site for 5-HT_{2C} receptor modulation of reward circuitry

As noted above, much of the circuitry-related data supporting 5-HT_{2C} receptor modulation of psychostimulant effects is focused on 5-HT_{2C} receptors expressed on GABA neurons of the VTA. We do not discount these findings. However, important rationale for our focus on 5-HT_{2C} receptors in the NAc are the observations that infusions of the selective 5-HT_{2C} agonist, WAY 161503, into the NAc, but not the VTA, decrease the reward-facilitating effects of cocaine (Katsidoni *et al.*, 2011). Moreover, infusions of the selective 5-HT_{2C} antagonist, SB 242084, into the VTA does not affect cocaine-induced dopamine release in the NAc, but when infused into the NAc, SB 242084 potentiates cocaine-induced dopamine release in the NAc (Navailles *et al.*, 2008). Also, the 5-HT_{2C} inverse agonist, SB 206553 increases basal dopamine release in the NAc when it is infused there, but not when it is infused in the VTA, suggesting 5-HT_{2C} constitutive activity in the NAc, but not VTA, modulates tonic NAc dopamine release (De Deurwaerdere *et al.*, 2013; Navailles *et al.*, 2006). In summary, these data suggest that activation of NAc 5-HT_{2C} receptors negatively modulates the effects of cocaine.

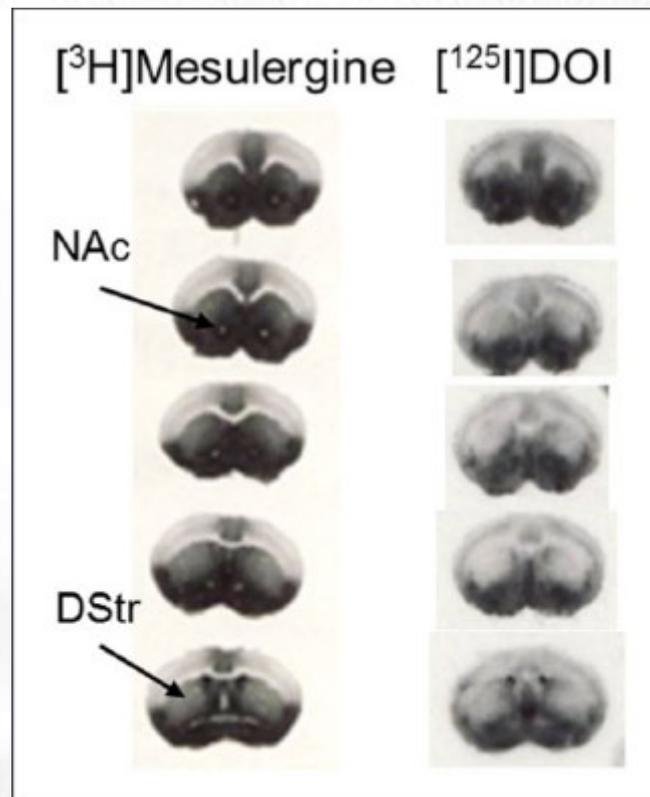


Figure 1. Autoradiographs of brain 5-HT_{2C} receptors from mice that overexpress 5-HT_{2C} (5-HT_{2C}-VGV) allowing clear observations of 5-HT_{2C} receptor distribution in the brain. Notably, 5-HT_{2C} is densely expressed in the nucleus accumbens (NAc), but not in the dorsal striatum (DStr); the darker the shade, the higher the receptor binding site density. [3H]Mesulergine (3 nM for eight weeks) or [125I]DOI (0.14 nM for 48 hours) was used in the presence of spiperone (100 nM) to label 5-HT_{2C} receptors. These sections were part of a set collected by Dr. Canal (Olaghere da Silva *et al.*, 2010). All sections labeled with [3H] Mesulergine or with [125I]DOI are from the same brain. Pictures from the latter were cropped and pasted to align them vertically.

Raphe nuclei send strong 5-HT projections to the NAc (Van Bockstaele and Pickel, 1993), and 5-HT_{2C} receptors are predominantly post-synaptic and excitatory (Austgen *et al.*, 2012; Invernizzi *et al.*, 2007), suggesting they reside on GABAergic MSN, which account for ~90% of NAc neurons (Meredith, 1999). Indeed, immunohistochemistry and neurophysiology studies show that 5-HT_{2C} receptors are expressed on MSN of the NAc (Clemett *et al.*, 2000; Graves *et al.*, 2015; Santana and Artigas, 2016). Furthermore, autoradiography data from mice that overexpress 5-HT_{2C} receptors (while maintaining the distribution pattern of 5-HT_{2C} receptors across neural systems that is observed in wild-type mice; Olaghere da Silva *et al.*, 2010) show clearly that 5-HT_{2C} receptors are densely expressed in the NAc, but not the dorsal striatum (see Figure 1; which receives dopaminergic projections from substantia nigra). This is particularly intriguing when considered in the context of observations of the effects of cocaine on dopamine release in the NAc compared with the dorsal striatum. As stated earlier, 5-HT_{2C} knockout mice, relative to WT mice, show an increase in cocaine-stimulated dopamine release in the NAc, but this effect is not observed in the dorsal striatum (Rocha *et al.*, 2002). Furthermore, 5-HT_{2C} agonists administered peripherally suppress cocaine-stimulated dopamine release in the NAc, but not the dorsal striatum (Manvich *et al.*, 2012b). Thus, we consider, like others (Navailles *et al.*, 2006, 2008), that 5-HT_{2C} receptors expressed in NAc are contributing significantly to the anti-addiction effects of 5-HT_{2C} agonists, with special relevance to cocaine addiction.

Several studies show that the shell region of the NAc is associated more closely than the core with the appetitive or reinforcing effects of addictive substances (Bari and Pierce, 2005; Di Chiara *et al.*, 2004; Ikemoto, 2010; Rodd-Henricks *et al.*, 2002; Sellings and Clarke, 2003). For example, non-contingent and self-administered cocaine preferentially increases dopamine in the NAc shell (Lecca *et al.*, 2004, 2007; Pontieri *et al.*, 1995), and a recent predictive model shows that cocaine treatment enhances the phasic signaling of dopamine neurons projecting to the NAc shell, but not to the core (Dreyer *et al.*, 2016). Also, others report, more generally, that the NAc shell codes reward value (Saddoris *et al.*, 2013). Furthermore, MSN of the NAc shell, specifically D1-containing MSN, send direct projections to the VTA, generating an inhibitory feedback circuit (Bocklisch *et al.*, 2013; Sesack and Grace, 2010); this circuit is necessary for the integration of our 5-

HT_{2C} mechanistic hypothesis, and 5-HT_{2C} regulation of NAc-VTA circuitry has been speculated (Filip and Cunningham, 2002). Interestingly, 5-HT projections to the NAc segregate in the core and shell regions; 5-HT terminals in the NAc shell are larger in diameter, contain more, large dense core vesicles, and form more symmetric contacts with dendrites (Brown and Molliver, 2000; Van Bockstaele and Pickel, 1993). Moreover, systemic administration of 5-HT_{2C} selective agonists decrease, and inverse agonists increase, dopamine release in the NAc shell (De Deurwaerdere *et al.*, 2004; Di Matteo *et al.*, 2000; Gobert *et al.*, 2000). Finally, immunohistochemistry results show that 5-HT_{2C} receptors are expressed at higher densities in the NAc shell, relative to the core (Clemett *et al.*, 2000). Thus, we speculate that 5-HT_{2C} receptors are expressed on D1-containing MSN of the NAc shell, and when activated, they enhance their activity, occluding effects of D1 activity, and thus increasing GABA release in the VTA. This is supported by the observations that 5-HT_{2C} receptor knockout mice show enhanced behavioral responses to the D1 receptor agonist SKF 81297 (Abdallah *et al.*, 2009).

5-HT_{2C} modulation of intrinsic plasticity via inhibition of NAc Kv1.x channels: A novel hypothesized mechanism for psychostimulant addiction treatment

Based on a synthesis of what is known in the literature regarding 5-HT_{2C} receptor function, neural circuitry, and neurochemistry underlying addiction, we hypothesize that activation of 5-HT_{2C} receptors, specifically on GABAergic MSN in the NAc shell (Graves *et al.*, 2015), inhibits Kv1.x channels, including Kv1.1, Kv1.2, and Kv1.3, leading to increased intrinsic activity (non-synaptic increases in neuronal firing capacity). Taken together with several reports that show NAc intrinsic activity is decreased by psychostimulant exposure (Coffey *et al.*, 2015; Graves *et al.*, 2015; Henry and White, 1995; Hu, 2007; Hu *et al.*, 2004; Zhang *et al.*, 2002), and germane to our hypothesis that Kv1.x channel conductance is enhanced by exposure to psychostimulants (Hu *et al.*, 2004; Kourrich and Thomas, 2009; Kourrich *et al.*, 2013, 2015), it is inferred that 5-HT_{2C} receptor activation may directly counteract effects of psychostimulants on intrinsic plasticity. Accordingly, the increase in NAc shell MSN cellular activity by 5-HT_{2C} receptor activation would directly counteract the decrease in NAc shell MSN activity caused by psychostimulants (Figure 2).

