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ORIGINAL INVESTIGATION

Effects of systemic and intra-nucleus accumbens 5-HT_{2C} receptor compounds on ventral tegmental area self-stimulation thresholds in rats

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Abstract
Rationale Serotonin 2C (5-HT_{2C}) receptors may play a role in regulating motivation and reward-related behaviours. To date, no studies have investigated the possible role of 5-HT_{2C} receptors in ventral tegmental area (VTA) intracranial self-stimulation (ICSS).
Objectives The current study investigated the hypotheses that 5-HT_{2C} receptors play an inhibitory role in VTA ICSS, and that 5-HT_{2C} receptors within the nucleus accumbens (NAc) shell may be involved.
Methods Male Sprague–Dawley rats were implanted with a VTA electrode and bilateral NAc shell cannulae for the experiment involving microinjections, and trained to respond for electrical self-stimulation. The systemic effects of the selective 5-HT_{2C} receptor agonist WAY 161503 (0–1.0 mg/kg), the 5-$HT_{1A/1B/2C}$ receptor agonist TFMPP (0.3 mg/kg) and the selective 5-HT_{2C} receptor antagonist SB 242084 (1.0 mg/kg) were compared using rate-frequency threshold analysis. Intra-NAc shell microinjections of WAY 161503 (0–1.5 μg/side) were investigated and compared to amphetamine (1.0 μg/side).
Results WAY 161503 (1.0 mg/kg) and TFMPP (0.3 mg/kg) significantly increased rate-frequency thresholds (M50 values) without altering maximal response rates (RMAX values). SB 242084 attenuated the effects of TFMPP; SB 242084 had no affect on M50 or RMAX values. Intra-NAc shell WAY 161503 had no effect on M50 or RMAX values; intra-NAc amphetamine decreased M50 values.
Conclusions These results suggest that 5-HT_{2C} receptors play an inhibitory role in regulating reward-related behaviour while 5-HT_{2C} receptor activation in the NAc shell did not appear to influence VTA ICSS behaviour under the present experimental conditions.

Keywords 5-HT_{2C} receptor · Rats · WAY 161503 · SB 242084 · TFMPP · Intracranial self-stimulation · Serotonin · Mesocorticolimbic · Dopamine · Reward

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Introduction

Activity of the mesocorticolimbic dopamine system is important for the regulation of motivation and reward-related behaviours (Wise 2004). Anatomical, pharmacological and behavioural data have all demonstrated the ventral tegmental area (VTA) and nucleus accumbens (NAc) as key brain areas involved in mediating natural and drug-induced reward (Ikemoto and Wise 2004; Kalivas and Volkow 2005), and this circuitry may be involved in depression, schizophrenia and drug abuse (Kalivas and Volkow 2005; Laviolette 2007; Nestler and Carlezon 2006). Though the exact role for dopaminergic cells is still under investigation, evidence indicates dopamine release in mesolimbic areas

may be associated with behavioural activation, reward valuation, prediction, incentive salience and conditioning (Nicola et al. 2005; Robbins 1997; Salamone et al. 2007; Tobler et al. 2005; Wyvell and Berridge 2000). Many of these findings are consistent with neuroimaging studies in humans (Cooper and Knutson 2008; Murray et al. 2008; O'Doherty 2004). For more information on the putative roles of mesolimbic dopamine, readers are referred to the recent special edition of Psychopharmacology (Dopamine—revised, 2007, 191(3)). Place conditioning, self-administration and intracranial self-stimulation (ICSS) are often used as animal models of reward-related behaviour (McBride et al. 1999; Tzschentke 2007; Wise 2002). Electrical stimulation of the VTA drives self-stimulation behaviour in rats and results in dopamine release in the NAc (Fiorino et al. 1993)—making VTA ICSS a sensitive and directed model of reward-related behaviour.

Serotonin (5-HT) is thought to play a role in the regulation of dopamine and reward-related behaviours (Benloucif et al. 1993; Hetey and Drescher 1986; Muramatsu et al. 1988). Previous studies have suggested both inhibitory and excitatory roles for 5-HT in ICSS behaviour (Broadbent and Greenshaw 1985; Poschel et al. 1974; Redgrave and Horrell 1976; Van Der Kooy et al. 1978) and these differential effects are likely related to the existence of many 5-HT receptor subtypes (Alex and Pehek 2007; Barnes and Sharp 1999). The 5-HT_{2C} receptor is expressed throughout the mesocorticolimbic system (Bubar and Cunningham 2007; Clemett et al. 2000) and is of interest as a potential target for antidepressants (Chanrion et al. 2007) and atypical antipsychotics (Reynolds et al. 2005). Studies have shown that 5-HT_{2C} receptor activation may inhibit the release of mesolimbic dopamine (Di Giovanni et al. 2000; Di Matteo et al. 1999). Behavioural studies generally agree with an inhibitory role for the 5-HT_{2C} receptor in reward-related behaviours. Activation of 5-HT_{2C} receptors attenuates nicotine-induced locomotion, food intake and self-administration (Grottick et al. 2001). Functional antagonism of the 5-HT_{2C} receptor also increases cocaine and ethanol responding in rodents (Fletcher et al. 2002; Rocha et al. 2002; Tomkins et al. 2002). While 5-HT_{2C} receptor compounds do not affect the expression of place conditioning on their own (Mosher et al. 2005), they may produce state-dependent place aversion conditioning (Mosher et al. 2006).

