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European Journal of Pharmacology 480 (2003) 151–162
www.elsevier.com/locate/ejphar

Serotonin and drug reward: focus on 5-HT_{2C} receptors

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Accepted 25 August 2003

Abstract

Pharmacological manipulation of the 5-hydroxytryptamine (5-HT; serotonin) system has long been associated with a regulation of feeding behaviour, however, the initial part of this article reviews evidence that central 5-HT systems similarly modulate reward-related behaviours, particularly drug reward. The second part of this article considers what we believe to be strong emerging pharmacological and genetic evidence that many of these effects are mediated through 5-HT_{2C} receptor signalling mechanisms. Finally, we consider the potential for selective 5-HT_{2C} agonists as therapies for substance abuse disorders and the medical implications for different 5-HT_{2C} receptor isoforms generated by RNA editing.

Keywords: Cocaine; 5-HT (5-hydroxytryptamine, serotonin); 5-HT_{2C} receptor knockout mouse; Drug self-administration; Feeding behaviour; RNA editing

1. Introduction

Until its withdrawal in 1997 from worldwide markets due to an association with valvular heart disease, the 5-hydroxytryptamine (5-HT) releaser/reuptake inhibitor D-fenfluramine (Redux®) was a widely prescribed and efficacious anorectic used to treat obesity (Rothman and Baumann, 2002). It has now been superceded by the mixed 5-HT/noradrenaline reuptake inhibitor sibutramine (Meridia®) (Heal et al., 1998), which recently gained approval for this condition. Together with an extensive preclinical literature (e.g., Blundell, 1984; Simansky, 1996), these clinical findings attest to a widely accepted role of 5-HT systems in the control of feeding behaviour. However, in addition to food, indirect 5-HT receptor agonists such as D-fenfluramine and selective 5-HT reuptake inhibitors also reduce the intake of other rewarding stimuli including drugs of abuse. Indeed, some workers have noted a very limited separation between effective doses required to reduce food intake and, for example, ethanol self-administration, suggesting that such drugs may affect consummatory behaviours in general (Amit et al., 1991; Sellers et al., 1992; Higgins et al., 1992b).

Traditionally the behavioural and neurochemical effects of drugs of abuse have been most closely associated with the functioning of dopamine systems, and particularly the mesolimbic dopamine system projecting from the ventral tegmental area to the nucleus accumbens. However, several other neurotransmitter systems have been linked to drug reward, either as modulators of dopamine function or as substrates, that function independently of dopamine (e.g., Bardo, 1998; Laviolette and van der Kooy, 2001; Wise, 2002). These include glutamate, γ-aminobutyric acid (GABA), acetylcholine, various peptides, notably the endogenous endorphins and enkephalins and 5-HT. The purpose of this article is to review work that has explored the role of 5-HT in modulating drug reward. In particular, we focus on the role of the 5-HT_{2C} receptor.

2. 5-HT and reward—brief overview

Most of the early studies in this area involved the use of treatments that induce generalized increases or decreases in brain 5-HT function. These include indirect agonists, and lesioning of 5-HT pathways induced by the selective serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT). The primary emphasis here is on studies that have investi-

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doi:10.1016/j.ejphar.2003.08.102

gated the effects of serotonergic manipulations on drug self-administration, or drug seeking behaviour. Where relevant, studies using other types of reward-related behaviours are mentioned, particularly those using drug-induced conditioned place preference and responding for brain stimulation reward.

2.1. Effects of nonselective increases in 5-HT function

Numerous studies have shown that various aspects of drug reward are modified by treatments that elevate serotonin function in a generalized manner. These treatments include selective serotonin reuptake inhibitors, e.g., fluoxetine, the 5-HT precursor L-tryptophan and the 5-HT releaser/reuptake inhibitor D-fenfluramine. Fluoxetine reduces both amphetamine (Fletcher et al., 1999a; Leccese and Lyness, 1984) and cocaine (Carroll et al., 1990; Howell and Byrd, 1995; Peltier and Schenk, 1993; Porrino et al., 1989; Richardson and Roberts, 1991) self-administration in a number of studies from different laboratories. Similarly, L-tryptophan reduces responding for amphetamine (Smith et al., 1986) and cocaine (McGregor et al., 1993). In at least some of these studies, drug reinforcement was delivered on a progressive ratio schedule, where treatment-induced reductions in responding are often taken as evidence for reductions in the reinforcing efficacy of the self-administered drug. The effects of D-fenfluramine on cocaine self-administration do not appear to have been reported although this treatment has been shown to reduce responding for methamphetamine (Munzar et al., 1999) and heroin (Higgins et al., 1994; Wang et al., 1995).

Recent studies have extended these analyses to examine the impact of serotonergic agents on cocaine-seeking in animals whose responding for cocaine had been extinguished. Both acute (Burmeister et al., 2003) and chronic (Baker et al., 2001) injections of fluoxetine attenuated reinstatement of responding elicited by cocaine-paired cues, though not by priming effects of cocaine itself. Acute injections of D-fenfluramine had a similar effect (Burmeister et al., 2003).

2.2. Effects of nonselective reductions in 5-HT function

A number of early studies demonstrated that widespread depletion of 5-HT following intracerebroventricular injection of 5,7-DHT increased responding for infusions of amphetamine on a fixed ratio schedule (Leccese and Lyness, 1984; Lyness et al., 1980). A more recent study did not replicate this finding using 5,7-DHT injected into the dorsal and median raphe nuclei, and additionally found that responding on a progressive ratio schedule was not altered by this means of depleting 5-HT (Fletcher et al., 1999a). The situation is further complicated by the fact that while the nonselective 5-HT receptor antagonist metergoline also increased responding for amphetamine (Lyness and Moore, 1983), other nonselective receptor antagonists including methysergide, cyproheptadine and cinanserin (Leccese and Lyness, 1984) reduced responding in a manner similar to the nonselective indirect agonists. Regarding cocaine self-administration, two reports (Loh and Roberts, 1990; Roberts et al., 1994) have found that responding for cocaine under a progressive ratio schedule is enhanced by intracerebroventricularly injected 5,7-DHT, as well as by local application of this neurotoxin into the amygdala, but not the nucleus accumbens (Loh and Roberts, 1990).