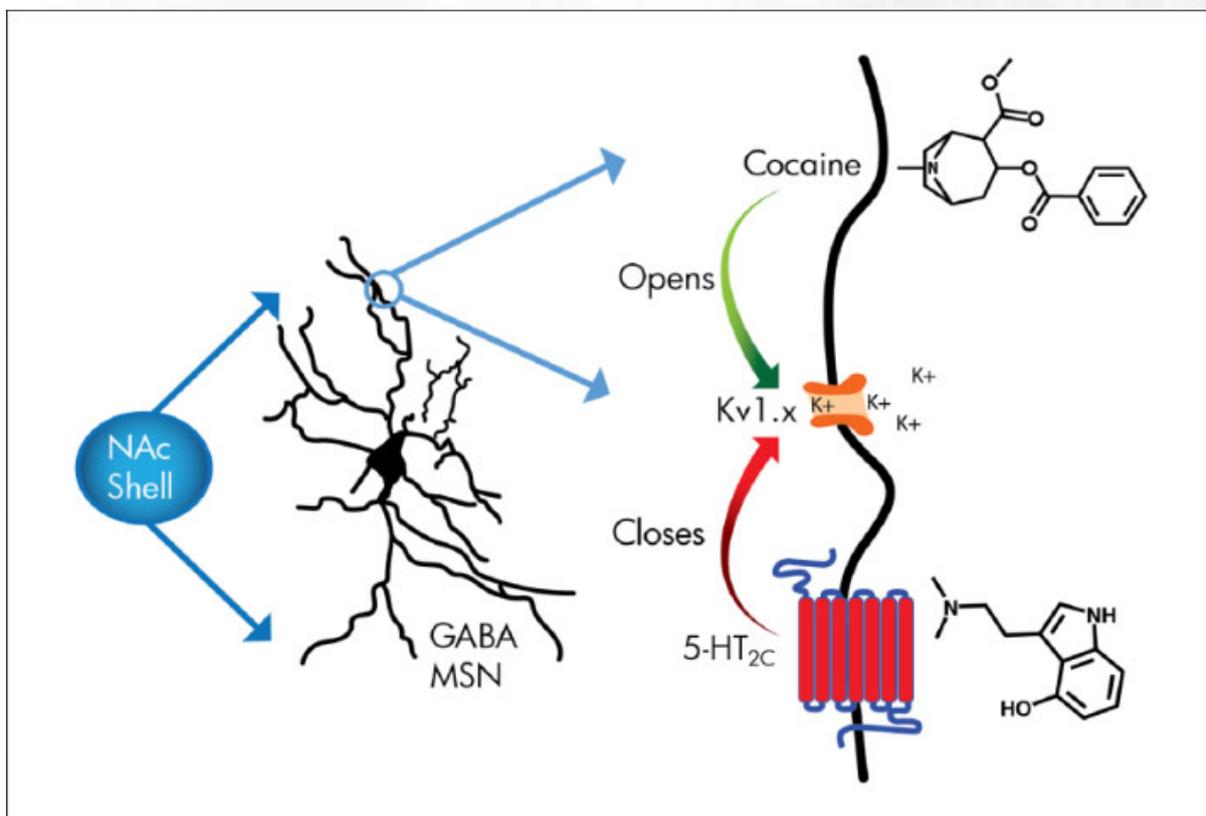


Figure 2. Proposed 5-HT_{2C} anti-cocaine addiction mechanism involving modulation of Kv1.x channels on GABAergic medium spiny neurons (MSN) of the NAc shell.

Potassium Kv1.x channels (Chandy and Gutman, 1993), Kv1.1-Kv1.8, are voltage-gated channels that regulate the intrinsic activity of neurons. Kv1.x channel conductance is critical for the generation and modulation of action potentials, regulating neurotransmitter release and neural circuit excitability. Kv1.x channels open upon membrane depolarization, permitting the flow of potassium ions from within the cell, leading to restoration of the resting membrane potential. In addition, activation of Kv1.x inhibits cell-firing frequency and delays the onset of action potentials (Lioudyno *et al.*, 2013). Conversely, Kv1.x channel blockers prevent the flow of potassium ions, causing spontaneous depolarization and increasing, for example, action potential frequency and neurotransmitter release (Ramirez-Navarro *et al.*, 2011; Simeone *et al.*, 2013; Tibbs *et al.*, 1996). There are several excellent reviews on Kv channel localization in the brain, their trafficking, structure, and function, and involvement in brain disease pathophysiology (D'Adamo *et al.*, 2013; Heusser and Schwappach, 2005; Johnston *et al.*, 2010; Robbins and Tempel, 2012; Robertson, 1997; Shah and Aizenman, 2014; Wang *et al.*, 1994).

Several studies, using both *ex vivo* and *in vitro* cell systems show clearly that 5-HT_{2C} activation suppresses Kv1.x channels. First, 5-HT_{2C} receptors are expressed in neural systems where Kv1.x channels are also expressed (D'Adamo *et al.*, 2013). For example, the choroid plexuses, where 5-HT_{2C} receptor expression is dense (Hartig *et al.*, 1990; Lopez-Gimenez *et al.*, 2001; Marazziti *et al.*, 1999), also robustly express Kv1.1 and Kv 1.3 channels (Speake *et al.*, 2004). Application of 5-HT to choroid plexus cells abolishes potassium currents, an effect reversed by addition of the 5-HT_{2C} antagonist, mesulergine (Speake *et al.*, 2004). Similarly, in heterologous oocyte systems expressing 5-HT_{2C} receptors and Kv1.1, Kv1.2, or Kv1.3 channels, application of 5-HT eliminates potassium generated currents from each channel (Aiyar *et al.*, 1993; Imbrici *et al.*, 2000). The effect of 5-HT_{2C} may be relegated to Kv1.x type channels, as 5-HT activation of 5-HT_{2C} receptors does not affect Kv3.1 channel activity (Aiyar *et al.*, 1993). The exact cell signaling pathways underlying these effects remain unclear, but studies suggest 5-HT_{2C}-Gα_q-PLC signaling and activation of protein kinase C and tyrosine kinases PYK2 and Src are important contributors (Aiyar *et al.*, 1993; Boland and Jackson, 1999; Imbrici *et al.*, 2000; Speake *et al.*, 2004).

Contrary to 5-HT_{2C} receptor's effects on Kv1.x channels, exposure to cocaine increases potassium currents, as measured in the NAc shell. Recent studies examining NAc shell GABAergic MSN show that these effects are mediated by an increase in the activity of Kv1.2 channels, leading to a decrease in excitability and firing rate (Hu *et al.*, 2004; Kourrich and Thomas, 2009; Kourrich *et al.*, 2013; Mu *et al.*, 2010). Furthermore, exposure to cocaine for 10 consecutive days increases the expression of Kv1.2 channels (Kourrich *et al.*, 2013). Importantly, the cocaine-induced depression of firing rate of MSN of the NAc shell is persistent, and decreases in the excitability of the NAc shell lead to enhanced locomotor responses and behavioral sensitization to cocaine and are associated with enhanced cocaine self-administration (Guillem *et al.*, 2014; Kourrich and Thomas, 2009). Moreover, cocaine's inhibitory effects on MSN activity are specific to the NAc shell, with cocaine actually increasing MSN firing in the NAc core (Kourrich and Thomas, 2009; Kourrich *et al.*, 2013; Mu *et al.*, 2010). Finally, overexpression of a hyperpolarizing, inwardlyrectifying potassium channel (Kir2.1) in NAc MSN enhances psychomotor effects of cocaine (Dong *et al.*, 2006), whereas knockdown of the Kv1.1 channel blocks behavioral effects of another psychostimulant, amphetamine (Ghelardini *et al.*, 2003). Thus, there is a strong argument that some psychostimulant effects are mediated by alterations in intrinsic plasticity in NAc shell MSN, driven by Kv1.x currents that decrease excitability (Kourrich *et al.*, 2015), and CH-mediated 5-HT_{2C} receptor activation may offset these effects (Figure 2).

Caveat emptor

5-HT_{2C} receptors are expressed in several neural systems, including the frontal and cingulate cortices, that regulate impulsivity, approach, and reward behavior, and activation of these receptors impacts neural circuitry to modulate the effects of addictive drugs (Anastasio *et al.*, 2014; Bubar and Cunningham, 2007; Daglish and Nutt, 2003; Liu *et al.*, 2007; Nocjar *et al.*, 2015). Our hypothesis regarding 5-HT_{2C} modulation of Kv1.x channels could be extended to these other neural systems. However, to maintain scope, we have focused on the NAc shell. Despite the logic regarding 5-HT_{2C} receptors and Kv1.x channels, there are reports that 5-HT_{2A} receptor activation also decreases Kv1.x activity, specifically Kv1.5 channels in cardiac tissue (Cogolludo *et al.*, 2006) and Kv1.2 channels in cortical pyramidal neurons (Lambe and Aghajanian, 2001). In this latter study, 5-HT blocked Kv1.2 currents in layer V pyramidal neurons; the authors concluded the effects were mediated by

5-HT_{2A} receptors because of their dense expression. Still, 5-HT_{2C} receptors are also expressed in the frontal cortex, and modulate excitatory activity there (Beique *et al.*, 2007). We acknowledge and appreciate that the modulatory activity of 5-HT₂ receptor subtypes that affects behavior is complex. 5-HT₂ receptor subtypes may modulate activity of unique Kv1.x channels, and the discovery of 5-HT₂ receptor subtype expression patterns within discrete neural circuits will likely lead to further elucidation of their individual functions. For example, 5-HT_{2A} receptors are found in the NAc shell and core (Lopez-Gimenez *et al.*, 2002; Mijster *et al.*, 1997), but (like 5-HT_{2C}) the functions of 5-HT_{2A} receptors in subregions of the NAc are unclear. Additional studies are needed to cull the specific Kv1.x channel subtypes that may associate with 5-HT_{2C} to lead to suppression of addictive behaviors.

Many cell types and many unique afferents are found within the NAc and VTA (Russo and Nestler, 2013). Thus, a complete picture must show which cells express 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors, the relative densities of receptors, and their unique contributions to network activity. Finally, 5-HT_{2C} chemical probes, including both agonists and antagonists, are, with few exceptions, notoriously non-selective (Canal and Morgan, 2012; Cussac *et al.*, 2002; Porter *et al.*, 1999). We have found, for example, that the "selective" 5-HT_{2C} agonist, Ro 60-0175, is a potent and efficacious 5-HT_{2A} agonist at the Gαq-PLC pathway, and when administered systemically at 3 mg/kg, Ro 60-0175 produces a HTR in C57BL/6J mice (unreported observations; data available upon request). It would be interesting to compare the behavioral and neurochemical effects of Ro 60-0175 directly to the more selective 5-HT_{2C} agonist lorcaserin, as well as to the recently reported selective 5-HT_{2A} agonist 25CN-NBOH (Fantegrossi *et al.*, 2015; Hansen *et al.*, 2014) to tease apart contributions of the 5-HT₂ receptor subtypes more clearly (see the section on testable hypotheses below).