Due to the relatively recent availability of pharmacologically selective 5-HT_{2C} receptor compounds, few studies have investigated the role of the 5-HT_{2C} receptor in ICSS; compounds with 5-HT_2 receptor (5-$HT_{2A/B/C}$) activity have been used in some ICSS studies. Sinden and Atrens (1978) suggested a reward-enhancing effect for lateral hypothalamic ICSS following administration of the mixed agonist 5-methoxy-*NN*-dimethyltryptamine, while Stark et al. (1964) demonstrated that another mixed agonist, bromlysergic acid diethylamide, showed biphasic effects in dogs responding for hypothalamic ICSS. Studies using VTA ICSS have suggested a possible inhibitory, and antidepressant, role for 5-HT_2 receptors (Grottick et al. 1997; Moreau et al. 1996). All of these ICSS studies have been limited by the use of non-selective compounds as well as restricted measurements of reward—underscoring the need for more studies in this context.

This study tested the hypothesis that 5-HT_{2C} receptor activation would result in increases in VTA ICSS thresholds using systemic administration of the mixed 5-$HT_{1A/1B/2C}$ receptor agonist TFMPP (0.3 mg/kg), the selective 5-HT_{2C} receptor agonist WAY 161503 (0.3, 0.6, 1.0 mg/kg) and the selective 5-HT_{2C} receptor antagonist SB 242084 (1.0 mg/kg). WAY 161503 and SB 242084 were chosen for their high selectivity at the 5-HT_{2C} receptor (Kennett et al. 1997; Rosenzweig-Lipson et al. 2006; Schlag et al. 2004). TFMPP was chosen as many studies have suggested its behavioural effects to be 5-HT_{2C} receptor-mediated (Kennett and Curzon 1988b; Lucki et al. 1989; Mora et al. 1997). As the NAc shell has been identified as a potential site for the inhibition of 5-HT_{2C} receptor-related dopamine efflux (Navailles et al. 2006b), the hypothesis that 5-HT_{2C} receptors in the NAc shell are involved in regulating VTA ICSS behaviour was tested using bilateral microinjections of WAY 161503 (0–1.5 μg/side).

Materials and methods

Subjects

Twenty-nine 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-h light/dark cycle with food and water freely available. All apparatus were cleaned between experiments with individual 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.

Surgery and histology

Using a previously described procedure (Greenshaw 1993), each animal (n=9 for the WAY 161503 dose response experiment; n=11 for the TFMPP and SB 242084 experiment; n=9 for the intra-NAc WAY 161503 experiment) was implanted with a stainless steel, monopolar, stimulating

electrode (E363/2; tip diameter 200 μm; Plastics One Ltd., Roanoke, VA, USA) directed to the VTA. A large silver indifferent electrode in the skull served as the relative ground. Animals used for microinjection were also implanted with bilateral cannulae (22 gauge) directed to the shell of the NAc. Stereotaxic coordinates were [mm]: VTA–AP +2.6, L +0.4–0.5, V +1.8–2.2; NAc shell–AP +11.0, L +0.4, V +2.8, 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 an angle of 20°, 20° lateral and anterior for the VTA and 16° lateral for the NAc shell (Greenshaw 1997). The guide cannulae were placed 1 mm above the actual injection sites. Electrode and cannulae placements were verified at the end of the experiment by microscopic inspection of flash-frozen coronal brain sections (40 μm); flash freezing was achieved using isopentane cooled on dry ice. Only animals with VTA and NAc placements were included in the analysis.

Intracranial self-stimulation (ICSS)

Monopolar stimulation of the VTA was 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 were as described by Ivanova and Greenshaw (1997). With this procedure, M50 is the threshold frequency at which half-maximal response rates occur; 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). Group-averaged rate-frequency regression curves are used to illustrate the shifts in M50 thresholds.

Drugs

The 5-HT_{2C} receptor agonist WAY 161503·HCl [8,9-dichloro-2,3,4,4a-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5(6*H*)-one hydrochloride] and the 5-$HT_{1A/1B/2A/2B/2C}$ receptor agonist TFMPP·HCl [N-[3-(trifluoromethyl)phenyl] piperazine hydrochloride] were purchased from Tocris Cookson Inc. (Ellisville, MO, USA). The 5-HT_{2C} receptor antagonist SB 242084·2HCl [6-chloro-5-methyl-1-[[2-(2-methylpyrid-3-yloxy)pyrid-5-yl]carbamoyl]indoline dihydrochloride hydrate] was purchased from Sigma Chemical Company (St. Louis, MO, USA). (+)-α-Methylphenethylamine (amphetamine) sulphate was purchased from Health and Welfare Canada. TFMPP was dissolved in 0.9% saline; all other compounds were dissolved in double-distilled water. All compounds were administered in a volume of 1.0 ml/kg. WAY 161503 (0–1 mg/kg) and TFMPP (0.3 mg/kg) were administered subcutaneously, 10 min prior to testing; SB 242084 (1.0 mg/kg) was administered intraperitoneally 30 min prior to testing. Artificial cerebrospinal fluid was freshly prepared (Elliott and Lewis 1950) and drug solutions made daily (pH 6.0–7.0). All drug doses are expressed as free base.