The effects of 5-HT depletion on cocaine seeking behaviour following extinction of self-administration behaviour have also been examined. Both *p*-chlorophenylalanine (PCPA) and central 5,7-DHT treatment attenuated reinstatement of cocaine-seeking behaviour elicited by cues previously associated with cocaine (Tran-Nguyen et al., 1999, 2001). In contrast 5,7-DHT lesions enhanced responding for cues associated with sucrose (Tran-Nguyen et al., 2001) or water (Fletcher et al., 1999b), and increased the priming effect of experimenter administered cocaine (Tran-Nguyen et al., 2001).

2.3. Effects of receptor selective agents on drug self-administration

Over the last decade, our understanding of central 5-HT systems in terms of receptor pharmacology, distribution and function has progressed considerably. At least 14 distinct 5-HT receptors have now been cloned, the majority of which appear to play functional roles in the central nervous system (CNS) (see Hoyer and Martin, 1997; Barnes and Sharp, 1999; Hoyer et al., 2002 for recent reviews). Not surprisingly, the roles of several 5-HT receptor subtypes on drug reward have been examined although this has not yet been done in a systematic fashion, perhaps in part because of the lack of availability of truly selective ligands for all of the receptor subtypes. The following section briefly summarises some of the major findings regarding the effects of ligands for the various 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_6 receptors on drug reward.

2.3.1. 5-HT_{1A} receptors

5-HT_{1A} receptors are located postsynaptically, as well as on 5-HT cell bodies in the dorsal and median raphe nuclei, where they function as autoreceptors. As a result, 5-HT_{1A} receptor stimulation can result in either increased or decreased 5-HT neurotransmission. Factors such as dose and route of injection (systemic versus intracerebral) are likely to be major determinants of the net effect of 5-HT_{1A} receptor stimulation. Only a few studies have examined the effects of 5-HT_{1A} receptor agonists on drug self-administration, with inconclusive results. In rats, a moderately high dose of the prototypic 5-HT_{1A} receptor agonist 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino) tetralin) (0.5 mg/kg) reduced responding for cocaine on a fixed ratio schedule (Peltier and Schenk, 1993). This effect is somewhat difficult to interpret both in terms of the behavioural significance of

the reduction in responding as well as the impact that this dose of 8-OH-DPAT has on 5-HT neurotransmission. Conflicting results have been found in nonhuman primates using other 5-HT_{1A} receptor agonists. In one study, buspirone and gepirone failed to alter cocaine self-administration (Gold and Balster, 1992); in a different study, buspirone, gepirone and 8-OH-DPAT, all administered at very low doses, increased response rate on a second-order schedule of cocaine reinforcement (Nader and Barrett, 1990). This latter effect is suggestive of increased efficacy of cocaine. In other reward procedures, 8-OH-DPAT induces a conditioned place preference (Papp and Willner, 1991; Shippenberg, 1991) and lowers thresholds for brain stimulation reward (Montgomery et al., 1991). In both cases these effects can be elicited by injecting 8-OH-DPAT into the midbrain raphe nuclei (Fletcher et al., 1993, 1995). This suggests that acute reductions in brain 5-HT function, resulting from activation of raphe somatodendritic 5-HT_{1A} autoreceptors, facilitate or enhance reward-related behaviour.

The 5-HT_{1A} receptor antagonist WAY100635 (*N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl) ethyl)-*N*-(2-pyridyl)-cyclohexanecarboxamide trichloride) did not alter amphetamine self-administration (Fletcher and Korth, 1999), although it did attenuate the response reinstating effects of cocaine in cocaine-abstinent rats (Schenk, 2000).

2.3.2. 5-HT_{1B} receptors

A number of studies have now documented changes in reward-related behaviour following treatment with 5-HT_{1B} receptor ligands. The mixed 5-$HT_{1A/1B}$ receptor agonist RU242969 (1*H*-indole, 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-butanedioate) and the more selective agonist CP94,253 (3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo [3,2-b] pyridine) injected systemically or intracerebroventricularly altered responding for cocaine in a manner consistent with an increase in the reinforcing efficacy of cocaine (Parsons et al., 1998). In contrast, systemic injection of RU24969 disrupted responding for amphetamine, in a 5-HT_{1B} receptor dependent manner (Fletcher and Korth, 1999). A similar effect was observed when RU24969 or CP93,129 (5*H*-pyrrolo [3,2-b] pyridine-5-one, 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl) were injected into the nucleus accumbens (Fletcher et al., 2002a). In another reward procedure, RU24969 elevated thresholds for brain stimulation reward (Harrison et al., 1999). Using a conditioned place preference test, 5-HT_{1B} agonists by themselves elicited place aversions, but enhanced the ability of low doses of cocaine to elicit a place preference (Cervo et al., 2002). Overall, 5-HT_{1B} receptor stimulation alters reward-related behaviour but the effects seem to vary with the type of rewarding stimulus used, as well as the site at which the drug is administered. These seemingly different effects of 5-HT_{1B} receptor agonists on different measures of reward may also result from the fact that 5-HT_{1B} receptors may modulate a number of different aspects of neural transmission. Thus, depending upon neuronal location, the 5-HT_{1B} receptor can function as a post-synaptic receptor, a terminal autoreceptor modulating 5-HT release, and a heteroreceptor modulating the release of other neurotransmitters (Barnes and Sharp, 1999).