Classic hallucinogens treat addiction

Literature from the 1950s through the 1970s, as well as modern reports, show that CH have positive effects on substance dependence (Bogenschutz and Johnson, 2016; Bogenschutz and Pommy, 2012; Dyck, 2006). Thus, not only do CH appear to be nonaddictive, several studies show that they reverse the addictive effects of other psychoactive drugs. CH have been used to alleviate neurotic symptoms by indigenous people for thousands of years (Grinspoon and Bakalar, 1986), and the discovery of LSD and its psychoactive effects sparked considerable interest in the therapeutic potential of CH. Most work focused on the use of these compounds as an adjunct to psychotherapy. Between 1950 and the mid-1960s, more than 1000 quasi-clinical trials were completed, several dozen books were published, and six international conferences were held providing data on approximately 40,000 patients that had undergone "psychedelic" therapy sessions (Grinspoon and Bakalar, 1986; Riedlinger and Riedlinger, 1994). In the context of the treatment of substance dependence, most studies focused on the use of LSD for the treatment of alcoholism (for reviews, see Abuzzahab and Anderson, 1971; Bogenschutz and Johnson, 2016; Dyck, 2005; Grinspoon and Bakalar, 1986; Mangini, 1998). These studies examined both single, high-dose, and repeated low-dose designs, follow-up periods of several years, control groups, and a total subject pool of well in excess of 1000 individuals (Abuzzahab and Anderson, 1971). Between 50% and 70% of the subjects showed reduced drinking or sobriety and/or improved social or professional functioning. Such a treatment effect is exceptional compared to current Food and Drug Administration-approved medications for alcoholism (i.e., disulfiram, naltrexone, and acamprosate). However, the relatively low number of participants in each study, lax designs, and suspect claims led many to question whether accurate conclusions could be made. Nevertheless, results from the six randomized trials of LSD for alcohol dependence that reported drinking outcomes (Bowen *et al.*, 1970; Hollister *et al.*, 1969; Ludwig *et al.*, 1969; Pahnke *et al.*, 1970; Smart *et al.*, 1966; Tomsovic and Edwards, 1970) recently underwent a meta-analysis (Krebs and Johansen, 2012) that demonstrated consistent treatment effects supporting the efficacy of LSD.

Work with CH largely terminated by the 1970s due to the governmental regulatory response to advocates of the use of these drugs outside of the medical arena. Nonetheless, in the last decade, there has been a resurgence in the study of CH in general, and in the use of CH for the treatment of substance dependence in particular. This recent work has foregone the use of LSD in favor of psilocybin, and has extended our knowledge of the beneficial effects of CH to nicotine dependence (Bogenschutz *et al.*, 2015; Johnson *et al.*, 2014). We note that some researchers appreciate that stimulation of 5-HT_{2A} receptors (which are generally what come to mind when people think of CH) may exacerbate substance dependence (as discussed above) and

have speculated that profound, rapid, and long-lasting agonist stimulated downregulation of 5-HT_{2A} receptors (i.e., functional antagonism) could be responsible for the anti-addiction effects of CH (Bogenschutz and Johnson, 2016).

Herein, we have proposed a non-exclusive and empirically testable hypothesis that the beneficial effects of CH for substance dependence are mediated by agonist stimulation of 5-HT_{2C} receptors. If, however, CH were both to stimulate 5-HT_{2C} receptors acutely and result in long-term downregulation of 5-HT_{2A} receptors, this may account for their purported therapeutic effects. Indeed, if CH treat addiction simply by stimulating 5-HT_{2C} receptors, it would likely be preferable to use a selective 5-HT_{2C} receptor agonist instead of CH. Although, others surmise that CH may be effective against addiction because of their psychedelic effects. They can elicit peak or mystical experiences, and afterglow effects, which can alter engrained personality domains such as openness (Maclean *et al.*, 2011; Majic *et al.*, 2015). These effects may be beneficial for psychotherapy and loosening relatively fixed behavioral patterns that underlie addiction.

Despite the potential for CH to treat addiction, it is important to caution that repeated exposure to CH could also chronically alter 5-HT_{2C} receptor expression and/or function, potentially leading to an enhanced susceptibility to addiction via a loss of intrinsic efficacy of 5-HT_{2C} receptors to modulate reward circuitry. Indeed, it does not escape our awareness that use of CH does not render persons immune to drug addiction, and a recent report shows that psilocybin users were significantly more likely to use addictive drugs (Hallock *et al.*, 2013). Thus, medical supervision, psychological support, and careful preparation to control for set and setting in the context of CH use are likely important requirements to produce therapeutic effects.

Testable hypotheses for unraveling the anti-addictive effects of classic hallucinogens

The literature we have reviewed above suggests a number of experiments that warrant testing in future studies. These experiments would serve to delineate more clearly the role of 5-HT₂ receptor subtypes underlying the low addiction liability of CH. Moreover, they would elucidate our understanding of the mechanisms involved, and the results would provide new testable hypotheses. Among these experiments are: (1) to determine whether recently synthesized compounds such as 25CN-NBOH, which shows ~90-fold higher selectivity for activating 5-HT_{2A} over 5-HT_{2C}, also show higher abuse liabilities than CH (caveat: that first the pharmacology of 25CN-NBOH is assessed at off-targets, e.g., opioid receptors, which would confound conclusions); (2) to determine whether animals with genetic deletion of the 5-HT_{2C} receptor will self-administer CH; (3) to determine the abuse liability of CH in the presence of a selective 5-HT_{2C} receptor antagonist; (4) to determine the precise localization of 5-HT_{2C} receptors in cells of the NAC, with particular emphasis on whether 5-HT_{2C} receptors are expressed on D1-expressing GABAergic MSN of the NAc shell (Caine *et al.*, 2007; Lobo *et al.*, 2010; Pacheco-Cano *et al.*, 1996; Pisanu *et al.*, 2015) - these MSN are the predominant MSN afferents of the VTA that modulate dopamine release in the NAc (Bocklisch *et al.*, 2013); and (5) to determine the nature of 5-HT_{2C}-Kv1.x interactions in forebrain regions implicated in addiction. We believe that these experiments would add greatly to the literature, and are enthused to see them completed.

Acknowledgements

We wish to thank the Communications Office of the Mercer University College of Pharmacy for their professional work to enhance Figure 2. In particular, we wish to thank David Holland and Jennifer Brock for their work on improving the artistic design of the graphic.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article. However, while the manuscript was under review, Drs. Canal and Murnane received 1R21DA040907-01 from NIDA.

References

1. Aarde SM, Huang PK, Dickerson TJ, *et al.* (2015) Binge-like acquisition of 3,4-methylenedioxypropylamphetamine (MDPV) self-administration and wheel activity in rats. *Psychopharmacology (Berl)* 232: 1867-1877.
2. Abdallah L, Bonasera SJ, Hopf FW, *et al.* (2009) Impact of serotonin 2C receptor null mutation on physiology and behavior associated with nigrostriatal dopamine pathway function. *J Neurosci* 29: 8156-8165.
3. Abreu ME, Bigelow GE, Fleisher L, *et al.* (2001) Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacology (Berl)* 154: 76-84.
4. Abuzzahab FS, Sr and Anderson BJ (1971) A review of LSD treatment in alcoholism. *Int Pharmacopsychiatry* 6: 223-235.
5. Aiyar J, Grissmer S and Chandy KG (1993) Full-length and truncated Kv1.3 K⁺ channels are modulated by 5-HT_{1c} receptor activation and independently by PKC. *Am J Physiol* 265: C1571-1578.
6. Alex KD and Pehek EA (2007) Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacol Ther* 113: 296-320.
7. American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association.
8. Anastasio NC, Stutz SJ, Fox RG, *et al.* (2014) Functional status of the serotonin 5-HT_{2C} receptor (5-HT_{2C}R) drives interlocked phenotypes that precipitate relapse-like behaviors in cocaine dependence. *Neuropsychopharmacology* 39: 370-382.
9. Auclair A, Drouin C, Cotecchia S, *et al.* (2004) 5-HT_{2A} and alpha1b-adrenergic receptors entirely mediate dopamine release, locomotor response and behavioural sensitization to opiates and psychostimulants. *Eur J Neurosci* 20: 3073-3084.
10. Auclair AL, Cathala A, Sarrazin F, *et al.* (2010) The central serotonin 2B receptor: a new pharmacological target to modulate the mesoaccumbens dopaminergic pathway activity. *J Neurochem* 114: 1323-1332.
11. Austgen JR, Dantzer HA, Barger BK, *et al.* (2012) 5-hydroxytryptamine 2C receptors tonically augment synaptic currents in the nucleus tractus solitarius. *J Neurophysiol* 108: 2292-2305.
12. Baker DA, Tran-Nguyen TL, Fuchs RA, *et al.* (2001) Influence of individual differences and chronic fluoxetine treatment on cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* 155: 18-26.
13. Ball KT and Slane M (2014) Tolerance to the locomotor-activating effects of 3,4-methylenedioxymethamphetamine (MDMA) predicts escalation of MDMA self-administration and cue-induced reinstatement of MDMA seeking in rats. *Behav Brain Res* 274: 143-148.
14. Banas SM, Doly S, Boutourlinsky K, *et al.* (2011) Deconstructing antiobesity compound action: requirement of serotonin 5-HT_{2B} receptors for dexfenfluramine anorectic effects. *Neuropsychopharmacology* 36: 423-433.
15. Bari AA and Pierce RC (2005) D1-like and D2 dopamine receptor antagonists administered into the shell subregion of the rat nucleus accumbens decrease cocaine, but not food, reinforcement. *Neuroscience* 135: 959-968.
16. Bauer CT, Banks ML, Blough BE, *et al.* (2015) Role of 5-HT_{2C} receptors in effects of monoamine releasers on intracranial self-stimulation in rats. *Psychopharmacology (Berl)* 232: 3249-3258.
17. Beart PM and McDonald D (1982) Neurochemical studies of the mesolimbic dopaminergic pathway: [3H]spiperone labels two binding sites in homogenates of the nucleus accumbens of rat brain. *J Neurochem* 39: 1452-1460.
18. Beique JC, Imad M, Mladenovic L, *et al.* (2007) Mechanism of the 5-hydroxytryptamine 2A receptor-mediated facilitation of synaptic activity in prefrontal cortex. *Proc Natl Acad Sci U S A* 104: 9870-9875.
19. Belleville RE, Fraser HF, Isbell H, *et al.* (1956) Studies on lysergic acid diethylamide (LSD-25). I. Effects in former morphine addicts and development of tolerance during chronic intoxication. *AMA Arch Neurol Psychiatry* 76: 468-478.
20. Benneyworth MA, Smith RL, Barrett RJ, *et al.* (2005) Complex discriminative stimulus properties of (+)lysergic acid diethylamide (LSD) in C57Bl/6J mice. *Psychopharmacology (Berl)* 179: 854-862.
21. Berg KA, Clarke WP, Sailstad C, *et al.* (1994) Signal transduction differences between 5-hydroxytryptamine type 2A and type 2C receptor systems. *Mol Pharmacol* 46: 477-484.
22. Berg KA, Stout BD, Maayani S, *et al.* (2001) Differences in rapid desensitization of 5-hydroxytryptamine 2A and 5-hydroxytryptamine 2C receptor-mediated phospholipase C activation. *J Pharmacol Exp Ther* 299: 593-602.
23. Bocklisch C, Pascoli V, Wong JC, *et al.* (2013) Cocaine disinhibits dopamine neurons by potentiation of GABA transmission in the ventral tegmental area. *Science* 341: 1521-1525.
24. Boess FG and Martin IL (1994) Molecular biology of 5-HT receptors. *Neuropharmacology* 33: 275-317.
25. Bogenschutz MP, Forchimes AA, Pommy JA, *et al.* (2015) Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol* 29: 289-299.
26. Bogenschutz MP and Johnson MW (2016) Classic hallucinogens in the treatment of addictions. *Prog Neuropsychopharmacol Biol Psychiatry* 64: 250-258.
27. Bogenschutz MP and Pommy JM (2012) Therapeutic mechanisms of classic hallucinogens in the treatment of addictions: from indirect evidence to testable hypotheses. *Drug Test Anal* 4: 543-555.
28. Boland LM and Jackson KA (1999) Protein kinase C inhibits Kv1.1 potassium channel function. *Am J Physiol* 277: C100-110.
29. Bonaccorso S, Meltzer HY, Li Z, *et al.* (2002) SR46349-B, a 5-HT(2A/2C) receptor antagonist, potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens. *Neuropsychopharmacology* 27: 430-441.
30. Bonhaus DW, Bach C, DeSouza A, *et al.* (1995) The pharmacology and distribution of human 5-hydroxytryptamine 2B (5-HT_{2B}) receptor gene products: comparison with 5-HT_{2A} and 5-HT_{2C} receptors. *Br J Pharmacol* 115: 622-628.
31. Bortolozzi A, Diaz-Mataix L, Scorza MC, *et al.* (2005) The activation of 5-HT receptors in prefrontal cortex enhances dopaminergic activity. *J Neurochem* 95: 1597-1607.
32. Bowen WT, Soskin RA and Chotlos JW (1970) Lysergic acid diethylamide as a variable in the hospital treatment of alcoholism: a follow-up study. *J Nerv Ment Dis* 150: 111-118.
33. Bowers BJ, Henry MB, Thielen RJ, *et al.* (2000) Serotonin 5-HT(2) receptor stimulation of dopamine release in the posterior but not anterior nucleus accumbens of the rat. *J Neurochem* 75: 1625-1633.
34. Brady JV, Griffiths RR, Hienz RD, *et al.* (1984) Abuse liability and behavioral toxicity assessment: progress report from the