Microinjection of drugs

Rats with bilateral cannulae in the NAc shell received a counterbalanced sequence of five treatments: artificial cerebrospinal fluid (CSF), WAY 161503 (0–1.5 μg/side) and amphetamine (1.0 μg/side), with at least 3 days between each microinjection. Each intra-NAc injection was administered in a total volume of 0.5 μl at a pump-controlled rate of 0.2 μl per minute (Beehive controller, Bioanalytical Systems, Inc.) and the injection cannulae remained in place for a further minute to allow for drug absorption. Immediately following each set of microinjections, each animal was tested for VTA self-stimulation. The highest dose of WAY 161503 chosen was based on its maximal solubility in water.

Statistical analysis

All effects of treatments were assessed using repeated measures analysis of variance (ANOVA) followed by Newman–Keuls post hoc tests (α=0.05) where appropriate. All data are presented as a percentage of average baseline performance of each animal. Statistical analyses were completed using statistical software (SPSS Inc., Chicago, IL, USA).

Results

Effects of systemic 5-HT_{2C} receptor agonist WAY 161503

Systemic administration of the selective 5-HT_{2C} receptor agonist WAY 161503 (0.3, 0.6, 1.0 mg/kg) resulted in a main effect for M50 thresholds [Fig. 1a, $F(2, 13)=7.719$, $p<0.05$] and a main effect for RMAX values [Fig. 1b, $F(2, 15)=4.764$, $p<0.05$]. Further analysis with Newman–Keuls revealed that the highest dose of WAY 161503 (1.0 mg/kg) produced a significant increase in M50 values (Fig. 1a); no dose affected RMAX values (Fig. 1b). Group-averaged rate-frequency regression curves are included to illustrate the dose-dependent rightward shift in M50 seen with WAY 161503 (indicating a decrease in reward) (Fig. 1c).

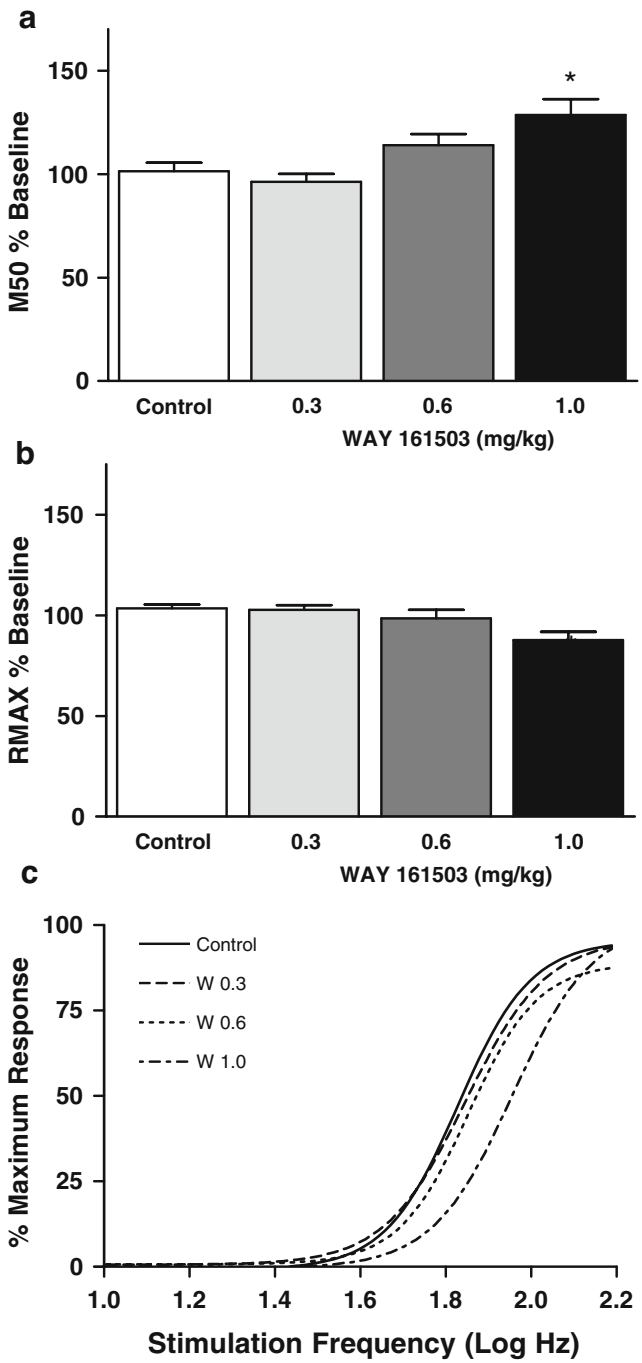


Fig. 1 **a**–**c** The effects of WAY 161503 (*W*; 0–1.0 mg/kg) on **a** rate-frequency thresholds (M50 values) and **b** maximal response rates (RMAX values) for VTA ICSS. **c** Group-averaged rate-frequency regression curves are included to illustrate the shifts in M50. Data shown are means±SEM expressed as a percentage of baseline performance. *Denotes significance from control at $p<0.05$ following Newman–Keuls post hoc tests