2.3.3. 5-HT_2 receptors

Three subtypes of the 5-HT_2 receptor exist, designated 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} (Baxter et al., 1995; Hoyer et al., 2002). The functions of the 5-HT_{2A} and 5-HT_{2C} receptors in the CNS have been studied much more extensively than the 5-HT_{2B} receptor. By and large the majority of studies performed have used receptor antagonists, due in part to a limited availability of selective agonists for these receptors. In rats the 5-$HT_{2A/2C}$ receptor antagonists ritanserin and ketanserin failed to alter cocaine or amphetamine self-administration (Fletcher, 1998; Lacosta and Roberts, 1993; Schenk, 2000). Ritanserin also did not affect response reinstatement induced by priming injections of cocaine (Schenk, 2000) or place preference elicited by amphetamine (Nomikos and Spyraki, 1988). In contrast, low doses of ketanserin and ritanserin enhanced responding of cocaine on a second-order schedule in squirrel monkeys (Howell and Byrd, 1995). Although the selective 5-HT_{2A} receptor antagonist M100907 ((+) 2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]) attenuates the locomotor stimulant effect of cocaine (McMahon and Cunningham, 2001; Fletcher et al., 2002b) and amphetamine (Moser et al., 1996), it did not alter cocaine self-administration (Fletcher et al., 2002b). Consistent with this action, M100907 also failed to affect either baseline responding for brain stimulation reward, or the facilitatory effects of amphetamine on this measure (Moser et al., 1996). The effects of 5-HT_{2C} receptors are discussed in the second half of this article.

2.3.4. 5-HT_3 receptors

Several studies on the role of 5-HT_3 receptors in drug reward have been conducted using conditioned place preference, drug self-administration and brain stimulation reward procedures. In some studies, 5-HT_3 receptor antagonists have been shown to block conditioned place preferences with morphine (Acquas et al., 1988; Higgins et al., 1992a) and nicotine (Acquas et al., 1988), but not amphetamine (Acquas et al., 1988). Results of studies with cocaine have been inconsistent with both a blockade of the effect of cocaine (Kankaanpaa et al., 2002) or no effect being observed (Cervo et al., 1996). In studies of intravenous drug self-administration, it has consistently been reported that 5-HT_3 receptor antagonists do not alter cocaine (Depoortere et al., 1993; Lacosta and Roberts, 1993; Peltier and Schenk, 1991), opioid (Higgins et al., 1994) or nicotine (Corrigall and Coen, 1994) self-administration. A similar lack of effect has been noted in studies using brain stimulation reward (Montgomery et al., 1993; Rompre et al., 1995). However, 5-HT_3 receptor antagonists do seem to consistently reduce oral self-administration of ethanol per-

haps by virtue of a direct action of ethanol at certain ion channels, including the 5-HT_3 receptor (see Grant, 1994).

2.3.5. 5-HT_6 receptors

Functions of the 5-HT_6 receptor are poorly understood at the present time (Barnes and Sharp, 1999). In the context of reward-related behaviour, the 5-HT_6 receptor antagonist SB-258510A (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)-phenyl]-5-chloro-3-methylbenzo-thiophene-2-yl sulfonamate monohydrochloride) increases self-administration of amphetamine but not cocaine (Frantz et al., 2002) in a manner consistent with facilitation of the reinforcing efficacy of amphetamine.

2.4. General conclusions

From this brief overview, it can be seen that there are a number of inconsistencies in the effects of serotonergic manipulations on reward-related behaviour. Despite this, two general conclusions can be drawn. First, there is a consensus between different laboratories using different self-administered drugs, and different schedules of reinforcement that generalized elevations in 5-HT neurotransmission appear to reduce cocaine and amphetamine self-administration. The fact that such effects are seen using progressive ratio schedules of reinforcement suggests a reduction in the reinforcing effectiveness of the self-administered drug. This effect also seems to extend to reinstatement of drug-seeking behaviour as well. The second conclusion is that under some circumstances, reduced 5-HT function can enhance reward-related behaviour. This effect is not always observed, and inconsistencies between experiments may be due to differences between the type of reinforcer used, the method of reducing 5-HT function, and, in the case of 5-HT lesions, the pattern and extent of 5-HT depletion.

3. The 5-HT_{2C} receptor

3.1. Introduction

The 5-HT_{2C} receptor (previously known as the 5-HT_{1C} receptor) has high sequence homology to other members of the 5-HT_2 subclass and is positively coupled to phospholipase C (see Baxter et al., 1995; Hoyer et al., 2002 for reviews). Until recently, this receptor has been fairly difficult to distinguish pharmacologically from the 5-HT_{2A} and 5-HT_{2B} receptors although selective antagonists for each are now available (Baxter et al., 1995; Hoyer et al., 2002; see Section 2.2.1). The 5-HT_{2C} receptor has a reasonably wide distribution in mammalian brain tissue and is expressed in dopaminergic cell body regions of the substantia nigra and ventral tegmental area as well as in terminal projection areas of the nucleus accumbens, striatum and prefrontal cortex (Pompeiano et al., 1994; Abramowski et al., 1995; Eberle-Wang et al., 1997). The moderately selective 5-HT_{2C} receptor agonist Ro 60-0175 ((*S*)-2-(6-chloro-5-fluoroindol-1-yl)-1-methlethylamine) (Martin et al., 1998) reduces the firing rate of mesolimbic dopamine neurons originating in the ventral tegmental area (Di Matteo et al., 2000a), leading to a reduction in dopamine release in terminal regions of the nucleus accumbens and frontal cortex (Di Matteo et al., 2000a; Gobert and Millan, 1999). These effects are reversed by the selective 5-HT_{2C} receptor antagonist SB-242084 (6-Chloro-5-methyl-1-[[2-[(2-methyl-3-pyridyl) oxy]-5-pyridyl] carbamoyl]-indole) (Di Matteo et al., 2000a; Gobert and Millan, 1999). Additionally, SB-242084 alone increases the burst-firing of dopaminergic neurons in the ventral tegmental area leading to increased release of dopamine in the nucleus accumbens (Di Matteo et al., 1999). Thus it appears that 5-HT_{2C} receptors may exert a tonic inhibitory influence over the activity of ascending dopamine neurons (Di Matteo et al., 1999, 2000b).

