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Effects of systemic 5-HT$_{1B}$ receptor compounds on ventral tegmental area intracranial self-stimulation thresholds in rats

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ABSTRACT

Serotonin 1B (5-HT$_{1B}$) receptors may play a role in regulating motivation and reward-related behaviours. To date, no studies have investigated the effects of the highly selective 5-HT$_{1B}$ receptor agonist CP 94253, on the reward model of ventral tegmental area intracranial self-stimulation. The current study investigated the hypothesis that 5-HT$_{1B}$ receptors play an inhibitory role in ventral tegmental area ICSS. Using Sprague–Dawley rats, the effects of the selective 5-HT$_{1B}$ receptor agonist CP 94253 (0–5.0 mg/kg) and the 5-HT$_{1B/1D}$ receptor antagonist GR 127935 (10.0 mg/kg) were investigated in rats trained to respond for ventral tegmental area ICSS; results were compared using rate-frequency threshold analysis. The highest dose of CP 94253 (5.0 mg/kg) tested in ventral tegmental area ICSS produced an increase in rate-frequency thresholds without affecting maximal response rates. This effect was attenuated by GR 127935 which did not show any effects when administered alone. These results suggest that 5-HT$_{1B}$ receptors play an inhibitory role in regulating ventral tegmental area ICSS.

1. Introduction

Interactions between serotonin and dopamine have received increased attention in the context of regulating cognitive, motor and emotional functions (Alex and Pehek, 2007; Daw et al., 2002). The midbrain serotonergic system shows extensive connectivity with dopamine-containing areas of the brain, suggesting an important role for serotonin in the regulation of these cells (McBride et al., 1999; Van Bockstaele et al., 1993, 1994). Dopamine has long been associated with reward functions in the brain, though its exact role is still debated (Nicola et al., 2005; Robbins, 1997; Schultz, 1998; Tobler et al., 2005; Wyvell and Berridge, 2000). The importance of research in this area is underscored by evidence indicating that dopamine functioning and reward-associated behaviour are altered in schizophrenia, depression and drug abuse (Juckel et al., 2006; Kalivas and Volkow, 2005; Laviolette, 2007; Nestler and Carlezon, 2006; Wise, 2002). Place conditioning, self-administration and intracranial self-stimulation (ICSS) are used as animal models of reward-related behaviour (McBride et al., 1999; Tzschentke, 2007; Wise, 2002). Electrical stimulation of the ventral tegmental area drives self-stimulation behaviour in rats and results in dopamine release in the nucleus accumbens (Fiorino et al., 1993) — making ventral tegmental area ICSS a sensitive and directed model of reward-related behaviour.

Serotonin acts at a number of receptor subtypes (Hannon and Hoyer, 2008), some of which may play a role in dopamine regulation (Alex and Pehek, 2007). Serotonin 1B (5-HT$_{1B}$) receptors are found in a number of reward-related areas of the brain (Bruinvels et al., 1993; Sari et al., 1999) and their activation may increase basal (Boulenguez et al., 1998, 1996; Iyer and Bradberry, 1996; O'Dell and Parsons, 2004; Yan and Yan, 2001a; Yan et al., 2004) and drug-induced (O'Dell and Parsons, 2004; Parsons et al., 1999; Yan et al., 2005) dopamine release in the mesocorticolimbic system. Behaviourally, 5-HT$_{1B}$ receptor activation induces conditioned place aversion on its own (Cervo et al., 2002) but may enhance the reinforcing properties of cocaine in place conditioning and self-administration studies (Barot et al., 2007; Cervo et al., 2002; Neumaier et al., 2002; Parsons et al., 1998; Przegalinski et al., 2007). Stimulation of the 5-HT$_{1B}$ receptor may also decrease responding for ethanol (Maurel et al., 1999; Tomkins and O'Neill, 2000) and amphetamine (Fletcher et al., 2002; Fletcher and Korth, 1999) although overexpression of ventral tegmental area 5-HT$_{1B}$ receptors may result in increased ethanol self-administration (Hoplight et al., 2006).

At least one study has suggested a role for the 5-HT$_{1B}$ receptor in ICSS, demonstrating decreased reward (measured by increases in lateral hypothalamic current thresholds) following systemic administration of the 5-HT$_{1A/1B/1D/2C}$ mixed agonist RU 24969 and subsequent attenuation by the 5-HT$_{1B/1D}$ receptor antagonist GR 127935. This same study also found that RU 24969 attenuated the threshold-reducing (reward-enhancing) effects of cocaine (Harrison et al., 1999). Together, these studies suggest that 5-HT$_{1B}$ receptor activation may alter the reinforcing effects of drugs of abuse and inhibit reward-

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related behaviours. The present study examined the effects of the selective 5-HT_{1B} receptor agonist CP 94253 and 5-$HT_{1B/1D}$ receptor antagonist GR 127935 in ventral tegmental area ICSS. It was hypothesized that 5-HT_{1B} receptor activation would result in increased ventral tegmental area ICSS frequency thresholds while 5-HT_{1B} receptor antagonism would not affect ventral tegmental area ICSS behaviour.