Effects of systemic TFMPP attenuated by SB 242084

Based on pilot data in our lab indicating significant increases in M50 values without effects on RMAX values, the dose of 0.3 mg/kg of TFMPP was chosen for this study. Analysis of M50 values revealed a main effect of TFMPP [$F(1, 10)=16.328$, $p<0.05$] and SB 242084 [$F(1, 10)=11.173$, $p<0.05$] and an interaction between TFMPP and SB 242084 [Fig. 2a; $F(1, 10)=5.289$, $p<0.05$]. Newman–Keuls post hoc tests revealed that TFMPP produced a significant increase in M50 thresholds while SB 242084 blocked this effect, without having any effects on its own. None of the compounds showed significant changes in RMAX values (Fig. 2b). Group-averaged rate-frequency regression curves are included to illustrate the rightward shift in M50 seen with TFMPP (indicating a decrease in reward) and attenuation of TFMPP by SB 242084 (Fig. 2c).

Effects of intra-NAc shell WAY 161503

Intra-NAc shell microinjections of WAY 161503 (0.15, 0.5, 1.5 μg/side) showed no change in M50 (Fig. 3a) or RMAX values (Fig. 3b). The positive control amphetamine (1.0 μg/side) significantly decreased M50 values [Fig. 3a; $F(1, 8)=26.192$, $p<0.05$] without affecting RMAX values (Fig. 3b). Group-averaged rate-frequency regression curves are included to compare the leftward shift in M50 seen with amphetamine (indicating an increase in reward) to the absence of effects by WAY 161503 (Fig. 3c).

Only rats with electrode placements in the VTA and bilateral cannulae in the NAc shell were included in the analysis. Representative photomicrographs of VTA stimulation sites and NAc shell microinjection sites are seen in Fig. 4a and c, respectively. Histological locations of electrode terminal sites and NAc shell microinjection sites are represented in Fig. 4b and d, respectively.

Discussion

The increase in rate-frequency thresholds (i.e. M50 values) following systemically administered WAY 161503 and TFMPP (Figs. 1a and 2a, respectively), without significant effects on maximal response rates (RMAX; indicating no overall motor effects) (Figs. 1b and 2b, respectively), supports the hypothesis that 5-HT_{2C} receptor activation plays an inhibitory role in VTA ICSS behaviour. The attenuation of TFMPP's effects by the highly selective 5-HT_{2C} receptor antagonist, SB 242084, supports the notion that these effects are 5-HT_{2C} receptor mediated (Fig. 2a).

Systemic TFMPP has been shown to stimulate 5-HT release in the NAc (Baumann et al. 2005), while intra-VTA mCPP (a mixed 5-$HT_{1B/2C}$ receptor agonist) reduced the firing rate of dopamine cells in this region (Prisco et al. 1994). Though TFMPP and mCPP are mixed 5-HT receptor agonists with only modest 5-HT_{2C} receptor binding (Barnes and Sharp 1999; Berg et al. 1998), a number of studies have suggested that their behavioural effects are 5-HT_{2C} recep-