3.2. Understanding the in vivo functions of the 5-HT_{2C} receptor

3.2.1. SB-242084 and Ro 60-0175 as pharmacological tools to probe 5-HT_{2C} receptor function in vivo

In 1997, researchers at SmithKline-Beecham reported the first truly selective 5-HT_{2C} receptor antagonist, SB-242084 (6-Chloro-5-methyl-1-[[2-[(2-methyl-3-pyridyl) oxy]-5-pyridyl] carbamoyl]-indole) (Bromidge et al., 1997; Kennett et al., 1997) (see Table 1). SB-242084 shows good CNS bioavailability following systemic administration, as demonstrated for example by a robust and dose-related inhibition of *m*-chlorophenylpiperazine (mCPP)-induced hypolocomotion in rodents (Kennett et al., 1997; Martin et al., 2002). At about the same time, workers at Hoffmann-La Roche and Organon, in a search for selective 5-HT_{2C} receptor agonists of CNS therapeutic potential, identified Ro 60-0175 (ORG35030) (Martin et al., 1998). A demonstration of the in vivo activity of this compound was provided by the induction of penile erection and hypolocomotion—both responses being hitherto proposed as 5-HT_{2C} (or 5-HT_{1C} at the time) receptor-mediated (see Kennett and Curzon, 1988; Berendsen et al., 1990).

Table 1
Pharmacological profile of Ro 60-0175 and SB-242084 at h5-HT_{2A}, h5-HT_{2B}, and h5-HT_{2C} receptors

	pEC_{50} or pK_i		
	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
Ro 60-0175	6.4 (0.69)	9.1 (0.79)	7.5 (0.84)
SB-242084	6.8	7.0	9.0

Data for Ro 60-0175 are expressed as pEC_{50} to stimulate Ca^{2+} influx in CHO cells expressing the relevant h5-HT_2 receptor. The figure in parentheses refers to the efficacy relative to 10 μM 5-HT. Data from Porter et al. (1999). Data for SB-242084 are binding affinity (pK_i) to relevant h5-HT_2 receptor expressed in HEK 293 cells. Data from Bromidge et al. (1997).

Considering the relative affinity of Ro 60-0175 for the 5-HT_{2C} receptor relative to other 5-HT_2 subtypes—notably 5-HT_{2B}—Ro 60-0175 shows little or no selectivity (Table 1; Porter et al., 1999). The same can be said for mCPP, which has even broader 5-HT receptor pharmacology (e.g., Barnes and Sharp, 1999; Hoyer et al., 2002). Yet in vivo both drugs produce behaviours typical of 5-HT_{2C} receptor activation, and even at high, seemingly non-selective doses, behaviour characteristics of other 5-HT receptors are typically not induced. A study by Haiser and Tecott (2000) examining the locomotor effects of mCPP in wild-type and 5-HT_{2C} receptor ko mice first shed light on this paradox. In wild-type mice, mCPP, as expected, reduced locomotor activity. However, in the 5-HT_{2C} ko mouse, mCPP pretreatment, rather than reduce activity, was found to elicit a marked hyperactivity (see Fig. 1A) that was attenuated by the selective 5-HT_{1B} receptor antagonist GR127935 (2-methyl-4-(5-methyl [1,2,4] oxadiazol-3-yl)-biphenyl-4-carboxylic acid [4-methodoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide) (Haiser and Tecott, 2000). Thus, in addition to confirming that the hypolocomotor effects of mCPP were indeed 5-HT_{2C}-mediated, the findings of Haiser and Tecott (2000) also demonstrated that preferential activation of 5-HT_{2C} receptors can prevent the expression of behaviours mediated through other 5-HT subtypes—in this case the 5-HT_{1B} receptor. Using the selective 5-HT_{2C} receptor antagonist, SB-242084, we essentially showed the same phenomena with Ro 60-0175 in the rat (Higgins et al., 2001). Thus in vehicle-pretreated rats, Ro 60-0175 from 1–10 mg/kg produced penile grooming, hypolocomotion but no significant sign of 5-HT_{2A}-mediated behaviour such as wet dog shakes and back muscle contractions. However, in SB-242084-pretreated rats, Ro 60-0175 (3–10 mg/kg) elicited a totally different behavioural profile including hyperactivity, wet dog shakes and back muscle contractions—effects that were blocked by the 5-HT_{2A} receptor antagonist M100907 (Higgins et al., 2001). In other words, blockade of 5-HT_{2C} receptors unmasked clear 5-HT_{2A} agonist effects of Ro 60-0175, although only at moderate to high doses (see Fig. 1B).