- behavioral biology laboratories of the Johns Hopkins University School of Medicine. *NIDA Res Monogr* 49: 92-108.
35. Broderick PA, Olabisi OA, Rahni DN, *et al.* (2004) Cocaine acts on accumbens monoamines and locomotor behavior via a 5-HT_{2A/2C} receptor mechanism as shown by ketanserin: 24-h follow-up studies. *Prog Neuropsychopharmacol Biol Psychiatry* 28: 547-557.
 36. Brown P and Molliver ME (2000) Dual serotonin (5-HT) projections to the nucleus accumbens core and shell: relation of the 5-HT transporter to amphetamine-induced neurotoxicity. *J Neurosci* 20: 1952-1963.
 37. Bubar MJ and Cunningham KA (2007) Distribution of serotonin 5-HT_{2C} receptors in the ventral tegmental area. *Neuroscience* 146: 286-297.
 38. Bubar MJ and Cunningham KA (2008) Prospects for serotonin 5-HT_{2R} pharmacotherapy in psychostimulant abuse. *Prog Brain Res* 172: 319-346.
 39. Bubar MJ, Stutz SJ and Cunningham KA (2011) 5-HT(2C) receptors localize to dopamine and GABA neurons in the rat mesoaccumbens pathway. *PLoS One* 6: e20508.
 40. Burbassi S and Cervo L (2008) Stimulation of serotonin_{2C} receptors influences cocaine-seeking behavior in response to drug-associated stimuli in rats. *Psychopharmacology (Berl)* 196: 15-27.
 41. Burmeister JJ, Lungren EM, Kirschner KF, *et al.* (2004) Differential roles of 5-HT receptor subtypes in cue and cocaine reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology* 29: 660-668.
 42. Burmeister JJ, Lungren EM and Neisewander JL (2003) Effects of fluoxetine and d-fenfluramine on cocaine-seeking behavior in rats. *Psychopharmacology (Berl)* 168: 146-154.
 43. Caine SB, Thomsen M, Gabriel KI, *et al.* (2007) Lack of self-administration of cocaine in dopamine D1 receptor knock-out mice. *J Neurosci* 27: 13140-13150.
 44. Callahan PM and Cunningham KA (1995) Modulation of the discriminative stimulus properties of cocaine by 5-HT_{1B} and 5-HT_{2C} receptors. *J Pharmacol Exp Ther* 274: 1414-1424.
 45. Canal CE, Cordova-Sintjago T, Liu Y, *et al.* (2013) Molecular pharmacology and ligand docking studies reveal a single amino acid difference between mouse and human serotonin 5-HT_{2A} receptors that impacts behavioral translation of novel 4-phenyl-2-dimethylaminotetralin ligands. *J Pharmacol Exp Ther* 347: 705-716.
 46. Canal CE and Morgan D (2012) Head-twitch response in rodents induced by the hallucinogen 2,5-dimethoxy-4-iodoamphetamine: a comprehensive history, a re-evaluation of mechanisms, and its utility as a model. *Drug Test Anal* 4: 556-576.
 47. Canal CE, Olaghere da Silva UB, Gresch PJ, *et al.* (2010) The serotonin 2C receptor potently modulates the head-twitch response in mice induced by a phenethylamine hallucinogen. *Psychopharmacology (Berl)* 209: 163-174.
 48. Carroll ME, Krattiger KL, Gieske D, *et al.* (1990a) Cocaine-base smoking in rhesus monkeys: reinforcing and physiological effects. *Psychopharmacology (Berl)* 102: 443-450.
 49. Carroll ME, Lac ST, Asencio M, *et al.* (1990b) Fluoxetine reduces intravenous cocaine self-administration in rats. *Pharmacol Biochem Behav* 35: 237-244.
 50. Cathala A, Devroye C, Maitre M, *et al.* (2015) Serotonin_{2C} receptors modulate dopamine transmission in the nucleus accumbens independently of dopamine release: behavioral, neurochemical and molecular studies with cocaine. *Addict Biol* 20: 445-457.
 51. Ceccarini J, Kuepper R, Kemels D, *et al.* (2015) [18F]MK-9470 PET measurement of cannabinoid CB1 receptor availability in chronic cannabis users. *Addict Biol* 20: 357-367.
 52. Chagraoui A, Thibaut F, Skiba M, *et al.* (2016) 5-HT_{2C} receptors in psychiatric disorders: a review. *Prog Neuropsychopharmacol Biol Psychiatry* 66: 120-135.
 53. Chandy KG and Gutman GA (1993) Nomenclature for mammalian potassium channel genes. *Trends Pharmacol Sci* 14: 434.
 54. Clemett DA, Punhani T, Duxon MS, *et al.* (2000) Immunohistochemical localisation of the 5-HT_{2C} receptor protein in the rat CNS. *Neuropharmacology* 39: 123-132.
 55. Cline EJ, Scheffel U, Boja JW, *et al.* (1992) Behavioral effects of novel cocaine analogs: a comparison with in vivo receptor binding potency. *J Pharmacol Exp Ther* 260: 1174-1179.
 56. Coffey KR, Barker DJ, Gayliard N, *et al.* (2015) Electrophysiological evidence of alterations to the nucleus accumbens and dorsolateral striatum during chronic cocaine self-administration. *Eur J Neurosci* 41: 1538-1552.
 57. Cogolludo A, Moreno L, Lodi F, *et al.* (2006) Serotonin inhibits voltagegated K⁺ currents in pulmonary artery smooth muscle cells: role of 5-HT_{2A} receptors, caveolin-1, and KV1.5 channel internalization. *Circ Res* 98: 931-938.
 58. Collins GT, Gerak LR, Javors MA, *et al.* (2016) Lorcaserin reduces the discriminative stimulus and reinforcing effects of cocaine in rhesus monkeys. *J Pharmacol Exp Ther* 356: 85-95.
 59. Cozzi NV, Gopalakrishnan A, Anderson LL, *et al.* (2009) Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. *J Neural Transm* 116: 1591-1599.
 60. Craige CP and Unterwald EM (2013) Serotonin (2C) receptor regulation of cocaine-induced conditioned place preference and locomotor sensitization. *Behav Brain Res* 238: 206-210.
 61. Cunningham KA, Fox RG, Anastasio NC, *et al.* (2011) Selective serotonin 5-HT(2C) receptor activation suppresses the reinforcing efficacy of cocaine and sucrose but differentially affects the incentive-salience value of cocainevs. sucrose-associated cues. *Neuropharmacology* 61: 513-523.
 62. Cussac D, Newman-Tancredi A, Quentric Y, *et al.* (2002) Characterization of phospholipase C activity at h5-HT_{2C} compared with h5-HT_{2B} receptors: influence of novel ligands upon membrane-bound levels of [3H]phosphatidylinositols. *Naunyn Schmiedebergs Arch Pharmacol* 365: 242-252.
 63. Czoty PW, Ginsburg BC and Howell LL (2002) Serotonergic attenuation of the reinforcing and neurochemical effects of cocaine in squirrel monkeys. *J Pharmacol Exp Ther* 300: 831-837.
 64. D'Adamo MC, Servetini I, Guglielmi L, *et al.* (2013) 5-HT₂ receptors-mediated modulation of voltage-gated K⁺ channels and neurophysiological correlates. *Exp Brain Res* 230: 453-462.
 65. Daghlish MR and Nutt DJ (2003) Brain imaging studies in human addicts. *Eur Neuropsychopharmacol* 13: 453-458.