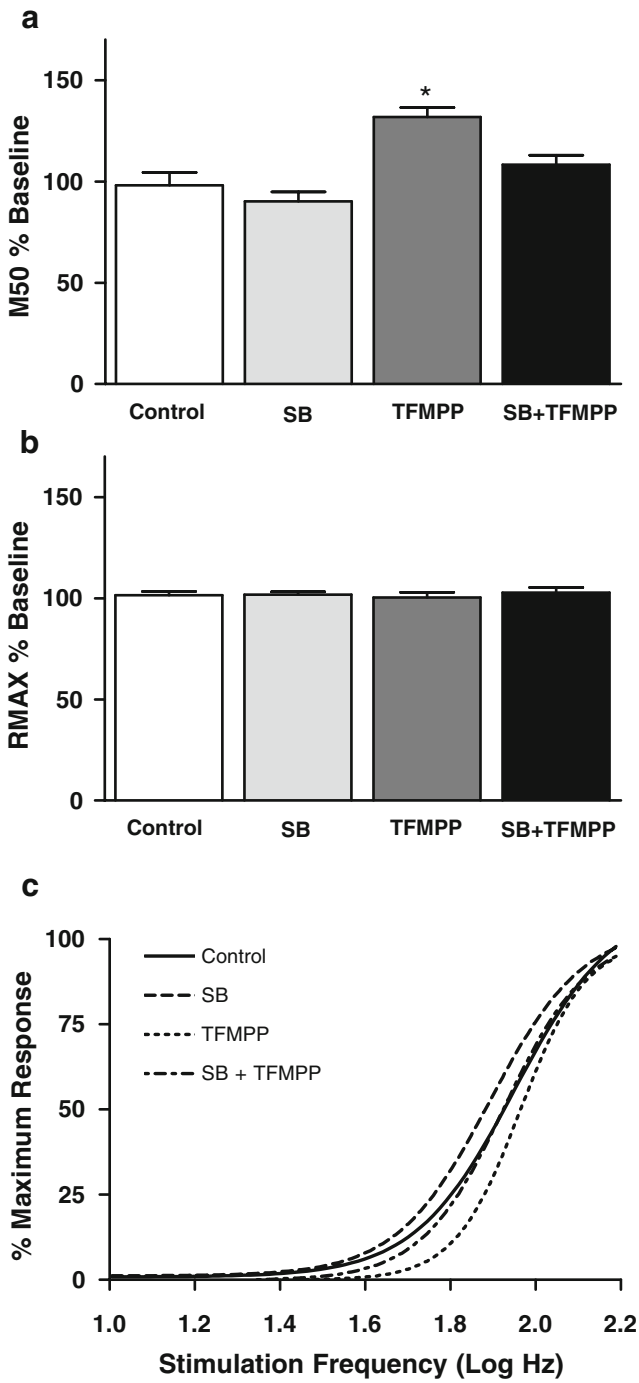


Fig. 2 **a**–**c** The effects of TFMPP (0.3 mg/kg) and SB 242084 (*SB*; 1.0 mg/kg) on **a** rate-frequency thresholds (M50 values) and **b** maximal response rates (RMAX values) for VTA ICSS. **c** Group-averaged rate-frequency regression curves are included to illustrate the shifts in M50. Data shown are means±SEM expressed as a percentage of baseline performance. *Denotes significance from control at $p<0.05$ following Newman–Keuls post hoc tests

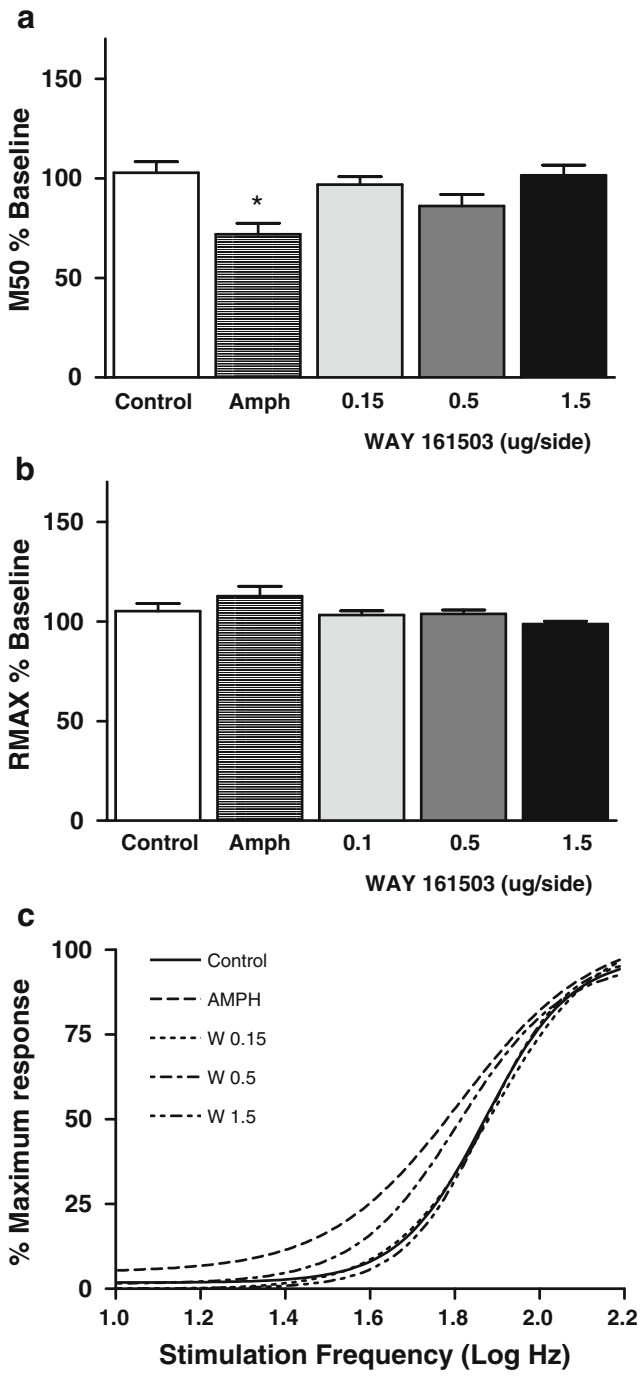


Fig. 3 **a**–**c** The effects of intra-NAc shell microinjections of WAY 161503 (*WAY*; 0–1.5 μg/side) and amphetamine (*AMPH*; 1.0 μg/side) compared to injections of artificial cerebrospinal fluid (*Control*) on **a** rate-frequency thresholds (M50 values) and **b** maximal response rates (RMAX values) for VTA ICSS. **c** Group-averaged rate-frequency regression curves are included to illustrate the shifts in M50. Data shown are means±SEM expressed as a percentage of baseline performance. *Denotes significance from control at $p<0.05$ following Newman–Keuls post hoc tests