2. Materials and methods

2.1. Subjects

Fourteen male Sprague–Dawley rats (Health Sciences Laboratory Animal Services, University of Alberta) weighing 200–300 g were housed individually in standard Plexiglas laboratory cages at 20 °C and 50% humidity, with a 12-hour light/dark cycle with food and water freely available. All apparatus were cleaned between animals with diluted (1:6) ammonia-based window cleaner (No Name® Glass Cleaner with ammonia). The care and use of animals were in accordance with guidelines of the University of Alberta Health Sciences Animal Welfare Committee and the Canadian Council on Animal Care.

2.2. Drugs

The 5-HT_{1B} receptor agonist CP 94253·HCl [5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-pyrrolo[3,2-b]pyridine hydrochloride] and the 5-$HT_{1B/1D}$ receptor antagonist GR 127935 · HCl [N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methy l-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1′-biphenyl-4-carboxamide hydrochloride] were purchased from Tocris Cookson Inc. (Ellisville, MO, USA). All compounds were dissolved in double-distilled water and were administered subcutaneously in a volume of 1.0 ml/kg. CP 94253 was administered 20 min prior to testing; GR 127935 was administered 40 min prior to testing. All drug doses are expressed as free-base.

2.3. Intracranial self-stimulation (ICSS)

Using a previously described procedure (Greenshaw, 1993), each animal was implanted with a stainless steel, monopolar, stimulating electrode (E363/2; tip diameter 200 μm; Plastics One Ltd., Roanoke, VA) directed to the ventral tegmental area. A large silver electrode in the skull served as the relative ground. Stereotaxic coordinates were [mm]: ventral tegmental area — AP+2.6, L+0.5, V+1.8 from inter-aural zero, with the incisor bar set at 2.4 mm below the inter-aural line (Paxinos and Watson, 1998). These coordinates were interpolated from the target site for angles of 20° lateral and 20° anterior (Greenshaw, 1997). Electrode placements were verified at the end of the experiment by microscopic inspection of flash-frozen, cresyl violet stained, coronal brain sections (40 μm). Flash-freezing was achieved using isopentane cooled on dry ice. Only animals with ventral tegmental area placements were included in the analysis.

Animals in both the CP 94253 dose response experiment (n=11) and CP 942543+GR 127935 experiment (n=8) were trained in ICSS using monopolar stimulation of the ventral tegmental area provided from constant current DC stimulators (cathodal monophasic pulse width of 200 ms; initial training frequency of 100 Hz; train length of 1 s) connected to each animal via a gold-track slip ring. Between pulses the active electrode and indifferent electrode were connected through a resistor to cancel any effects of electrode polarisation (Greenshaw, 1986). The apparatus and rate-frequency analysis (Gallistel and Karras, 1984) were as described by Ivanova and Greenshaw (1997). With this procedure, M50 is the threshold frequency at which half-maximal response rates occur (i.e. rate-frequency threshold); RMAX is the maximal rate of responding in a session. While M50 is a measure of reward sensitivity (which is dissociable from non-specific changes in behaviour), RMAX is a measure of response performance (see Gallistel and Karras, 1984; Greenshaw and Wishart, 1987). Animals received a randomized counterbalanced sequence of treatments with 3 days of baseline frequency testing between each treatment. The dose chosen for GR 1279835 (10.0 mg/kg) was based on prior behavioural studies and pilot study data (Cervo et al., 2002; Hayes et al., 2006; Maurel et al., 1998). To minimize the use of animals, animals with stable implants and ICSS behaviour at the end of the dose response experiment were used in the CP 94253+GR 127935 experiment.

2.4. Statistical analysis

Experimental effects in the ICSS dose response experiment were determined using one-way repeated measures ANOVA followed by Newman–Keuls post hoc tests (α=0.05). Experimental effects in the CP 94253+GR 127935 ICSS experiment were determined using two-way repeated measures ANOVA. Greenhouse–Geisser corrected degrees of freedom are used as a conservative estimate of the F-