66. De Deurwaerdere P, Lagiere M, Bosc M, *et al.* (2013) Multiple controls exerted by 5-HT_{2C} receptors upon basal ganglia function: from physiology to pathophysiology. *Exp Brain Res* 230: 477-511.
67. De Deurwaerdere P, Navailles S, Berg KA, *et al.* (2004) Constitutive activity of the serotonin_{2C} receptor inhibits in vivo dopamine release in the rat striatum and nucleus accumbens. *J Neurosci* 24: 3235-3241.
68. De Deurwaerdere P and Spampinato U (1999) Role of serotonin(2A) and serotonin(2B/2C) receptor subtypes in the control of accumbal and striatal dopamine release elicited in vivo by dorsal raphe nucleus electrical stimulation. *J Neurochem* 73: 1033-1042.
69. Deneau G, Yanagita T and Seevers MH (1969) Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* 16: 30-48.
70. Devroye C, Cathala A, Maitre M, *et al.* (2015) Serotonin_{2C} receptor stimulation inhibits cocaine-induced Fos expression and DARPP-32 phosphorylation in the rat striatum independently of dopamine outflow. *Neuropharmacology* 89: 375-381.
71. Devroye C, Filip M, Przegalinski E, *et al.* (2013) Serotonin_{2C} receptors and drug addiction: focus on cocaine. *Exp Brain Res* 230: 537-545.
72. Di Chiara G, Bassareo V, Fenu S, *et al.* (2004) Dopamine and drug addiction: the nucleus accumbens shell connection. *Neuropharmacology* 47 Suppl 1: 227-241.
73. Di Giovanni G, De Deurwaerdere P, Di Mascio M, *et al.* (1999) Selective blockade of serotonin-2C/2B receptors enhances mesolimbic and mesostriatal dopaminergic function: a combined in vivo electrophysiological and microdialysis study. *Neuroscience* 91: 587-597.
74. Di Giovanni G, Di Matteo V, Di Mascio M, *et al.* (2000) Preferential modulation of mesolimbic vs. nigrostriatal dopaminergic function by serotonin(2C/2B) receptor agonists: a combined in vivo electrophysiological and microdialysis study. *Synapse* 35: 53-61.
75. Di Giovanni G, Di Matteo V, La Grutta V, *et al.* (2001) m-Chlorophenyl-piperazine excites non-dopaminergic neurons in the rat substantia nigra and ventral tegmental area by activating serotonin-2C receptors. *Neuroscience* 103: 111-116.
76. Di Giovanni G, Di Matteo V, Pierucci M, *et al.* (2006) Central serotonin_{2C} receptor: from physiology to pathology. *Curr Top Med Chem* 6: 1909-1925.
77. Di Matteo V, Di Giovanni G, Di Mascio M, *et al.* (1999) SB 242084, a selective serotonin_{2C} receptor antagonist, increases dopaminergic transmission in the mesolimbic system. *Neuropharmacology* 38: 1195-1205.
78. Di Matteo V, Di Giovanni G, Di Mascio M, *et al.* (2000) Biochemical and electrophysiological evidence that RO 60-0175 inhibits mesolimbic dopaminergic function through serotonin(2C) receptors. *Brain Res* 865: 85-90.
79. Di Matteo V, Di Giovanni G, Pierucci M, *et al.* (2008) Serotonin control of central dopaminergic function: focus on in vivo microdialysis studies. *Prog Brain Res* 172: 7-44.
80. Di Matteo V, Pierucci M and Esposito E (2004) Selective stimulation of serotonin_{2C} receptors blocks the enhancement of striatal and accumbal dopamine release induced by nicotine administration. *J Neurochem* 89: 418-429.
81. Diaz SL, Doly S, Narboux-Neme N, *et al.* (2012) 5-HT(2B) receptors are required for serotonin-selective antidepressant actions. *Mol Psychiatry* 17: 154-163.
82. Doly S, Valjent E, Setola V, *et al.* (2008) Serotonin 5-HT_{2B} receptors are required for 3,4-methylenedioxymethamphetamine-induced hyperlocomotion and 5-HT release in vivo and in vitro. *J Neurosci* 28: 2933-2940.
83. Dong Y, Green T, Saal D, *et al.* (2006) CREB modulates excitability of nucleus accumbens neurons. *Nat Neurosci* 9: 475-477.
84. Dreyer JK, Vander Weele CM, Lovic V, *et al.* (2016) Functionally distinct dopamine signals in nucleus accumbens core and shell in the freely moving rat. *J Neurosci* 36: 98-112.
85. Duxon MS, Flanigan TP, Reavley AC, *et al.* (1997) Evidence for expression of the 5-hydroxytryptamine-2B receptor protein in the rat central nervous system. *Neuroscience* 76: 323-329.
86. Dyck E (2005) Flashback: psychiatric experimentation with LSD in historical perspective. *Can J Psychiatry* 50: 381-388.
87. Dyck E (2006) "Hitting highs at rock bottom": LSD treatment for alcoholism, 1950-1970. *Soc History Med* 19: 313-329.
88. Fantegrossi WE, Gray BW, Bailey JM, *et al.* (2015) Hallucinogen-like effects of 2-([2-(4-cyano-2,5-dimethoxyphenyl)ethylamino]methyl) phenol (25CN-NBOH), a novel N-benzylphenethylamine with 100-fold selectivity for 5-HT(2)A receptors, in mice. *Psychopharmacology (Berl)* 232: 1039-1047.
89. Fantegrossi WE, Harrington AW, Eckler JR, *et al.* (2005) Hallucinogen-like actions of 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7) in mice and rats. *Psychopharmacology (Berl)* 181: 496-503.
90. Fantegrossi WE, Woods JH and Winger G (2004a) Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. *Behav Pharmacol* 15: 149-157.
91. Fantegrossi WE, Woolverton WL, Kilbourn M, *et al.* (2004b) Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. *Neuropsychopharmacology* 29: 1270-1281.
92. Filip M, Bubar MJ and Cunningham KA (2004) Contribution of serotonin (5-hydroxytryptamine; 5-HT) 5-HT₂ receptor subtypes to the hyperlocomotor effects of cocaine: acute and chronic pharmacological analyses. *J Pharmacol Exp Ther* 310: 1246-1254.
93. Filip M, Bubar MJ and Cunningham KA (2006) Contribution of serotonin (5-HT) 5-HT₂ receptor subtypes to the discriminative stimulus effects of cocaine in rats. *Psychopharmacology (Berl)* 183: 482-489.
94. Filip M and Cunningham KA (2002) Serotonin 5-HT(2C) receptors in nucleus accumbens regulate expression of the hyperlocomotive and discriminative stimulus effects of cocaine. *Pharmacol Biochem Behav* 71: 745-756.
95. Fletcher PJ, Chintoh AF, Sinyard J, *et al.* (2004) Injection of the 5-HT_{2C} receptor agonist Ro60-0175 into the ventral tegmental area reduces cocaine-induced locomotor activity and cocaine self-administration. *Neuropsychopharmacology* 29: 308-318.
96. Fletcher PJ, Grottick AJ and Higgins GA (2002) Differential effects of the 5-HT(2A) receptor antagonist M100907 and the 5-HT(2C) receptor antagonist SB242084 on cocaine-induced locomotor activity, cocaine self-administration and cocaine-induced reinstatement of responding. *Neuropsychopharmacology* 27: 576-586.
97. Fletcher PJ, Rizos Z, Sinyard J, *et al.* (2008) The 5-HT_{2C} receptor agonist Ro60-0175 reduces cocaine self-administration and reinstatement induced by the stressor yohimbine, and contextual cues. *Neuropsychopharmacology* 33: 1402-1412.
98. Fletcher PJ, Sinyard J and Higgins GA (2006) The effects of the 5-HT(2C) receptor antagonist SB242084 on locomotor activity induced by selective, or mixed, indirect serotonergic and dopaminergic agonists. *Psychopharmacology (Berl)* 187: 515-525.

99. Fontanilla D, Johannessen M, Hajipour AR, *et al.* (2009) The hallucinogen *N,N*-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. *Science* 323: 934-937.
100. Frankel PS and Cunningham KA (2004) m-Chlorophenylpiperazine (mCPP) modulates the discriminative stimulus effects of cocaine through actions at the 5-HT_{2C} receptor. *Behav Neurosci* 118: 157-162.
101. Geyer MA, Puerto A, Dawsey WJ, *et al.* (1976) Histologic and enzymatic studies of the mesolimbic and mesostriatal serotonergic pathways. *Brain Res* 106: 241-256.
102. Ghelardini C, Quattrone A, Galeotti N, *et al.* (2003) Antisense knockdown of the Shaker-like Kv1.1 gene abolishes the central stimulatory effects of amphetamines in mice and rats. *Neuropsychopharmacology* 28: 1096-1105.
103. Gobert A, Rivet JM, Lejeune F, *et al.* (2000) Serotonin(2C) receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. *Synapse* 36: 205-221.
104. Goldberg SR, Morse WH and Goldberg DM (1976) Behavior maintained under a second-order schedule by intramuscular injection of morphine or cocaine in rhesus monkeys. *J Pharmacol Exp Ther* 199: 278-286.
105. Gomez TH, Roache JD and Meisch RA (2002) Orally delivered alprazolam, diazepam, and triazolam as reinforcers in rhesus monkeys. *Psychopharmacology (Berl)* 161: 86-94.
106. Gonzalez-Maeso J and Sealfon SC (2009) Agonist-trafficking and hallucinogens. *Curr Med Chem* 16: 1017-1027.
107. Gonzalez-Maeso J, Weisstaub NV, Zhou M, *et al.* (2007) Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 53: 439-452.
108. Graves SM, Clark MJ, Traynor JR, *et al.* (2015) Nucleus accumbens shell excitability is decreased by methamphetamine self-administration and increased by 5-HT_{2C} receptor inverse agonism and agonism. *Neuropharmacology* 89: 113-121.
109. Green AR (2006) Neuropharmacology of 5-hydroxytryptamine. *Br J Pharmacol* 147 Suppl 1: S145-152.
110. Griffiths RR (1980) Common factors in human and infrahuman drug self-administration. *Psychopharmacol Bull* 16: 45-47.
111. Griffiths RR, Bigelow GE and Henningfield JE (1980) Similarities in animal and human drug-taking behavior. In Mello NK (ed) *Advances in Substance Abuse*. Greenwich, CT: JAI Press, pp.1-90.
112. Griffiths RR, Bigelow GE and Liebson I (1978) Experimental drug self-administration: generality across species and type of drug. *NIDA Res Monogr* 24-43.
113. Griffiths RR, Johnson MW, Richards WA, *et al.* (2011) Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berl)* 218: 649-665.
114. Grinspoon L and Bakalar JB (1986) Can drugs be used to enhance the psychotherapeutic process? *Am J Psychother* 40: 393-404.
115. Grottick AJ, Fletcher PJ and Higgins GA (2000) Studies to investigate the role of 5-HT(2C) receptors on cocaine and food-maintained behavior. *J Pharmacol Exp Ther* 295: 1183-1191.
116. Guillem K, Ahmed SH and Peoples LL (2014) Escalation of cocaine intake and incubation of cocaine seeking are correlated with dissociable neuronal processes in different accumbens subregions. *Biol Psychiatry* 76: 31-39.
117. Haber SN and Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35: 4-26.
118. Halberstadt AL (2015) Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. *Behav Brain Res* 277: 99-120.
119. Halliday GM and Tork I (1989) Serotonin-like immunoreactive cells and fibres in the rat ventromedial mesencephalic tegmentum. *Brain Res Bull* 22: 725-735.
120. Hallock RM, Dean A, Knecht ZA, *et al.* (2013) A survey of hallucinogenic mushroom use, factors related to usage, and perceptions of use among college students. *Drug Alcohol Depend* 130: 245-248.
121. Hanks JB and Gonzalez-Maeso J (2013) Animal models of serotonergic psychedelics. *ACS Chem Neurosci* 4: 33-42.
122. Hansen M, Phonekeo K, Paine JS, *et al.* (2014) Synthesis and structure-activity relationships of N-benzyl phenethylamines as 5-HT_{2A/2C} agonists. *ACS Chem Neurosci* 5: 243-249.
123. Hartig PR, Hoffman BJ, Kaufman MJ, *et al.* (1990) The 5-HT_{1C} receptor. *Ann N Y Acad Sci* 600: 149-166; discussion 166-147.
124. Harvey-Lewis C, Li Z, Higgins GA, *et al.* (2016) The 5-HT_{2C} receptor agonist lorcaserin reduces cocaine self-administration, reinstatement of cocaine-seeking and cocaine induced locomotor activity. *Neuropharmacology* 101: 237-245.
125. Heffter A (1898) Ueber Pellote. *Archiv für experimentelle Pathologie und Pharmakologie* 40: 385-429.
126. Henry DJ and White FJ (1995) The persistence of behavioral sensitization to cocaine parallels enhanced inhibition of nucleus accumbens neurons. *J Neurosci* 15: 6287-6299.
127. Hertz L, Rothman DL, Li B, *et al.* (2015) Chronic SSRI stimulation of astrocytic 5-HT_{2B} receptors change multiple gene expressions/editings and metabolism of glutamate, glucose and glycogen: a potential paradigm shift. *Front Behav Neurosci* 9: 25.
128. Herve D, Pickel VM, Joh TH, *et al.* (1987) Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. *Brain Res* 435: 71-83.
129. Heusser K and Schwappach B (2005) Trafficking of potassium channels. *Curr Opin Neurobiol* 15: 364-369.
130. Higgins GA and Fletcher PJ (2015) Therapeutic potential of 5-HT_{2C} receptor agonists for addictive disorders. *ACS Chem Neurosci* 6: 1071-1088.
131. Hofmann A (1970) Notes and documents concerning the discovery of LSD. *Agents Actions* 1: 148-150.
132. Hollister LE, Shelton J and Krieger G (1969) A controlled comparison of lysergic acid diethylamide (LSD) and dextroamphetamine in alcoholics. *Am J Psychiatry* 125: 1352-1357.
133. Howell LL and Byrd LD (1995) Serotonergic modulation of the behavioral effects of cocaine in the squirrel monkey. *J Pharmacol Exp Ther* 275: 1551-1559.
134. Howell LL and Cunningham KA (2015) Serotonin 5-HT₂ receptor interactions with dopamine function: implications for therapeutics in cocaine use disorder. *Pharmacol Rev* 67: 176-197.
135. Howell LL, Hoffman JM, Votaw JR, *et al.* (2002) Cocaine-induced brain activation determined by positron emission tomography neuroimaging in conscious rhesus monkeys. *Psychopharmacology (Berl)* 159: 154-160.