tor-mediated (Dalton et al. 2006; Hayashi et al. 2005; Kennett and Curzon 1988b; Lucki et al. 1989; Mora et al. 1997). Alternately, some studies have identified behavioural effects for TFMPP that appear to be 5-HT_{1B} receptor

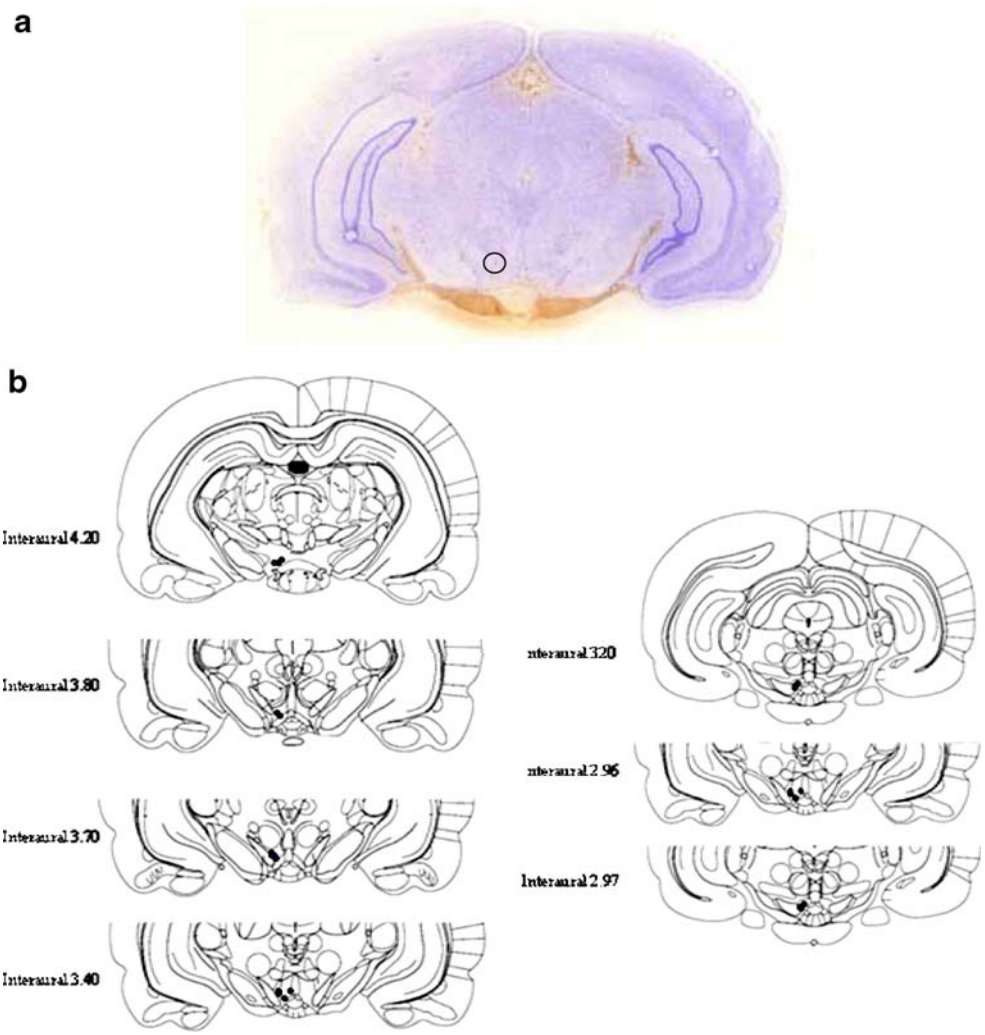


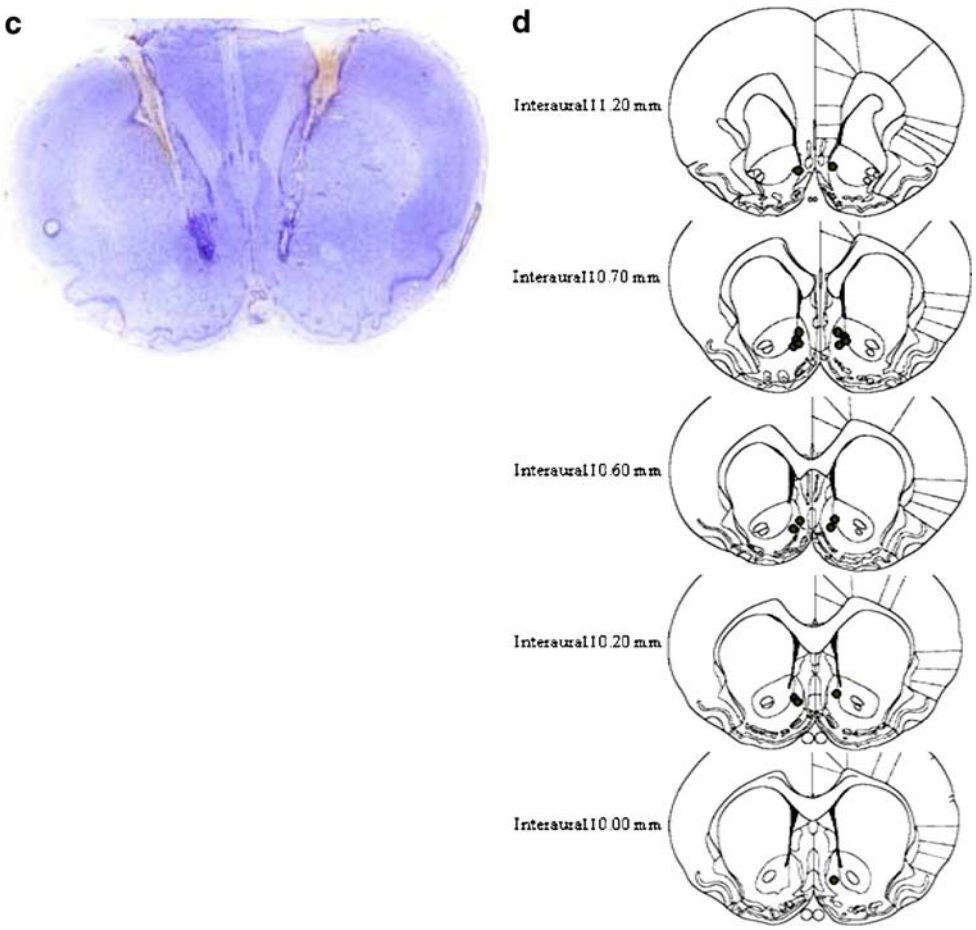
Fig. 4 **a**–**d** Histological verification of VTA and NAc shell sites. **a** Representative photomicrograph (*circle* identifies VTA electrode terminal) and **b** histological locations of VTA stimulation sites. **c** Representative photomicrograph and **d** histological locations of NAc shell microinjection sites. Brain diagrams from Paxinos and Watson (1998)

mediated (Kennett and Curzon 1988a; Rodriguez-Manzo et al. 2002; Schechter 1988). As activation of the 5-HT_{1B} receptor has also been shown to increase M50 values in lateral hypothalamic and VTA ICSS experiments (Harrison et al. 1999; Hayes et al. 2006), the present results demonstrating an attenuation of TFMPP's effects by SB 242084 provide evidence that TFMPP's effects on VTA ICSS are largely 5-HT_{2C} receptor-mediated. Nonetheless, it is important to note that there is some evidence for 5-HT_{1B} and 5-HT_{2C} receptor interactions (Clifton et al. 2003; Dalton et al. 2006; Nonogaki et al. 2007; Wang et al. 2008). SB 242084 had no effect on VTA ICSS (Fig. 2a) which is interesting as previous studies have shown that