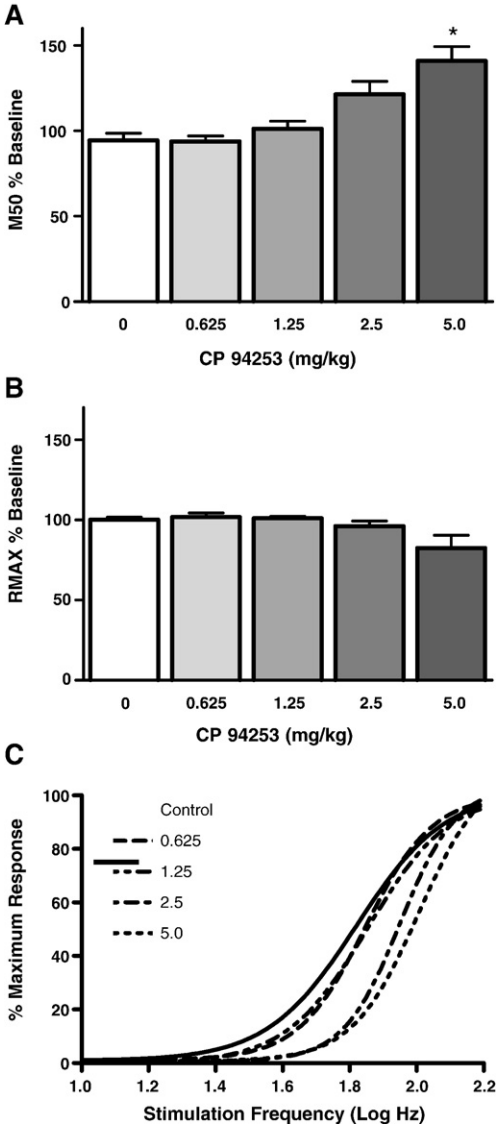

Fig. 1. A–C. Effects of CP 94253 (0–5.0 mg/kg) on rate-frequency thresholds (M50 values) and maximal response rates (RMAX values) for ventral tegmental area ICSS. (A) The highest dose of CP 94253 tested (5.0 mg/kg) produced a significant increase in M50 values; (B) without affecting RMAX values. (C) Group-averaged rate-frequency regression curves are included to illustrate the dose-dependent rightward shift in M50 seen with CP 94253 (indicating a decrease in reward). Data shown are means±S.E.M. *Significant at P<0.05 following Newman–Keuls post hoc tests.

ratio. All ICSS data are presented as a percentage of average baseline performance of each animal. Statistical analyses for all experiments were completed using statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Effects of CP 94253 on ICSS

Analysis following systemic administration of CP 94253 (0–5.0 mg/kg) revealed significant main effects for both M50 thresholds [Fig. 1A; $F(3, 26)=11.218$, $P<0.05$] and RMAX values [Fig. 1B; $F(2, 16)=4.136$, $P<0.05$]. Further analysis using Newman–Keuls post hoc tests ($\alpha=0.05$) revealed that only the highest dose (5.0 mg/kg) produced a significant increase in M50 thresholds compared to control (Fig. 1A) and that none of the doses resulted in significant changes in RMAX values (Fig. 1B). Given the appearance of motor effects at the highest dose of CP 94253, the non-transformed (raw) RMAX data were also analysed; no RMAX effects were noted (results not shown). Group-averaged rate-frequency regression curves are included to illustrate the dose-dependent rightward shift in M50 seen with CP 94253 (indicating a decrease in reward) (Fig. 1C).

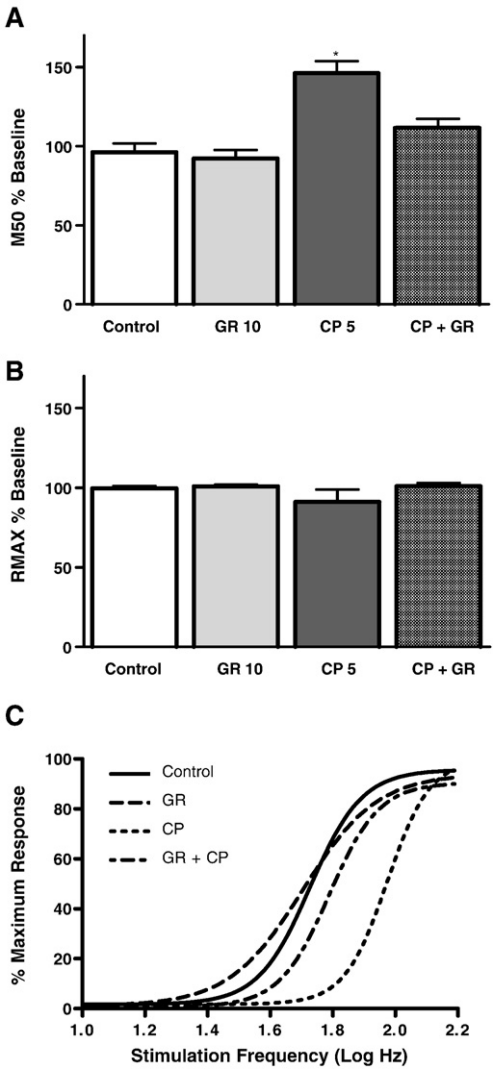

Fig. 2. A–C. Effects of CP 94253 (5.0 mg/kg) and GR 127935 (10.0 mg/kg) on rate-frequency thresholds (M50 values) and maximal response rates (RMAX values) for ventral tegmental area ICSS. (A) The highest dose of CP 94253 tested (5.0 mg/kg) produced a significant increase in M50 values, while GR 127935 had no effect on M50 values. The effects of CP 94253 on frequency thresholds were significantly decreased by GR 127935. (B) None of the treatments had significant effects on RMAX. (C) Group-averaged rate-frequency regression curves are included to further contrast the rightward shift in M50 seen with CP 94253 (indicating a decrease in reward) to all other treatments, which are similar to control (animals receiving two vehicle injections). Data shown are means ± S.E.M. *Significant at $P<0.05$ following Newman–Keuls post hoc tests.