136. Howell LL and Murnane KS (2008) Nonhuman primate neuroimaging and the neurobiology of psychostimulant addiction. *Ann N Y Acad Sci* 1141: 176-194.
137. Hoyer D, Clarke DE, Fozard JR, *et al.* (1994) International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* 46: 157-203.
138. Hoyer D, Hannon JP and Martin GR (2002) Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* 71: 533-554.
139. Hu XT (2007) Cocaine withdrawal and neuro-adaptations in ion channel function. *Mol Neurobiol* 35: 95-112.
140. Hu XT, Basu S and White FJ (2004) Repeated cocaine administration suppresses HVA-Ca²⁺ potentials and enhances activity of K⁺ channels in rat nucleus accumbens neurons. *J Neurophysiol* 92: 1597-1607.
141. Huang M, Dai J and Meltzer HY (2011) 5-HT_{2A} and 5-HT_{2C} receptor stimulation are differentially involved in the cortical dopamine efflux-Studied in 5-HT_{2A} and 5-HT_{2C} genetic mutant mice. *Eur J Pharmacol* 652: 40-45.
142. Hutcheson JD, Setola V, Roth BL, *et al.* (2012) Serotonin receptors and heart valve disease - it was meant 2B. *Pharmacol Ther* 132: 146-157.
143. Ikemoto S (2010) Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. *Neurosci Biobehav Rev* 35: 129-150.
144. Imbrici P, Tucker SJ, D'Adamo MC, *et al.* (2000) Role of receptor protein tyrosine phosphatase alpha (RPTPalpha) and tyrosine phosphorylation in the serotonergic inhibition of voltage-dependent potassium channels. *Pflugers Arch* 441: 257-262.
145. Invernizzi RW, Pierucci M, Calcagno E, *et al.* (2007) Selective activation of 5-HT_{2C} receptors stimulates GABA-ergic function in the rat substantia nigra pars reticulata: a combined in vivo electrophysiological and neurochemical study. *Neuroscience* 144: 1523-1535.
146. Iversen L, Gibbons S, Treble R, *et al.* (2013) Neurochemical profiles of some novel psychoactive substances. *Eur J Pharmacol* 700: 147-151.
147. Ji SP, Zhang Y, Van Cleemput J, *et al.* (2006) Disruption of PTEN coupling with 5-HT_{2C} receptors suppresses behavioral responses induced by drugs of abuse. *Nat Med* 12: 324-329.
148. Johnson MW, Garcia-Romeu A, Cosimano MP, *et al.* (2014) Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol* 28: 983-992.
149. Johnston J, Forsythe ID and Kopp-Scheinflug C (2010) Going native: voltage-gated potassium channels controlling neuronal excitability. *J Physiol* 588: 3187-3200.
150. Jones DL, Mogenson GJ and Wu M (1981) Injections of dopaminergic, cholinergic, serotonergic and GABAergic drugs into the nucleus accumbens: effects on locomotor activity in the rat. *Neuropharmacology* 20: 29-37.
151. Katsidoni V, Apazoglou K and Panagis G (2011) Role of serotonin 5-HT_{2A} and 5-HT_{2C} receptors on brain stimulation reward and the reward-facilitating effect of cocaine. *Psychopharmacology (Berl)* 213: 337-354.
152. Kleven MS and Woolverton WL (1993) Effects of three monoamine uptake inhibitors on behavior maintained by cocaine or food presentation in rhesus monkeys. *Drug Alcohol Depend* 31: 149-158.
153. Knauer CS, Campbell JE, Chio CL, *et al.* (2009) Pharmacological characterization of mitogen-activated protein kinase activation by recombinant human 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors. *Naunyn Schmiedebergs Arch Pharmacol* 379: 461-471.
154. Kometer M, Schmidt A, Jancke L, *et al.* (2013) Activation of serotonin 2A receptors underlies the psilocybin-induced effects on alpha oscillations, N170 visual-evoked potentials, and visual hallucinations. *J Neurosci* 33: 10544-10551.
155. Kourrich S, Calu DJ and Bonci A (2015) Intrinsic plasticity: an emerging player in addiction. *Nat Rev Neurosci* 16: 173-184.
156. Kourrich S, Hayashi T, Chuang JY, *et al.* (2013) Dynamic interaction between sigma-1 receptor and Kv1.2 shapes neuronal and behavioral responses to cocaine. *Cell* 152: 236-247.
157. Kourrich S and Thomas MJ (2009) Similar neurons, opposite adaptations: psychostimulant experience differentially alters firing properties in accumbens core versus shell. *J Neurosci* 29: 12275-12283.
158. Krebs TS and Johansen PO (2012) Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. *J Psychopharmacol* 26: 994-1002.
159. Kuhar MJ, McGirr KM, Hunter RG, *et al.* (1999) Studies of selected phenyltropanes at monoamine transporters. *Drug Alcohol Depend* 56: 9-15.
160. Kursar JD, Nelson DL, Wainscott DB, *et al.* (1994) Molecular cloning, functional expression, and mRNA tissue distribution of the human 5-hydroxytryptamine_{2B} receptor. *Mol Pharmacol* 46: 227-234.
161. Lambe EK and Aghajanian GK (2001) The role of Kv1.2-containing potassium channels in serotonin-induced glutamate release from thalamocortical terminals in rat frontal cortex. *J Neurosci* 21: 9955-9963.
162. Lecca D, Cacciapaglia F, Valentini V, *et al.* (2007) Differential neurochemical and behavioral adaptation to cocaine after response contingent and noncontingent exposure in the rat. *Psychopharmacology (Berl)* 191: 653-667.
163. Lecca D, Piras G, Driscoll P, *et al.* (2004) A differential activation of dopamine output in the shell and core of the nucleus accumbens is associated with the motor responses to addictive drugs: a brain dialysis study in Roman high- and low-avoidance rats. *Neuropharmacology* 46: 688-699.
164. Leysen JE, Janssen PF and Niemegeers CJ (1989) Rapid desensitization and down-regulation of 5-HT₂ receptors by DOM treatment. *Eur J Pharmacol* 163: 145-149.
165. Lioudyno MI, Birch AM, Tanaka BS, *et al.* (2013) Shaker-related potassium channels in the central medial nucleus of the thalamus are important molecular targets for arousal suppression by volatile general anesthetics. *J Neurosci* 33: 16310-16322.
166. Liu S, Bubar MJ, Lanfranco MF, *et al.* (2007) Serotonin_{2C} receptor localization in GABA neurons of the rat medial prefrontal cortex: implications for understanding the neurobiology of addiction. *Neuroscience* 146: 1677-1688.
167. Lobo MK, Covington HE, 3rd, Chaudhury D, *et al.* (2010) Cell type-specific loss of BDNF signaling mimics optogenetic control of cocaine reward. *Science* 330: 385-390.
168. Lopez-Gimenez JF, Mengod G, Palacios JM, *et al.* (2001) Regional distribution and cellular localization of 5-HT_{2C} receptor mRNA in monkey brain: comparison with [3H]mesulergine binding sites and choline acetyltransferase mRNA. *Synapse* 42: 12-26.
169. Lopez-Gimenez JF, Tecott LH, Palacios JM, *et al.* (2002) Serotonin 5-HT_{2C} receptor knockout mice: autoradiographic