SB 242084 can increase the firing rates of VTA dopamine cells and increase dopamine release in the NAc (Di Giovanni et al. 2000; Di Matteo et al. 1999). In addition, SB 242084 has been shown to potentiate cocaine- and ethanol-induced self-administration in rats (Fletcher et al. 2002; Tomkins et al. 2002).

Increased M50 values in ICSS following the 1.0 mg/kg dose of WAY 161503 (Fig. 1a) are in agreement with other studies investigating 5-HT_{2C} receptor stimulation using behavioural models of motivation and reward as demonstrated in state-dependent place conditioning (Mosher et al. 2006) and cocaine-, nicotine-, ethanol- and food-maintained operant responding (Fletcher et al. 2004; Grottick et al. 2001; Grottick et al. 2000; Tomkins et al. 2002). Doses of WAY 161503 and TFMPP used in the present experiments (and in previous unpublished replications) do not affect RMAX values, while higher doses of WAY 161503 (Hayes and Greenshaw 2005) and TFMPP (results not shown) may eliminate all responding. These data are consistent with in vivo studies demonstrating that 5-HT_{2C} receptor agonists preferentially affect dopamine efflux in mesolimbic over nigrostriatal regions (Di Giovanni et al. 2000; Di Matteo et al. 1999), as these two regions are broadly associated with regulating motivated and sensorimotor aspects of behaviour, respectively (O'Doherty 2004; Salamone 1996; White 1986; Wise 2002).