3.2. Effects of CP 94253 and GR 127935 on ICSS

To further characterize the 5-HT_{1B} receptor-related behavioural component of CP 94253, the effects of the 5-$HT_{1B/1D}$ receptor antagonist GR 127935 (10.0 mg/kg), alone and in combination with CP 94253 (5.0 mg/kg), were investigated (Fig. 2A and B). A main effect of CP 94253 was seen with M50 thresholds [Fig. 2A; $F(1, 7)=44.11$, $P<0.05$] though not with RMAX values [Fig. 2B; $F(1, 7)=1.15$, $P>0.05$]. A main effect of GR 127935 was seen with M50 [$F(1, 7)=17.08$, $P<0.05$] though not with RMAX values [$F(1, 7)=1.39$, $P>0.05$]. An interaction was seen for M50 [$F(1, 7)=6.24$, $P<0.05$] though not for RMAX values [$F(1, 7)=0.88$, $P>0.05$]. Newman–Keuls post hoc tests revealed that the 5.0 mg/kg dose of CP 94253 produced a significant increase in M50 values compared to all other treatments. Group-averaged rate-frequency regression curves are included to further contrast the rightward shift in M50 seen with CP 94253 (indicating a decrease in reward) to the other treatments, which are similar to control (Fig. 2C). Only rats with electrode placements in the ventral tegmental area were included in the analysis. One animal was removed from the experiment due to a misplaced electrode, located in the substantia nigra, which produced large motor effects during training.

4. Discussion

The attenuation of the CP 94253-induced (5.0 mg/kg) increases in M50 thresholds by the 5-$HT_{1B/D}$ receptor antagonist GR 127935 (10 mg/kg) supports the hypothesis that the reward-decreasing effects of CP 94253 are 5-HT_{1B} receptor-mediated (Fig. 1A and C; Fig. 2A and C). These results are consistent with data demonstrating RU 24969-induced increases in lateral hypothalamic ICSS current thresholds (Harrison et al., 1999) and CP 94253-induced conditioned place aversion (Cervo et al., 2002). It has been suggested that rearing or vertical locomotor activity may be an indicator of appetitive arousal (Cabeza de Vaca et al., 2007; Swanson et al., 1997); in this context, the decrease in rearing behaviour seen following systemic administration of CP 94253 (Halford and Blundell, 1996; unpublished observations) is consistent with the idea that 5-HT_{1B} receptor activation may inhibit reward-related behaviour. The fact that GR 127935 alone had no effect on ICSS is consistent both with Harrison et al.'s (1999) work and the notion that reward-related behaviours do not appear to be under tonic control of the 5-HT_{1B} receptor (Cervo et al., 2002; Fletcher et al., 2002; Fletcher and Korth, 1999; Parsons et al., 1998; Tomkins and O'Neill, 2000).

The absence of motor performance effects (RMAX; Figs. 1B and 2B) suggests that CP 94253's effects are reward-related and not due to non-specific drug effects. Further supporting the notion that 5-HT_{1B} receptor stimulation does not affect motor performance, CP 94253 (Cervo et al., 2002; Halford and Blundell, 1996; Koe et al., 1992) and other ligands selective for the 5-HT_{1B} receptor (Martinez-Price and Geyer, 2002; Papla et al., 2002; Tatarczynska et al., 2005) may not alter horizontal locomotor activity. Notably, intra-subthalamic nucleus microinjections of the selective 5-HT_{1B} receptor agonist CP 93129 may increase locomotor activity, an exception not seen following global 5-HT_{1B} receptor activation and which may reflect local modulation of motor circuitry (Martinez-Price and Geyer, 2002).

5-HT_{1B} receptors are found mainly as presynaptic auto- and heteroreceptors throughout the brain (Sari, 2004; Sari et al., 1999). It seems unlikely that stimulation of 5-HT_{1B} autoreceptors is involved in the reward-decreasing effects of CP 94253 as stimulation of presynaptic 5-HT_{1A} autoreceptors, via systemic or intra-raphe injection

of 8-OH-DPAT, induces robust place preference (Fletcher et al., 1993; Papp and Willner, 1991; Shippenberg, 1991) and decreases M50 thresholds in ventral tegmental area ICSS (Ahn et al., 2005). However, the involvement of a decrease in serotonergic tone in areas other than those involved in 8-OH-DPAT's rewarding effects cannot be excluded.

As 5-HT_{1B} heteroreceptors are found on a number of cell types, including those containing GABA (Johnson et al., 1992; Parsons et al., 1999; Yan and Yan, 2001b; Yan et al., 2004), glutamate (Boeijinga and Boddeke, 1996) and acetylcholine (Cassel et al., 1995), it may be difficult to map the precise circuitry involved in reward-related behaviour. One current line of evidence suggests that 5-HT_{1B} heteroreceptors on GABA-containing cells may be involved in regulating dopamine- and reward-related behaviours (Johnson et al., 1992; Parsons et al., 1999; Stanford and Lacey, 1996). GABAergic cells within the ventral tegmental area can act as interneurons or project to the ventral striatum and other cortical regions (Steffensen et al., 1998). Dopaminergic cells are a major target of these GABA projections (Bayer and Pickel, 1991) and 5-HT_{1B} receptor stimulation can reduce ventral tegmental area GABA release (Yan and Yan, 2001b) and increase nucleus accumbens and ventral tegmental area dopamine release (Yan et al., 2004). Behavioural evidence indicates that blockade of $GABA_A$ receptors, using systemically administered picrotoxin, produces a conditioned place aversion (Acquas et al., 1989; File, 1986) and increases M50 thresholds in ventral tegmental area ICSS (Hayes et al., 2007). These results suggest that the inhibitory effects of 5-HT_{1B} receptor activation on reward may be mediated by a GABAergic mechanism.