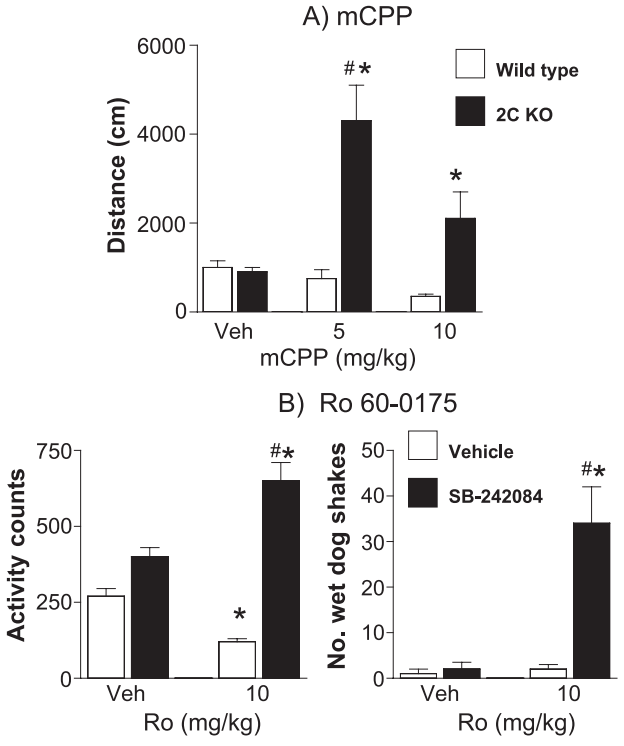

Fig. 1. (A) Effect of mCPP on locomotor activity in wild-type and 5-HT_{2C} receptor ko mice. In wild-type mice, mCPP produced a reduction in activity. Conversely, in the mutant group, mCPP elicited a marked hyperactivity. *$P<0.05$ vs. vehicle-treated group; #$P<0.05$ vs. wild-type group at equivalent dose. (B) Effect of Ro 60-0175 on locomotor activity and wet dog shake behaviour in male Sprague–Dawley rats either pretreated with vehicle or the 5-HT_{2C} receptor antagonist SB-242084 (0.5 mg/kg IP). In vehicle-pretreated rats, Ro 60-0175 (10 mg/kg) produced a marked hypoactivity and little or no wet dog shakes. In SB-242084-pretreated rats, this same dose of Ro 60-0175 elicited a marked hyperactivity and marked wet dog shakes. *$P<0.05$ vs. vehicle-treated group, #$P<0.05$ vs. vehicle/Ro 60-0175-treated group. (A) Partial data set redrawn from Haiser and Tecott (2000); (B) partial data set redrawn from Higgins et al. (2001). See text and original references for further details.

Taken together, the studies of Haiser and Tecott (2000) and Higgins et al. (2001) indicate that although mCPP and Ro 60-0175 have limited receptorial selectivity for the 5-HT_{2C} subtype over certain other 5-HT receptors, in vivo both drugs seem to show selectivity at this subtype, probably because preferential activation of the 5-HT_{2C} receptor prevents the expression of behaviours elicited through other 5-HT receptors. Thus, Ro 60-0175 represents a valid 5-HT_{2C} receptor agonist suitable for in vivo use.

3.2.2. Pharmacological evidence that the 5-HT_{2C} receptor influences reward-related behaviour

Because of the earlier evidence that indirect 5-HT receptor agonists, i.e. fluoxetine and D-fenfluramine, reduced a wide range of drug-maintained behaviours (see Section 2.1), and the fact that the 5-HT_{2C} receptor was a mediator of at least some in vivo effects of the 5-HT releaser D-fenfluramine (e.g., Vickers et al., 2001), we examined the effect of Ro 60-0175 pretreatment on cocaine self-administration and hyperlocomotion (Grottick et al., 2000).

Separate groups of Sprague–Dawley rats were trained to self-administer cocaine either under a Fixed ratio 5, 60-s timeout schedule (FR5TO60s) or progressive ratio schedule. Once stable rates of responding had been acquired, the effect of Ro 60-0175 (0.3–3 mg/kg) pretreatment was studied and compared to the effect seen in a further group of rats trained to respond for food under the identical FR5TO60s schedule. The results demonstrated a robust and dose-related reduction in cocaine self-administration, over a similar dose range to that which reduced food-maintained responding—even though response rates varied markedly between the two reinforcers (Grottick et al., 2000). Subsequent experiments extended these findings to show that Ro 60-0175 reduced intravenous nicotine (Grottick et al., 2001) and oral ethanol (Tomkins et al., 2002) self-

administration. The ED_{50} dose of Ro 60-0175 did not significantly differ between each reinforcer, the range being 0.7 mg/kg (ethanol)–1.7 mg/kg (cocaine) (see Fig. 2). Furthermore, the effects of Ro 60-0175 on food-, cocaine- and ethanol-maintained responding are each blocked by SB-242084 (0.5 mg/kg) pretreatment (Grottick et al., 2000; Tomkins et al., 2002; Fletcher et al., 2003).

While these observations might suggest a generalized suppression of motivated behaviour, control experiments demonstrated little or no motor or neurological impairments, at least over the 0.3–1 mg/kg dose range of Ro 60-0175 (Grottick et al., 2000, 2001). Also, in the cocaine self-administration studies, initial rates of responding and mean inter-infusion intervals were similar to controls—suggesting an earlier termination of responding following Ro 60-0175 treatment. Consequently, these data suggest that 5-HT_{2C} receptor stimulation has a generalized effect to reduce motivation that is not a product of some indiscriminate neurological or motor disturbance.

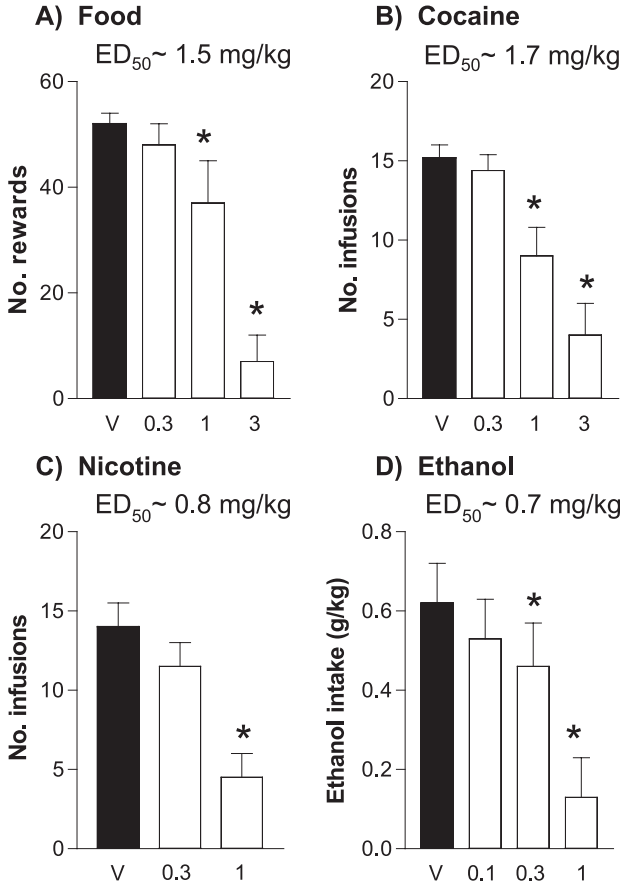

Fig. 2. Dose response for Ro 60-0175 (0.1–3 mg/kg, SC route, 10–30 min pretreatment) against (A) food (45-mg Noyes pellet) available under a Fixed ratio 5, 60-s timeout (FR5TO60s) schedule, (B) intravenous cocaine (0.25 mg/infusion) available under an FR5TO60s schedule, (C) intravenous nicotine (0.03 mg/infusion) available under an FR5TO60s schedule, (D) oral 12% w/v ethanol available under an FR4 schedule. Test session length was 60 min, except ethanol which was 30 min. ED_{50} measures were calculated using Prism v. 3.0. Data redrawn from Grottick et al. (2000, 2001) and Tomkins et al. (2002). See text and original references for further details.