WAY 161503 had no effect on VTA ICSS when microinjected into the NAc shell (Fig. 3a–c), in contrast to the well-established reward-enhancing effects of am-

Fig. 4 (continued)



phetamine (Colle and Wise 1988; Schaefer and Michael 1988). This suggests that NAc shell 5-HT_{2C} receptor activation may not play a primary role in regulating VTA ICSS behaviour. This was unexpected as VTA ICSS results in an increase of dopamine release in the NAc shell (Fiorino et al. 1993) and systemically administered 5-HT_{2C} receptor agonists decrease dopamine efflux in the NAc which is attenuated with systemically administered, intra-NAc, and intra-VTA, 5-HT_{2C} receptor antagonists (Di Giovanni et al. 2000; Di Matteo et al. 1999; Navailles et al. 2006b). In addition, 5-HT_{2C} receptor activation in the VTA inhibits cocaine-induced dopamine release while intra-NAc 5-HT_{2C} receptor activation produces biphasic effects on cocaine-induced dopamine release (Navailles et al. 2008). In a behavioural study, Filip and Cunningham (2002) showed that 5-HT_{2C} receptor activation in the NAc shell potentiated cocaine-induced increases in locomotion and increased the discriminability of subthreshold doses of cocaine.

Though intra-NAc shell administration of 5-HT_{2C} receptor agonists appears to potentiate cocaine-induced behaviour, studies to date have reported no effects on basal dopamine efflux or behaviour following intra-NAc 5-HT_{2C} receptor stimulation (Filip and Cunningham 2002; Navailles et al. 2008). Because of the relatively recent development of WAY 161503 as a selective ligand for the 5-HT_{2C} receptor (Rosenzweig-Lipson et al. 2006; Schlag et al. 2004), there are no other studies reporting the effects of intracranial administration and most studies have relied on other agonists to stimulate this receptor. As such, future replications of the present study may benefit from the use of other selective 5-HT_{2C} receptor agonists. Nonetheless, it remains that no 5-HT_{2C} receptor agonist to date, including WAY 161503—a compound that acts as full 5-HT_{2C} receptor agonist in stimulating 5-HT_{2C} receptor-coupled inositol phosphate formation and calcium mobilisation (Rosenzweig-Lipson et al. 2006) and whose activity in behavioural studies is currently believed to be 5-HT_{2C} receptor mediated (Cryan and Lucki 2000; Egashira et al. 2007; Hayes et al. 2008; Mosher et al. 2005)—demonstrates effects on its own following intra-NAc shell administration.

As the systemically administered 5-HT_{2C} receptor agonists produced increases in M50 thresholds and 5-HT_{2C} receptors appear to be located exclusively in the central nervous system (Barnes and Sharp 1999), reward-related circuitry may be involved in the mediation of these effects. The VTA, dorsal raphe and prefrontal cortex are good candidates in this regard—though others such as the

amygdala cannot be ruled out (Simmons et al. 2007)—as these areas support ICSS and contain 5-HT_{2C} receptors that alter dopamine efflux in the NAc (Broadbent and Greenshaw 1985; Bubar and Cunningham 2007; De Deurwaerdere and Spampinato 1999; Fiorino et al. 1993; Liu et al. 2007; Phillips and Fibiger 1978). Neurotransmitter interactions should also be taken into consideration as recent studies have identified 5-HT_{2C} receptors on GABA interneurons in the dorsal raphe (Serrats et al. 2005), and on GABA-containing cells within the VTA (Bubar and Cunningham 2007; Di Giovanni et al. 2001); it has been suggested that 5-HT_{2C} receptor activation decreases dopamine efflux indirectly through an inhibition of GABAergic cells (Boothman et al. 2006; Di Giovanni et al. 2001; Serrats et al. 2005).

5-HT_{2C} receptors have been proposed to play a role in many psychiatric disorders that demonstrate altered mesocorticolimbic function and/or structure. In this context, it is notable that some antipsychotic and antidepressant drugs may act upon 5-HT_{2C} receptors (Chanrion et al. 2007; Navailles et al. 2006a; Rauser et al. 2001); these findings, together with other reports of 5-HT_{2C} receptor involvement in appetitive behaviour and drug abuse, suggest that the 5-HT_{2C} receptor may be a useful target for the treatment of schizophrenia, depression and possibly drug abuse (Dremencov et al. 2005; Hill and Reynolds 2007; Nilsson 2006; Siuciak et al. 2007). In addition, given that mesolimbic dopamine may be involved in a diverse array of behavioural functions such as action selection, decision making, and Pavlovian conditioning (Bassareo et al. 2007; Nicola 2007; Pattij et al. 2007; Phillips et al. 2007), the 5-HT_{2C} receptor may also be of interest in these contexts. Indeed, at least one recent study has proposed a role for the 5-HT_{2C} receptor in decision making and impulsive behaviour (Fletcher et al. 2007). The present results provide support for the hypothesis that 5-HT_{2C} receptor activation regulates VTA ICSS behaviour. While the precise circuitry has not been mapped, it appears that 5-HT_{2C} receptor activation in the NAc shell does not play a primary role in the mediation of VTA ICSS under the present experimental conditions.

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