Though 5-HT_{1B} receptor activation increases dopamine release throughout the mesocorticolimbic system (Boulenguez et al., 1998, 1996; Iyer and Bradberry, 1996; O'Dell and Parsons, 2004; Yan and Yan, 2001a; Yan et al., 2004), this change does not consistently lead to increases in reward-related behaviour. If changes in dopamine are related to the inhibition of ICSS behaviour seen in the present study, one possible explanation relies on data demonstrating dopamine release during exposure to aversive stimuli (Guarraci and Kapp, 1999; Salamone, 1994; Schultz, 2007). Another possibility is that the aversive effects of 5-HT_{1B} receptor stimulation are not reward-related but instead may be related to its anxiogenic effects (Benjamin et al., 1990; Lin and Parsons, 2002). This idea is supported by studies which have demonstrated conditioned place aversions or increases in ICSS M50 thresholds following administration of known anxiogenic compounds such as yohimbine or picrotoxin (Acquas et al., 1990; File, 1986; Hayes et al., 2007). It is important to note, however, that some anxiogenic compounds may not produce aversive behaviours in all behavioural tests (Alves et al., 2004; Kennett et al., 1989; Mosher et al., 2005) and that 5-HT_{1B} receptor stimulation does not always result in anxiety-related behaviours and may in fact be anxiolytic under some conditions (Bell et al., 1995; Chojnacka-Wojcik et al., 2005).

5-HT_{1B} receptors have been proposed to play a role in aggressive behaviour and psychiatric disorders that demonstrate altered mesocorticolimbic function and/or structure such as drug addiction, depression and anxiety (Alex and Pehek, 2007; Olivier and van Oorschot, 2005; Sari, 2004). The present results support the hypothesis that 5-HT_{1B} receptors are involved in the inhibition of ventral tegmental area ICSS without significant effects on motor performance. These findings suggest that 5-HT_{1B} receptors may be involved in regulating dopamine- and reward-related behaviours and may prove useful targets for the treatment of some psychiatric disorders.