We further examined the effect of Ro 60-0175 on the reinstatement of cocaine self-administration, elicited after a period of extinction by a priming injection of cocaine (De Witt and Stewart, 1981). Ro 60-0175 reduced the priming effect of acute cocaine on subsequent responding, although the effect seemed quite variable. Further studies should investigate the effect of a 5-HT_{2C} receptor agonist in such a relapse model in more detail. For example, Le et al. (1999) reported that fluoxetine was more effective at blocking stress (electroshock)-induced reinstatement of ethanol self-administration compared to that elicited by a priming injection of ethanol. Importantly, during the course of these studies, we found that acute Ro 60-0175 did not engender cocaine-appropriate responding, suggesting that Ro 60-0175 was not reducing cocaine self-administration by substitution (Grottick et al., 2000).

Taken together, these data may be consistent with the biochemical and electrophysiological evidence that 5-HT_{2C} receptor activation reduces mesolimbic function (see Section 3.1). Conversely, pharmacological blockade of this receptor has been reported to produce the opposite profile, i.e. increase ventral tegmental area cell firing and accumbens dopamine release (Di Matteo et al., 1999, 2000b). Such a bidirectional effect has also been observed behaviourally, with SB-242084 pretreatment increasing break points for cocaine self-administration and potentiating cocaine-induced hyperactivity (Fletcher et al., 2001, 2000b) (see Fig. 3). SB-242084 also increased ethanol intake in a limited access schedule (see Tomkins et al., 2002) and potentiated the response reinstating effect of cocaine (Fletcher et al., 2001, 2000b) (see Table 2 for summary). Furthermore, SB-242084 produced a robust increase in schedule-induced polydipsia in rats receiving food according to a fixed interval 60-s (FI60s) schedule of reinforcement, again contrasting the marked suppression of this behaviour by Ro 60-0175 (Martin et al., 1998, 2002). The finding that SB-242084 increases a compulsive-type behaviour, such as schedule-induced polydipsia, is of interest given its potentiation of break-point for cocaine self-administration.

To date, these pharmacological studies are confined to Ro 60-0175 and SB-242084, although Cunningham and coworkers reported similar potentiation of cocaine-mediated hyperactivity with the 5-$HT_{2B/2C}$ selective antagonist SB-206553 at a single dose (McCreary and Cunningham, 1999). It will be important to extend these observations to other 5-HT_{2C} receptor-selective drugs to test the generality of the findings. However, supporting evidence to our pharmacological data is now emerging from the 5-HT_{2C} receptor knockout mouse reported by Tecott et al. (1995).

3.2.3. Genetic evidence that the 5-HT_{2C} receptor influences reward-related behaviour: the 5-HT_{2C} receptor ko mouse

Genetic deletion of the 5-HT_{2C} receptor gene in the mouse resulted in increased body weight gain and seizure

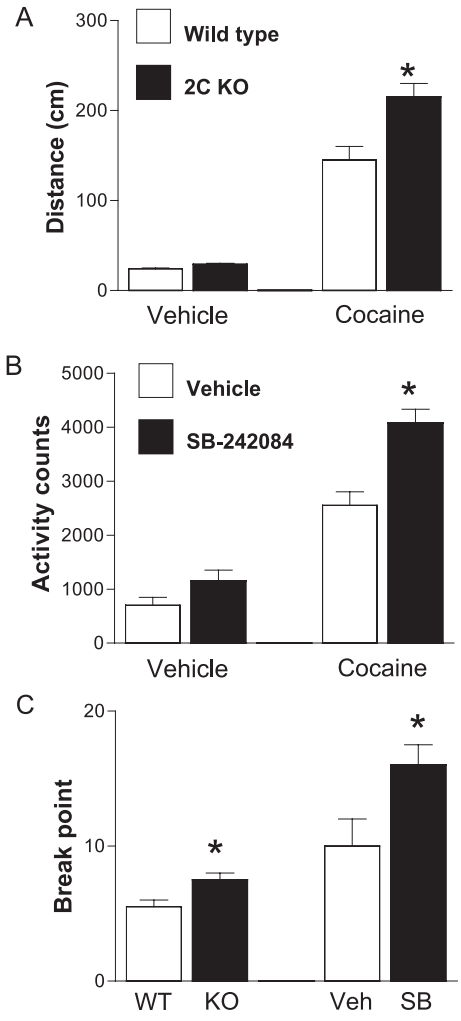

Fig. 3. (A) Effect of acute vehicle or cocaine (30 mg/kg IP) injection on locomotor activity in wild-type and 5-HT_{2C} receptor ko mice. In the mutant group, cocaine elicited a more intense locomotor response. *$P<0.05$ vs. wild-type group. (B) Effect of acute vehicle or cocaine (10 mg/kg IP) injection on locomotor activity in male Sprague–Dawley rats pretreated with either vehicle or SB-242084 (0.5 mg/kg). In SB-242084-pretreated animals, cocaine elicited a more intense locomotor response. *$P<0.05$ vs. vehicle group. (C) Break point for intravenous cocaine self-administration available under a progressive ratio schedule of reinforcement in either wild-type or 5-HT_{2C} receptor ko mice or Sprague–Dawley rats pretreated with either vehicle or SB-242084 (0.5 mg/kg). (A) Partial data set redrawn from Rocha et al. (2002). (B) Partial data set redrawn from Fletcher et al. (2002a,b). (C) Redrawn from Rocha et al. (2002) and Fletcher et al. (2002a,b). See text and original references for further details.

liability (Tecott et al., 1995). Subsequently, more detailed studies in this mouse line have revealed an interaction between seizure susceptibility and genetic background (Applegate and Tecott, 1998) and electrophysiological evidence that this knockout line is more responsive to excitatory stimulation, suggesting the 5-HT_{2C} receptor may have a tonic inhibitory function at specific neuronal loci (Reuter et al., 2000). This would seem consistent with the increased ventral tegmental area cell firing observed following systemic SB-242084 treatment (Di Matteo et al., 1999).