- analysis of multiple serotonin receptors. *J Neurosci Res* 67: 69-85.
170. Loric S, Launay JM, Colas JF, *et al.* (1992) New mouse 5-HT₂-like receptor. Expression in brain, heart and intestine. *FEBS Lett* 312: 203-207.
 171. Ludwig A, Levine J, Stark L, *et al.* (1969) A clinical study of LSD treatment in alcoholism. *Am J Psychiatry* 126: 59-69.
 172. Maclean KA, Johnson MW and Griffiths RR (2011) Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *J Psychopharmacol* 25: 1453-1461.
 173. Majic T, Schmidt TT and Gallinat J (2015) Peak experiences and the afterglow phenomenon: when and how do therapeutic effects of hallucinogens depend on psychedelic experiences? *J Psychopharmacol* 29: 241-253.
 174. Mangini M (1998) Treatment of alcoholism using psychedelic drugs: a review of the program of research. *J Psychoactive Drugs* 30: 381-418.
 175. Manvich DF, Kimmel HL, Cooper DA, *et al.* (2012a) The serotonin 2C receptor antagonist SB 242084 exhibits abuse-related effects typical of stimulants in squirrel monkeys. *J Pharmacol Exp Ther* 342: 761-769.
 176. Manvich DF, Kimmel HL and Howell LL (2012b) Effects of serotonin 2C receptor agonists on the behavioral and neurochemical effects of cocaine in squirrel monkeys. *J Pharmacol Exp Ther* 341: 424-434.
 177. Marazziti D, Rossi A, Giannaccini G, *et al.* (1999) Distribution and characterization of [3H]mesulergine binding in human brain postmortem. *Eur Neuropsychopharmacol* 10: 21-26.
 178. Marcinkiewicz CA (2015) Serotonergic systems in the pathophysiology of ethanol dependence: relevance to clinical alcoholism. *ACS Chem Neurosci* 6: 1026-1039.
 179. Marquis KL, Sabb AL, Logue SF, *et al.* (2007) WAY-163909 [(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4] diazepino[6,7,1hi]indole]: a novel 5-hydroxytryptamine 2C receptor-selective agonist with preclinical antipsychotic-like activity. *J Pharmacol Exp Ther* 320: 486-496.
 180. Marsch LA, Bickel WK, Badger GJ, *et al.* (2001) Effects of infusion rate of intravenously administered morphine on physiological, psychomotor, and self-reported measures in humans. *J Pharmacol Exp Ther* 299: 1056-1065.
 181. McLean TH, Parrish JC, Braden MR, *et al.* (2006) 1-Aminomethylbenzo-cycloalkanes: conformationally restricted hallucinogenic phenethylamine analogues as functionally selective 5-HT_{2A} receptor agonists. *J Med Chem* 49: 5794-5803.
 182. McMahan LR and Cunningham KA (2001) Antagonism of 5-hydroxytryptamine(2a) receptors attenuates the behavioral effects of cocaine in rats. *J Pharmacol Exp Ther* 297: 357-363.
 183. McMahan LR, Filip M and Cunningham KA (2001) Differential regulation of the mesoaccumbens circuit by serotonin 5-hydroxy-tryptamine (5-HT)_{2A} and 5-HT_{2C} receptors. *J Neurosci* 21: 7781-7787.
 184. Meredith GE (1999) The synaptic framework for chemical signaling in nucleus accumbens. *Ann N Y Acad Sci* 877: 140-156.
 185. Meyer JS (2013) 3,4-methylenedioxymethamphetamine (MDMA): current perspectives. *Subst Abuse Rehabil* 4: 83-99.
 186. Mijster MJ, Raimundo AG, Koskuba K, *et al.* (1997) Regional and cellular distribution of serotonin 5-hydroxytryptamine_{2A} receptor mRNA in the nucleus accumbens, olfactory tubercle, and caudate putamen of the rat. *J Comp Neurol* 389: 1-11.
 187. Mu P, Moyer JT, Ishikawa M, *et al.* (2010) Exposure to cocaine dynamically regulates the intrinsic membrane excitability of nucleus accumbens neurons. *J Neurosci* 30: 3689-3699.
 188. Muller CP and Homberg JR (2015) The role of serotonin in drug use and addiction. *Behav Brain Res* 277: 146-192.
 189. Murnane KS, Andersen ML, Rice KC, *et al.* (2013a) Selective serotonin 2A receptor antagonism attenuates the effects of amphetamine on arousal and dopamine overflow in non-human primates. *J Sleep Res* 22: 581-588.
 190. Murnane KS and Howell LL (2011) Neuroimaging and drug taking in primates. *Psychopharmacology (Berl)* 216: 153-171.
 191. Murnane KS, Winschel J, Schmidt KT, *et al.* (2013b) Serotonin 2A receptors differentially contribute to abuse-related effects of cocaine and cocaine-induced nigrostriatal and mesolimbic dopamine overflow in nonhuman primates. *J Neurosci* 33: 13367-13374.
 192. Navailles S, Moison D, Cunningham KA, *et al.* (2008) Differential regulation of the mesoaccumbens dopamine circuit by serotonin_{2C} receptors in the ventral tegmental area and the nucleus accumbens: an in vivo microdialysis study with cocaine. *Neuropsychopharmacology* 33: 237-246.
 193. Navailles S, Moison D, Ryczko D, *et al.* (2006) Region-dependent regulation of mesoaccumbens dopamine neurons in vivo by the constitutive activity of central serotonin_{2C} receptors. *J Neurochem* 99: 1311-1319.
 194. Nedergaard S, Bolam JP and Greenfield SA (1988) Facilitation of a dendritic calcium conductance by 5-hydroxytryptamine in the substantia nigra. *Nature* 333: 174-177.
 195. Neisewander JL and Acosta JI (2007) Stimulation of 5-HT_{2C} receptors attenuates cue and cocaine-primed reinstatement of cocaine-seeking behavior in rats. *Behav Pharmacol* 18: 791-800.
 196. Nelson RA, Boyd SJ, Ziegelstein RC, *et al.* (2006) Effect of rate of administration on subjective and physiological effects of intravenous cocaine in humans. *Drug Alcohol Depend* 82: 19-24.
 197. Nic Dhonnchadha BA, Fox RG, Stutz SJ, *et al.* (2009) Blockade of the serotonin 5-HT_{2A} receptor suppresses cue-evoked reinstatement of cocaine-seeking behavior in a rat self-administration model. *Behav Neurosci* 123: 382-396.
 198. Nichols DE (2004) Hallucinogens. *Pharmacol Ther* 101: 131-181.
 199. Nichols DE, Frescas SP, Chemel BR, *et al.* (2008) High specific activity tritium-labeled N-(2-methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine (INBMeO): a high-affinity 5-HT_{2A} receptor-selective agonist radioligand. *Bioorg Med Chem* 16: 6116-6123.
 200. Nichols DE, Sassano MF, Halberstadt AL, *et al.* (2015) N-Benzyl-5-methoxytryptamines as potent serotonin 5-HT₂ receptor family agonists and comparison with a series of phenethylamine analogues. *ACS Chem Neurosci* 6: 1165-1175.
 201. Nocjar C, Alex KD, Sonneborn A, *et al.* (2015) Serotonin-2C and -2a receptor co-expression on cells in the rat medial prefrontal cortex. *Neuroscience* 297: 22-37.
 202. Nutt DJ, King LA, Phillips LD, *et al.* (2010) Drug harms in the UK: a multicriteria decision analysis. *Lancet* 376: 1558-1565.
 203. Olaghere da, Silva UB, Morabito MV, Canal CE, *et al.* (2010) Impact of RNA editing on functions of the serotonin 2C receptor in vivo. *Front Neurosci* 4: 26.
 204. Orejarena MJ, Lanfumey L, Maldonado R, *et al.* (2011) Involvement of 5-HT_{2A} receptors in MDMA reinforcement and cue-induced reinstatement of MDMA-seeking behaviour. *Int J Neuropsychopharmacol* 14: 927-940.
 205. Pacheco-Cano MT, Bargas J, Hernandez-Lopez S, *et al.* (1996) Inhibitory action of dopamine involves a subthreshold Cs(+)-