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References

Acquas, E., Carboni, E., Leone, P., Di Chiara, G., 1989. SCH 23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade? Psychopharmacology 99, 151–155.
Acquas, E., Carboni, E., Garau, L., Di Chiara, G., 1990. Blockade of acquisition of drug-conditioned place aversion by 5HT3 antagonists. Psychopharmacology 100, 459–463.
Ahn, K.C., Pazderka-Robinson, H., Clements, R., Ashcroft, R., Ali, T., Morse, C., Greenshaw, A.J., 2005. Differential effects of intra-midbrain raphe and systemic 8-OH-DPAT on VTA self-stimulation thresholds in rats. Psychopharmacology 178, 381–388.
Alex, K.D., Pehek, E.A., 2007. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacol. Ther. 113, 296–320.
Alves, S.H., Pinheiro, G., Motta, V., Landeira-Fernandez, J., Cruz, A.P., 2004. Anxiogenic effects in the rat elevated plus-maze of 5-HT(2C) agonists into ventral but not dorsal hippocampus. Behav. Pharmacol. 15, 37–43.
Barot, S.K., Ferguson, S.M., Neumaier, J.F., 2007. 5-HT(1B) receptors in nucleus accumbens efferents enhance both rewarding and aversive effects of cocaine. Eur. J. Neurosci. 25, 3125–3131.
Bayer, V.E., Pickel, V.M., 1991. GABA-labeled terminals form proportionally more synapses with dopaminergic neurons containing low densities of tyrosine hydroxylase-immunoreactivity in rat ventral tegmental area. Brain Res. 559, 44–55.
Bell, R., Donaldson, C., Gracey, D., 1995. Differential effects of CGS 12066B and CP-94,253 on murine social and agonistic behaviour. Pharmacol. Biochem. Behav. 52, 7–16.
Benjamin, D., Lal, H., Meyerson, L.R., 1990. The effects of 5-HT1B characterizing agents in the mouse elevated plus-maze. Life Sci. 47, 195–203.
Boeijinga, P.H., Boddeke, H.W., 1996. Activation of 5-HT1B receptors suppresses low but not high frequency synaptic transmission in the rat subicular cortex in vitro. Brain Res. 721, 59–65.
Boulenguez, P., Rawlins, J.N., Chauveau, J., Joseph, M.H., Mitchell, S.N., Gray, J.A., 1996. Modulation of dopamine release in the nucleus accumbens by 5-HT1B agonists: involvement of the hippocampo-accumbens pathway. Neuropharmacology 35, 1521–1529.
Boulenguez, P., Peters, S.L., Mitchell, S.N., Chauveau, J., Gray, J.A., Joseph, M.H., 1998. Dopamine release in the nucleus accumbens and latent inhibition in the rat following microinjections of a 5-HT1B agonist into the dorsal subiculum: implications for schizophrenia. J. Psychopharmacol. (Oxford, England) 12, 258–267.
Bruinvels, A.T., Palacios, J.M., Hoyer, D., 1993. Autoradiographic characterisation and localisation of 5-HT1D compared to 5-HT1B binding sites in rat brain. Naunyn-Schmiedeberg's Arch. Pharmacol. 347, 569–582.
Cabeza de Vaca, S., Kannan, P., Pan, Y., Jiang, N., Sun, Y., Carr, K.D., 2007. The adenosine A2A receptor agonist, CGS-21680, blocks excessive rearing, acquisition of wheel running, and increases nucleus accumbens CREB phosphorylation in chronically food-restricted rats. Brain Res. 1142, 100–109.
Cassel, J.C., Jeltsch, H., Neufang, B., Lauth, D., Szabo, B., Jackisch, R., 1995. Downregulation of muscarinic- and 5-HT1B-mediated modulation of [3H]acetylcholine release in hippocampal slices of rats with fimbria–fornix lesions and intrahippocampal grafts of septal origin. Brain Res. 704, 153–166.
Cervo, L., Rozio, M., Ekalle-Soppo, C.B., Carnovali, F., Santangelo, E., Samanin, R., 2002. Stimulation of serotonin1B receptors induces conditioned place aversion and facilitates cocaine place conditioning in rats. Psychopharmacology 163, 142–150.
Chojnacka-Wojcik, E., Klodzinska, A., Tatarczynska, E., 2005. The anxiolytic-like effect of 5-HT1B receptor ligands in rats: a possible mechanism of action. J. Pharm. Pharmacol. 57, 253–257.
Daw, N.D., Kakade, S., Dayan, P., 2002. Opponent interactions between serotonin and dopamine. Neural Netw. 15, 603–616.
File, S.E., 1986. Aversive and appetitive properties of anxiogenic and anxiolytic agents. Behav. Brain Res. 21, 189–194.
Fiorino, D.F., Coury, A., Fibiger, H.C., Phillips, A.G., 1993. Electrical stimulation of reward sites in the ventral tegmental area increases dopamine transmission in the nucleus accumbens of the rat. Behav. Brain Res. 55, 131–141.
Fletcher, P.J., Korth, K.M., 1999. RU-24969 disrupts D-amphetamine self-administration and responding for conditioned reward via stimulation of 5-HT1B receptors. Behav. Pharmacol. 10, 183–193.
Fletcher, P.J., Ming, Z.H., Higgins, G.A., 1993. Conditioned place preference induced by microinjection of 8-OH-DPAT into the dorsal or median raphe nucleus. Psychopharmacology 113, 31–36.
Fletcher, P.J., Azampanah, A., Korth, K.M., 2002. Activation of 5-HT(1B) receptors in the nucleus accumbens reduces self-administration of amphetamine on a progressive ratio schedule. Pharmacol. Biochem. Behav. 71, 717–725.
Gallistel, C.R., Karras, D., 1984. Pimozide and amphetamine have opposing effects on the reward summation function. Pharmacol. Biochem. Behav. 20, 73–77.
Greenshaw, A.J. (Ed.), 1986. Electrical and Chemical Stimulation of Brain Tissue In Vivo. Humana Press, Clifton, New Jersey, pp. 233–277.
Greenshaw, A.J., 1993. Differential effects of ondansetron, haloperidol and clozapine on electrical self-stimulation of the ventral tegmental area. Behav. Pharmacol. 4, 479–485.
Greenshaw, A.J., 1997. A simple technique for determining stereotaxic coordinates for brain implantation of probes at rotated angles in one or two planes. J. Neurosci. Methods 78, 169–172.
Greenshaw, A.J., Wishart, T.B., 1987. Drug action and reward processes. In: Greenshaw, A.J., Dourish, C.T. (Eds.), Experimental Psychopharmacology: Concepts and Methods. Humana Press, Clifton, New Jersey, pp. 299–340.
Guarraci, F.A., Kapp, B.S., 1999. An electrophysiological characterization of ventral tegmental area dopaminergic neurons during differential Pavlovian fear conditioning in the awake rabbit. Behav. Brain Res. 99, 169–179.