Regarding the increased body weight gain phenotype in the 5-HT_{2C} ko mouse, Tecott et al. (1995), using a paired feeding analysis, concluded that the increased body mass was the result of increased food intake rather than metabolic change. Furthermore, leptin signaling pathways in these mice seem similar to wild-type controls (Nonogaki et al., 1998). Thus, a behavioural change resulting in an increased propensity for 5-HT_{2C} ko mice to consume food was identified—perhaps related to delayed satiety. Importantly, this phenotype appears to have been robustly maintained over successive generations of 5-HT_{2C} ko mice (see Tecott et al., 1995; Nonogaki et al., 1998).

Most recently, 5-HT_{2C} receptor ko mice have shown an increased propensity to self-administer intravenous cocaine under a progressive ratio schedule (Rocha et al., 2002). The findings that 5-HT_{2C} receptor ko mice respond to higher break points for intravenous cocaine infusions are very similar to our observation that SB-242084 pretreatment results in higher break points in rats responding for cocaine under an equivalent reinforcement schedule (Fletcher et al., 2001, 2000b; see Fig. 3). Furthermore, 5-HT_{2C} receptor ko mice show a heightened locomotor response to novelty and acute cocaine injection, again similar to our own observations with SB-242084 pretreatment in rats (Fletcher et al., 2001, 2000b; see Fig. 3).

In the final part to the studies of Rocha et al. (2002), 5-HT_{2C} receptor ko mice exhibited enhanced cocaine-induced elevations of dopamine in the nucleus accumbens following acute systemic cocaine injection. In contrast, striatal increases in dopamine release following cocaine injection were similar between the mutant and wild-type group. Again these findings support the electrophysiological and neurochemical findings of Di Matteo et al. (1999), suggesting that the mesolimbic (A10) dopamine pathway is under a greater 5-HT_{2C} receptor control than the nigrostriatal (A9) pathway.

Table 2
Summary of effects of Ro 60-0175 and SB-242084 on motivated and psychostimulant-related behaviour: evidence for bidirectional effects following pharmacological modulation of the 5-HT_{2C} receptor

Behaviour	Ro 60-0175	SB-242084
Cocaine self-administration	↓[a]	↑[c]
Reinstatement model of cocaine self-administration	↓[a]	↑[c]
Cocaine-induced hyperactivity	↓[a]	↑[c]
Feeding behaviour	↓[a]	–[a]
Nicotine self-administration	↓[b]	NAD
Nicotine-induced hyperactivity	↓[b]	–[b]
Ethanol self-administration	↓[e]	↑[e]
Schedule-induced polydipsia	↓[d]	↑[d]
Spontaneous locomotor activity	↓[b]	–[a,b,c,d]

↓, decrease; ↑, increase; NAD, no available data; –, no consistent effect. All effects of Ro 60-0175 seen 0.1–3 mg/kg, SB-242084 (0.5 mg/kg). Data summarised from Grottick et al. (2000)[a], Grottick et al. (2001)[b], Fletcher et al. (2002a,b)[c], Martin et al. (2002)[d], Tomkins et al. (2002)[e].

Finally, and perhaps analogous to the increase in schedule-induced polydipsia elicited by SB-242084 pretreatment in rats (Martin et al., 2002), the 5-HT_{2C} ko mouse has been recently reported to display compulsive-like behaviour in certain test situations (Chou-Green et al., 2003). These behaviours include: (a) increased chewing of a non-nutritive kaolin clay, (b) a distinct chewing pattern of round, plastic screens, and (c) delayed habituation of head-dipping behaviour in an open field compared to wild-type littermate controls. Consequently, Chou-Green et al. (2003) have proposed the 5-HT_{2C} ko mouse to represent a novel murine model of compulsive behaviour.

4. The 5-HT_{2C} receptor: a dominant role as a mediator of central 5-HT function?

As outlined in Section 1, one of the more consistent findings across laboratories investigating 5-HT and reward-related behaviour is that treatments which broadly increase this neurotransmitter function tend to reduce drug self-administration. It is quite likely that many of these agents are doing so principally through activation of the 5-HT_{2C} receptor. Although by no means rigorously tested, the pharmacology of the anorectic and ethanol suppressant effect of D-fenfluramine principally seems consistent with 5-HT_{2C} receptor mediation (Vickers et al., 2001; Tomkins et al., 2002; see also Wang et al., 1995). The anorectic effects of D-fenfluramine are also attenuated in the 5-HT_{2C} receptor ko mouse (Vickers et al., 1999). Furthermore, the generalized effect of Ro 60-0175 against cocaine, ethanol, nicotine self-administration as well as food intake is reminiscent of our findings with D-fenfluramine against a variety of rewards, as well as selective serotonergic reuptake inhibitor drugs and L-tryptophan against psychostimulant self-administration (see Section 2).