- sensitive conductance in neostriatal neurons. *Exp Brain Res* 110: 205-211.
206. Pahnke WN, Kurland AA, Unger S, *et al.* (1970) The experimental use of psychedelic (LSD) psychotherapy. *JAMA* 212: 1856-1863.
207. Parent A, Descarries L and Beaudet A (1981) Organization of ascending serotonin systems in the adult rat brain. A radioautographic study after intraventricular administration of [3H]5-hydroxytryptamine. *Neuroscience* 6: 115-138.
208. Pascoli V, Terrier J, Hiver A, *et al.* (2015) Sufficiency of mesolimbic dopamine neuron stimulation for the progression to addiction. *Neuron* 88: 1054-1066.
209. Pehek EA, Nocjar C, Roth BL, *et al.* (2006) Evidence for the preferential involvement of 5-HT_{2A} serotonin receptors in stress- and drug-induced dopamine release in the rat medial prefrontal cortex. *Neuropsychopharmacology* 31: 265-277.
210. Pisanu A, Lecca D, Valentini V, *et al.* (2015) Impairment of acquisition of intravenous cocaine self-administration by RNA-interference of dopamine D1-receptors in the nucleus accumbens shell. *Neuropharmacology* 89: 398-411.
211. Pontieri FE, Tanda G and Di Chiara G (1995) Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. *Proc Natl Acad Sci U S A* 92: 12304-12308.
212. Porras G, Di Matteo V, Fracasso C, *et al.* (2002) 5-HT_{2A} and 5-HT_{2C/2B} receptor subtypes modulate dopamine release induced in vivo by amphetamine and morphine in both the rat nucleus accumbens and striatum. *Neuropsychopharmacology* 26: 311-324.
213. Porter RH, Benwell KR, Lamb H, *et al.* (1999) Functional characterization of agonists at recombinant human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors in CHO-K1 cells. *Br J Pharmacol* 128: 13-20.
214. Quarta D, Naylor CG and Stolerman IP (2007) The serotonin 2C receptor agonist Ro-60-0175 attenuates effects of nicotine in the five-choice serial reaction time task and in drug discrimination. *Psychopharmacology (Berl)* 193: 391-402.
215. Ramirez-Navarro A, Glazebrook PA, Kane-Sutton M, *et al.* (2011) Kv1.3 channels regulate synaptic transmission in the nucleus of solitary tract. *J Neurophysiol* 105: 2772-2780.
216. Ray TS (2010) Psychedelics and the human receptorome. *PLoS One* 5: e9019.
217. Richardson NR and Roberts DC (1991) Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. *Life Sci* 49: 833-840.
218. Riedlinger TJ and Riedlinger JE (1994) Psychedelic and entactogenic drugs in the treatment of depression. *J Psychoactive Drugs* 26: 41-55.
219. Ritz MC, Boja JW, George FR, *et al.* (1989) Cocaine binding sites related to drug self-administration. *NIDA Res Monogr* 95: 239-246.
220. Ritz MC and Kuhar MJ (1989) Relationship between self-administration of amphetamine and monoamine receptors in brain: comparison with cocaine. *J Pharmacol Exp Ther* 248: 1010-1017.
221. Robbins CA and Tempel BL (2012) Kv1.1 and Kv1.2: similar channels, different seizure models. *Epilepsia* 53 Suppl 1: 134-141.
222. Roberts DC, Morgan D and Liu Y (2007) How to make a rat addicted to cocaine. *Prog Neuropsychopharmacol Biol Psychiatry* 31: 1614-1624.
223. Robertson B (1997) The real life of voltage-gated K⁺ channels: more than model behaviour. *Trends Pharmacol Sci* 18: 474-483.
224. Robison AJ and Nestler EJ (2011) Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neurosci* 12: 623-637.
225. Rocha BA, Goulding EH, O'Dell LE, *et al.* (2002) Enhanced locomotor, reinforcing, and neurochemical effects of cocaine in serotonin 5-hydroxytryptamine 2C receptor mutant mice. *J Neurosci* 22: 10039-10045.
226. Rodd-Henricks ZA, McKinzie DL, Li TK, *et al.* (2002) Cocaine is self-administered into the shell but not the core of the nucleus accumbens of Wistar rats. *J Pharmacol Exp Ther* 303: 1216-1226.
227. Roth BL (2007) Drugs and valvular heart disease. *New Engl J Med* 356: 6-9.
228. Roth BL, Lopez E, Patel S, *et al.* (2000) The multiplicity of serotonin receptors: uselessly diverse molecules or an embarrassment of riches? *Neuroscientist* 6: 252-262.
229. Rothman RB and Baumann MH (2009) Serotonergic drugs and valvular heart disease. *Expert Opin Drug Saf* 8: 317-329.
230. Rothman RB, Blough BE, Woolverton WL, *et al.* (2005) Development of a rationally designed, low abuse potential, biogenic amine releaser that suppresses cocaine self-administration. *J Pharmacol Exp Ther* 313: 1361-1369.
231. Ruedi-Bettschen D, Spealman RD and Platt DM (2015) Attenuation of cocaine-induced reinstatement of drug seeking in squirrel monkeys by direct and indirect activation of 5-HT_{2C} receptors. *Psychopharmacology (Berl)* 232: 2959-2968.
232. Russo SJ and Nestler EJ (2013) The brain reward circuitry in mood disorders. *Nat Rev Neurosci* 14: 609-625.
233. Sadoris MP, Sugam JA, Cacciapaglia F, *et al.* (2013) Rapid dopamine dynamics in the accumbens core and shell: learning and action. *Front Biosci (Elite Ed)* 5: 273-288.
234. Sanders-Bush E, Fentress H and Hazelwood L (2003) Serotonin 5-HT₂ receptors: molecular and genomic diversity. *Mol Interv* 3: 319-330.
235. Santana N and Artigas F (2016) Expression of serotonin 2C receptors in pyramidal and GABAergic neurons of rat prefrontal cortex: a comparison with striatum. *Cereb Cortex*. Epub ahead of print 1 June 2016.
236. Sawyer EK, Mun J, Nye JA, *et al.* (2012) Neurobiological changes mediating the effects of chronic fluoxetine on cocaine use. *Neuropsychopharmacology* 37: 1816-1824.
237. Sellings LH and Clarke PB (2003) Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. *J Neurosci* 23: 6295-6303.
238. Sesack SR and Grace AA (2010) Cortico-basal ganglia reward network: microcircuitry. *Neuropsychopharmacology* 35: 27-47.
239. Shah NH and Aizenman E (2014) Voltage-gated potassium channels at the crossroads of neuronal function, ischemic tolerance, and neurodegeneration. *Transl Stroke Res* 5: 38-58.
240. Shulgin A and Shulgin A (1991) *PIHKAL: A Chemical Love Story*. Berkeley, CA: Transform Press.
241. Shulgin A and Shulgin A (1997) *TIHKAL: The Continuation*. Berkeley, CA: Transform Press, p.804.
242. Shulgin AT, Manning T and Daley PF (2011) *The Shulgin Index: Volume One*. Berkeley, CA: Transform Press.
243. Siegel RK and Jarvik ME (1980) DMT self-administration by monkey in isolation. *Bull Psychon Soc* 16: 117-120.

244. Simeone TA, Simeone KA, Samson KK, *et al.* (2013) Loss of the Kv1.1 potassium channel promotes pathologic sharp waves and high frequency oscillations in in vitro hippocampal slices. *Neurobiol Dis* 54: 68-81.
245. Smart RG, Storm T, Baker EF, *et al.* (1966) A controlled study of lysergide in the treatment of alcoholism. 1. The effects on drinking behavior. *Q J Stud Alcohol* 27: 469-482.
246. Smith DA, Bailey JM, Williams D, *et al.* (2014) Tolerance and cross-tolerance to head twitch behavior elicited by phenethylamine- and tryptamine-derived hallucinogens in mice. *J Pharmacol Exp Ther* 351: 485-491.
247. Speake T, Kibble JD and Brown PD (2004) Kv1.1 and Kv1.3 channels contribute to the delayed-rectifying K⁺ conductance in rat choroid plexus epithelial cells. *Am J Physiol Cell Physiol* 286: C611-620.
248. Spealman RD (1993) Modification of behavioral effects of cocaine by selective serotonin and dopamine uptake inhibitors in squirrel monkeys. *Psychopharmacology (Berl)* 112: 93-99.
249. Stamets P (1996) *Psilocybin Mushrooms of the World: An Identification Guide*. Berkeley, CA: Ten Speed Press.
250. Stone AL, Storr CL and Anthony JC (2006) Evidence for a hallucinogen dependence syndrome developing soon after onset of hallucinogen use during adolescence. *Int J Methods Psychiatr Res* 15: 116-130.
251. Strassman RJ (1996) Human psychopharmacology of *N,N*-dimethyl-tryptamine. *Behav Brain Res* 73: 121-124.
252. Strassman RJ and Qualls CR (1994) Dose-response study of *N,N*-dimethyltryptamine in humans: I. neuroendocrine, autonomic, and cardiovascular effects. *Arch Gen Psychiatry* 51: 85-97.
253. Strassman RJ, Qualls CR and Berg LM (1996) Differential tolerance to biological and subjective effects of four closely spaced doses of *N,N*-dimethyltryptamine in humans. *Biol Psychiatry* 39: 784-795.
254. Studerus E, Gamma A, Kometer M, *et al.* (2012) Prediction of psilocybin response in healthy volunteers. *PLoS One* 7: e30800.
255. Tibbs GR, Dolly JO and Nicholls DG (1996) Evidence for the induction of repetitive action potentials in synaptosomes by K⁺-channel inhibitors: an analysis of plasma membrane ion fluxes. *J Neurochem* 67: 389-397.
256. Tomsovic M and Edwards RV (1970) Lysergide treatment of schizophrenic and nonschizophrenic alcoholics: a controlled evaluation. *Q J Stud Alcohol* 31: 932-949.
257. Van Bockstaele EJ and Pickel VM (1993) Ultrastructure of serotonin-immunoreactive terminals in the core and shell of the rat nucleus accumbens: cellular substrates for interactions with catecholamine afferents. *J Comp Neurol* 334: 603-617.
258. Volkow ND, Wang GJ, Fischman MW, *et al.* (2000) Effects of route of administration on cocaine induced dopamine transporter blockade in the human brain. *Life Sci* 67: 1507-1515.
259. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, *et al.* (1998) Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* 9: 3897-3902.
260. Wacker D, Wang C, Katritch V, *et al.* (2013) Structural Features for Functional Selectivity at Serotonin Receptors. *Science* 340: 615-619.
261. Wang H, Kunkel DD, Schwartzkroin PA, *et al.* (1994) Localization of Kv1.1 and Kv1.2, two K channel proteins, to synaptic terminals, somata, and dendrites in the mouse brain. *J Neurosci* 14: 4588-4599.
262. Wee S, Anderson KG, Baumann MH, *et al.* (2005) Relationship between the serotonergic activity and reinforcing effects of a series of amphetamine analogs. *J Pharmacol Exp Ther* 313: 848-854.
263. Winter JC, Rice KC, Amorosi DJ, *et al.* (2007) Psilocybin-induced stimulus control in the rat. *Pharmacol Biochem Behav* 87: 472-480.
264. Woolverton WL and Wang Z (2004) Relationship between injection duration, transporter occupancy and reinforcing strength of cocaine. *Eur J Pharmacol* 486: 251-257.
265. Xu P, He Y, Cao X, *et al.* (2016) Activation of serotonin 2C receptors in dopamine neurons inhibits binge-like eating in mice. *Biol Psychiatry*. Epub ahead of print 9 June 2016. DOI: 10.1016/j.biopsych.2016.06.005.
266. Yan QS (2000) Activation of 5-HT_{2A/2C} receptors within the nucleus accumbens increases local dopaminergic transmission. *Brain Res Bull* 51: 75-81.
267. Yanagita T (1986) Intravenous self-administration of (-)-cathinone and 2-amino-1-(2,5-dimethoxy-4-methyl)phenylpropane in rhesus monkeys. *Drug Alcohol Depend* 17: 135-141.
268. You I-J, Wright SR, Garcia-Garcia AL, *et al.* (2016) 5-HT_{1A} autoreceptors in the dorsal raphe nucleus convey vulnerability to compulsive cocaine seeking. *Neuropsychopharmacology* 41: 1210-1222.
269. Zaniwska M, McCreary AC, Przegalinski E, *et al.* (2007) Effects of the serotonin 5-HT_{2A} and 5-HT_{2C} receptor ligands on the discriminative stimulus effects of nicotine in rats. *Eur J Pharmacol* 571: 156-165.
270. Zhang XF, Cooper DC and White FJ (2002) Repeated cocaine treatment decreases whole-cell calcium current in rat nucleus accumbens neurons. *J Pharmacol Exp Ther* 301: 1119-1125.