Halford, J.C., Blundell, J.E., 1996. The 5-HT1B receptor agonist CP-94,253 reduces food intake and preserves the behavioural satiety sequence. Physiol. Behav. 60, 933–939.
Hannon, J., Hoyer, D., 2008. Molecular biology of 5-HT receptors. Behav. Brain Res. 195, 198–213.
Harrison, A.A., Parsons, L.H., Koob, G.F., Markou, A., 1999. RU 24969, a 5-HT1A/1B agonist, elevates brain stimulation reward thresholds: an effect reversed by GR 127935, a 5-HT1B/1D antagonist. Psychopharmacology 141, 242–250.
Hayes, D.J., Graham, D., Greenshaw, A.J., 2006. Serotonin 1B receptor activation decreases brain self-stimulation in rats: first evidence for a specific receptor role. Int. J. Neuropsychopharmacol. 9, S1.
Hayes, D.J., Hoang, J., Greenshaw, A.J., 2007. Effects of serotonin 2C and GABA A receptor ligands in brain stimulation reward and locomotor activity. Eur. Neuropsychopharmacol. 17, S278.
Hoplight, B.J., Sandygren, N.A., Neumaier, J.F., 2006. Increased expression of 5-HT1B receptors in rat nucleus accumbens via virally mediated gene transfer increases voluntary alcohol consumption. Alcohol (Fayetteville, N.Y) 38, 73–79.
Ivanova, S., Greenshaw, A.J., 1997. Nicotine-induced decreases in VTA electrical self-stimulation thresholds: blockade by haloperidol and mecamylamine but not scopolamine or ondansetron. Psychopharmacology 134, 187–192.
Iyer, R.N., Bradberry, C.W., 1996. Serotonin-mediated increase in prefrontal cortex dopamine release: pharmacological characterization. J. Pharmacol. Exp. Ther. 277, 40–47.
Johnson, S.W., Mercuri, N.B., North, R.A., 1992. 5-hydroxytryptamine1B receptors block the GABAB synaptic potential in rat dopamine neurons. J. Neurosci. 12, 2000–2006.
Juckel, G., Schlagenhauf, F., Koslowski, M., Filonov, D., Wustenberg, T., Villringer, A., Knutson, B., Kienast, T., Gallinat, J., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology 187, 222–228.
Kalivas, P.W., Volkow, N.D., 2005. The neural basis of addiction: a pathology of motivation and choice. Am. J. Psychiatry 162, 1403–1413.
Kennett, G.A., Whitton, P., Shah, K., Curzon, G., 1989. Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-HT1C receptor antagonists. Eur. J. Pharmacol. 164, 445–454.
Koe, B.K.N., J., A., Macor, J.E., Heym, J., 1992. Biochemical and behavioral studies of the 5-HT, a receptor agonist, CP-94,253. Drug Dev. Res. 26, 241–250.
Laviolette, S.R., 2007. Dopamine modulation of emotional processing in cortical and subcortical neural circuits: evidence for a final common pathway in schizophrenia? Schizophr. Bull. 33, 971–981.
Lin, D., Parsons, L.H., 2002. Anxiogenic-like effect of serotonin(1B) receptor stimulation in the rat elevated plus-maze. Pharmacol. Biochem. Behav. 71, 581–587.
Martinez-Price, D.L., Geyer, M.A., 2002. Subthalamic 5-HT(1A) and 5-HT(1B) receptor modulation of RU 24969-induced behavioral profile in rats. Pharmacol. Biochem. Behav. 71, 569–580.
Maurel, S., Schreiber, R., De Vry, J., 1998. Role of 5-HT1B, 5-HT2A and 5-HT2C receptors in the generalization of 5-HT receptor agonists to the ethanol cue in the rat. Behav. Pharm. 9, 337–343.
Maurel, S., De Vry, J., Schreiber, R., 1999. 5-HT receptor ligands differentially affect operant oral self-administration of ethanol in the rat. Eur. J. Pharmacol. 370, 217–223.
McBride, W.J., Murphy, J.M., Ikemoto, S., 1999. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav. Brain Res. 101, 129–152.
Mosher, T., Hayes, D., Greenshaw, A., 2005. Differential effects of 5-HT2C receptor ligands on place conditioning and locomotor activity in rats. Eur. J. Pharmacol. 515, 107–116.
Nestler, E.J., Carlezon Jr., W.A., 2006. The mesolimbic dopamine reward circuit in depression. Biol. Psychiatry 59, 1151–1159.
Neumaier, J.F., Vincow, E.S., Arvanitogiannis, A., Wise, R.A., Carlezon Jr., W.A., 2002. Elevated expression of 5-HT1B receptors in nucleus accumbens efferents sensitizes animals to cocaine. J. Neurosci. 22, 10856–10863.
Nicola, S.M., Taha, S.A., Kim, S.W., Fields, H.L., 2005. Nucleus accumbens dopamine release is necessary and sufficient to promote the behavioral response to reward-predictive cues. Neuroscience 135, 1025–1033.
O'Dell, L.E., Parsons, L.H., 2004. Serotonin1B receptors in the ventral tegmental area modulate cocaine-induced increases in nucleus accumbens dopamine levels. J. Pharmacol. Exp. Ther. 311, 711–719.
Olivier, B., van Oorschot, R., 2005. 5-HT1B receptors and aggression: a review. Eur. J. Pharmacol. 526, 207–217.
Papla, I., Filip, M., Przegalinski, E., 2002. Effect of intra-tegmental microinjections of 5-HT1B receptor ligands on the amphetamine-induced locomotor hyperactivity in rats. Pol. J. Pharmacol. 54, 351–357.