Some of the work reviewed in Section 2 indicates that, under certain conditions, reduced 5-HT function facilitates reward-related behaviour. A prominent view of 5-HT function for many years has linked reduced 5-HT to impulsivity (Soubrie, 1986). This is supported by numerous demonstrations that reduced 5-HT function also leads to deficits in response control. For example, 5,7-DHT lesions seem to impair an animal's ability to withhold responding, e.g. reducing inter-response times and response efficiency, when behaviour is maintained by a differential low rate of responding (DRL), and to promote premature responding in the five-choice serial reaction time test (Wogar et al., 1992; Fletcher et al., 1995; Harrison et al., 1997). Recently, we have observed a similar behavioural tendency in rats pretreated with SB-242084 (Higgins et al., in press) (see Fig. 4). It will be interesting to see if the 5-HT_{2C} receptor ko mouse displays impulsive-type behaviour. The recent report of Chou-Green et al. (2003) describing compulsive-like behaviour in this knockout relative to wild-type littermate controls would suggest these animals have impaired aspects

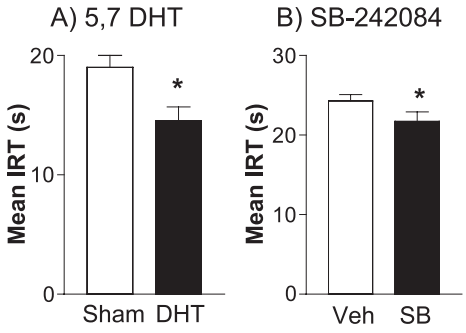

Fig. 4. (A) Effect of combined dorsal raphe (DRN) and median raphe (MRN) 5,7-DHT lesions on mean inter-response time for rats performing a differential low rate of responding 20 s (DRL20) schedule of food reinforcement. (B) Effect of SB-242084 pretreatment (0.5 mg/kg) on mean inter-response time for rats performing a differential low rate of responding 24-s (DRL24) schedule of food reinforcement. *$P<0.05$ vs. relevant control group. (A) Partial data set taken from Fletcher (1995). (B) Partial data set taken from Higgins et al. (2003). See text and original references for further details.

of response control. It is not yet clear whether such impulsive-type behaviour is related to the increased drug taking that is sometimes seen in 5-HT-depleted rats (Cicocioppo, 1999). Nevertheless, the similarities between 5-HT depletion and 5-HT_{2C} receptor blockade are quite striking. A suggested contribution of impaired 5-HT_{2C} receptor-mediated function to the expression of behavioural changes in 5-HT depleted rats is further emphasized by the findings that the 5-HT_{2A} receptor antagonist M100907 tended to reduce impulsive-type behaviour (Higgins et al., in press; Winstanley et al., 2003).

Thus, of the 14 presently known 5-HT receptor subtypes (Barnes and Sharp, 1999; Hoyer et al., 2002), the 5-HT_{2C} subtype appears highly responsive to global pharmacological activators of this system, and certain behavioural sequalae observed following generalized lesioning to this system may be mimicked by acute SB-242084 pretreatment. Our work examining the in vivo effects of Ro 60-0175 and SB-242084 indicates that this receptor exerts a bidirectional modulation of the behavioural effects of cocaine and ethanol in the rat. This is consistent with the bidirectional effects of 5-HT_{2C} receptor-mediated activity on electrophysiological and neurochemical aspects of dopaminergic function, largely outlined by Esposito and colleagues (see Section 3.1). This bidirectionality of 5-HT_{2C} receptor function has at least two potentially important implications.

First, the 5-HT_{2C} receptor may represent a possible therapeutic target for the development of selective agonists as treatments for aspects of drug abuse. The observation that Ro 60-0175 reduces responding for intravenous cocaine and nicotine, and oral ethanol consumption in rats in the absence of overt generalized disruption, suggests a potential for selective 5-HT_{2C} receptor agonists in the treatment of various substance abuse disorders including smoking cessation. The demonstration that Ro 60-0175 is also effective in a model of drug reinstatement (Grottick et al., 2000)

would further suggest that such a drug may have potential to reduce the likelihood of relapse after cessation of drug taking. For a few years now, 5-HT_{2C} agonists have been proposed as potential anorectics (Bickerdike et al., 1999)—our results would suggest this potential could be extended to a variety of agents whose uncontrolled usage leads to medical and social problems.

Secondly, the fact that blockade of 5-HT_{2C} receptor-mediated transmission, through either pharmacological or gene deletion techniques, enhances cocaine and ethanol-mediated behaviours indicates a role for possible endogenous modulation by 5-HT_{2C} receptors of these effects. The 5-HT_{2C} receptor is currently the only known G-protein-coupled receptor that undergoes RNA editing by the conversion of five adenosine residues to inosine (Burns et al., 1997; Hoyer et al., 2002). This posttranscriptional modification can give rise to functionally distinct receptor isoforms through coding changes for up to three amino acid residues on the second intracellular loop (Burns et al., 1997). For at least some of these receptor isoforms, there is evidence that this can reduce basal receptor activity, resulting from less efficient G-protein coupling (Fitzgerald et al., 1999; Herrick-Davis et al., 1999; Niswender et al., 1999). Distinct patterns of RNA editing of the 5-HT_{2C} receptor gene have been linked to depression and suicide (Gurevich et al., 2002; Niswender et al., 2001) and to schizophrenia (Sodhi et al., 2001). Given that reduced 5-HT_{2C} receptor-mediated neurotransmission enhances the effects of cocaine, it could be speculated that distinct patterns of 5-HT_{2C} receptor isoforms might underlie individual differences in responsivity to cocaine and ethanol, and perhaps vulnerability to drug abuse. In this regard, it is interesting to note that 5-HT_{2C} receptor blockade also enhances the stimulant effects of two other recreationally used drugs, phencyclidine (Hutson et al., 2000) and methylenedioxymethamphetamine (MDMA) (Fletcher et al., 2002c). Viewed in this context, studies investigating the impact of 5-HT_{2C} receptor blockade on the expression of behavioural effects of other drugs of abuse are clearly warranted.

Acknowledgements

We would like to thank Drs. Andrew Grottick, Denise Tomkins, Bill Corrigall and Jim Martin for collaborating on various aspects of this work. PJF is supported by grants from the Canadian Institutes of Health Research. We would also like to thank Dr. Laurence Tecott for graciously allowing us to reproduce some of his work in Figs. 1 and 3.

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