Papp, M., Willner, P., 1991. 8-OH-DPAT-induced place preference and place aversion: effects of PCPA and dopamine antagonists. Psychopharmacology 103, 99–102.
Parsons, L.H., Weiss, F., Koob, G.F., 1998. Serotonin1B receptor stimulation enhances cocaine reinforcement. J. Neurosci. 18, 10078–10089.
Parsons, L.H., Koob, G.F., Weiss, F., 1999. RU 24969, a 5-HT1B/1A receptor agonist, potentiates cocaine-induced increases in nucleus accumbens dopamine. Synapse (New York, N.Y) 32, 132–135.
Paxinos, G., Watson, C., 1998. The Rat Brain in Stereotaxic Coordinates, 4th edn. Academic Press, San Diego, USA.
Przegalinski, E., Golda, A., Frankowska, M., Zaniewska, M., Filip, M., 2007. Effects of serotonin 5-HT1B receptor ligands on the cocaine- and food-maintained self-administration in rats. Eur. J. Pharmacol. 559, 165–172.
Robbins, T.W., 1997. Arousal systems and attentional processes. Biol. Psychol. 45, 57–71.
Salamone, J.D., 1994. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. Behav. Brain Res. 61, 117–133.
Sari, Y., 2004. Serotonin1B receptors: from protein to physiological function and behavior. Neurosci. Biobehav. Rev. 28, 565–582.
Sari, Y., Miquel, M.C., Brisorgueil, M.J., Ruiz, G., Doucet, E., Hamon, M., Verge, D., 1999. Cellular and subcellular localization of 5-hydroxytryptamine1B receptors in the rat central nervous system: immunocytochemical, autoradiographic and lesion studies. Neuroscience 88, 899–915.
Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27.
Schultz, W., 2007. Behavioral dopamine signals. Trends Neurosci. 30, 203–210.
Shippenberg, T.S., 1991. Conditioned reinforcing effects of 8-hydroxy-2-(di-N-propylamino) tetralin: involvement of 5-hydroxytryptamine 1A and D1 dopamine receptors. Neurosci. Lett. 121, 136–138.
Stanford, I.M., Lacey, M.G., 1996. Differential actions of serotonin, mediated by 5-HT1B and 5-HT2C receptors, on GABA-mediated synaptic input to rat substantia nigra pars reticulata neurons in vitro. J. Neurosci. 16, 7566–7573.
Steffensen, S.C., Svingos, A.L., Pickel, V.M., Henriksen, S.J., 1998. Electrophysiological characterization of GABAergic neurons in the ventral tegmental area. J. Neurosci. 18, 8003–8015.
Swanson, C.J., Heath, S., Stratford, T.R., Kelley, A.E., 1997. Differential behavioral responses to dopaminergic stimulation of nucleus accumbens subregions in the rat. Pharmacol. Biochem. Behav. 58, 933–945.
Tatarczynska, E., Antkiewicz-Michaluk, L., Klodzinska, A., Stachowicz, K., Chojnacka-Wojcik, E., 2005. Antidepressant-like effect of the selective 5-HT1B receptor agonist CP 94253: a possible mechanism of action. Eur. J. Pharmacol. 516, 46–50.
Tobler, P.N., Fiorillo, C.D., Schultz, W., 2005. Adaptive coding of reward value by dopamine neurons. Science 1642–1645 (New York, N.Y 307).
Tomkins, D.M., O'Neill, M.F., 2000. Effect of 5-HT(1B) receptor ligands on self-administration of ethanol in an operant procedure in rats. Pharmacol. Biochem. Behav. 66, 129–136.
Tzschentke, T.M., 2007. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict. Biol. 12, 227–462.
Van Bockstaele, E.J., Biswas, A., Pickel, V.M., 1993. Topography of serotonin neurons in the dorsal raphe nucleus that send axon collaterals to the rat prefrontal cortex and nucleus accumbens. Brain Res. 624, 188–198.
Van Bockstaele, E.J., Cestari, D.M., Pickel, V.M., 1994. Synaptic structure and connectivity of serotonin terminals in the ventral tegmental area: potential sites for modulation of mesolimbic dopamine neurons. Brain Res. 647, 307–322.
Wise, R.A., 2002. Brain reward circuitry: insights from unsensed incentives. Neuron 36, 229–240.
Wyvell, C.L., Berridge, K.C., 2000. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. J. Neurosci. 20, 8122–8130.
Yan, Q.S., Yan, S.E., 2001a. Activation of 5-HT(1B/1D) receptors in the mesolimbic dopamine system increases dopamine release from the nucleus accumbens: a microdialysis study. Eur. J. Pharmacol. 418, 55–64.
Yan, Q.S., Yan, S.E., 2001b. Serotonin-1B receptor-mediated inhibition of [(3)H]GABA release from rat ventral tegmental area slices. J. Neurochem. 79, 914–922.
Yan, Q.S., Zheng, S.Z., Yan, S.E., 2004. Involvement of 5-HT1B receptors within the ventral tegmental area in regulation of mesolimbic dopaminergic neuronal activity via GABA mechanisms: a study with dual-probe microdialysis. Brain Res. 1021, 82–91.
Yan, Q.S., Zheng, S.Z., Feng, M.J., Yan, S.E., 2005. Involvement of 5-HT1B receptors within the ventral tegmental area in ethanol-induced increases in mesolimbic dopaminergic transmission. Brain Res. 1060, 126–137.