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## Intra-prefrontal 8-OH-DPAT and M100907 improve visuospatial attention and decrease impulsivity on the five-choice serial reaction time task in rats

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**Abstract** *Rationale:* The central serotonergic systems are a major target for drugs used to treat neuropsychiatric disorders such as depression and schizophrenia in which disruption of frontal cortex function has been implicated. However, it is not known precisely how serotonin (5-HT) modulates the medial prefrontal cortex (mPFC) to affect cognitive function and behaviour. *Objective:* To investigate the roles of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors in mPFC on performance of the five-choice serial reaction time task (5CSRT), which assesses visuospatial attention, impulsivity and motivational processes. *Methods:* Following training on the 5CSRT, rats were implanted with bilateral guide cannulae aimed at the mPFC. Rats received intra-mPFC infusions of either 8-OH-DPAT (10, 30 and 100 ng) or M100907 (30, 100 and 300 ng) according to a Latin square design. *Results:* Both 8-OH-DPAT and M100907 selectively enhanced accuracy of target detection. When the stimulus duration was shortened, infusions of 8-OH-DPAT continued to improve accuracy, whereas M100907 decreased premature responding and omissions, thus partly dissociating the effects of these two compounds. Similar effects were obtained following systemic administration of M100907 and 8-OH-DPAT. The effects of 8-OH-DPAT were blocked by the 5-HT<sub>1A</sub> antagonist WAY 100635, at a dose that itself had no significant effects on behaviour. *Conclusions:* These results indicate that modulation of 5-

HT function within the mPFC via distinct receptors can enhance performance on the 5CSRT. These findings suggest a mechanism by which serotonergic agents improve cognitive function, which may be relevant to their therapeutic benefit in the treatment of neuropsychiatric disorders.

**Keywords** 5-HT<sub>1A</sub> receptor · 5-HT<sub>2A</sub> receptor · Prefrontal cortex · Attention · Impulsivity · Schizophrenia

### Introduction

The serotonergic innervation of medial prefrontal cortex (mPFC) is increasingly recognised as a major target for antidepressant and antipsychotic agents (Blier and Demontigny 1987; Meltzer 1999; Millan 2000). Evidence from a variety of studies in experimental animals and humans implicates the mPFC in a number of cognitive and affective functions disrupted in depression and schizophrenia, including working memory, decision making and the regulation of attention (Goldman-Rakic 1997; Robbins 2000). However, the contribution of different serotonergic receptors in the mPFC to the regulation of such cognitive functions is unknown.

One way of measuring attentional processes in the rat is through use of the five-choice serial reaction time task (5CSRT) which provides somewhat independent measures of accuracy of discrimination, speed and impulsivity of responding, and motivation (Carli et al. 1983). Lesions to different regions of frontal cortex in the rat impair performance on the task, with damage to prelimbic cortex impairing accuracy and increasing response latencies, while damage to anterior cingulate cortex increases the frequency of premature responding, an index of impulsive behaviour (Muir et al. 1996; Christakou et al. 2001). Similarly, global 5-HT depletion also increases premature responding as well as reducing the number of trials omitted (Harrison et al. 1997a), indicating a role for

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serotonin in controlling behaviour sensitive to frontal damage.

Atypical antipsychotic agents such as clozapine show high levels of agonism at the 5-HT<sub>1A</sub> receptor and antagonism at the 5-HT<sub>2A</sub> receptor in addition to antagonism at D<sub>2</sub> receptors (Leysen et al. 1993; Newman-Tancredi et al. 1998). Such compounds differ from older antipsychotics not only in their reduced tendency to produce extrapyramidal side effects, but also in their treatment of cognitive dysfunction, including attentional deficits associated with schizophrenia (McGurk and Meltzer 2000; Meltzer and McGurk 1999; Meltzer et al. 1999). Local infusions of the D<sub>2</sub> antagonist sulpiride into the mPFC has no beneficial effects on performance of the 5CSRT (Granon et al. 2000), but the effects of local application of 5-HT<sub>1A</sub> agonists or 5-HT<sub>2A</sub> antagonists have not been assessed.

The serotonergic innervation of the neocortex arises predominantly from the dorsal raphe nucleus (DRN) over the median raphe nucleus (MRN) (Pazos and Palacios 1985). The mPFC is one of the few brain regions that sends a strong reciprocal projection back to the DRN (Hajos et al. 1998). Serotonergic lesions of the DRN lead to an increase in premature responding on the 5CSRT, but also increase the accuracy of performance, an effect which is not seen following serotonergic MRN lesions (Harrison et al. 1997b). Such dissociations suggest that the serotonergic modulation of cortical areas such as mPFC could serve to optimise performance on the 5CSRT.

Serotonergic 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors are found post-synaptically on non-serotonergic neurons in raphe projection areas such as mPFC (Verge et al. 1986; Kia et al. 1996; Barnes and Sharp 1999), but 5-HT<sub>1A</sub> receptors are also found pre-synaptically on the soma and dendrites of serotonergic cells in the raphe nuclei. Mechanisms of behavioural changes following systemic administration of selective 5-HT<sub>1A</sub> agonists such as 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) are therefore difficult to interpret. 8-OH-DPAT has a high affinity for the 5-HT<sub>1A</sub> receptor, compared with other 5-HT receptors, and exhibits low affinity for  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors and D<sub>2</sub> dopamine receptors (Peroutka 1986; Hoyer et al. 1994; Assie and Koek 2000).

Although it has previously been reported that systemic administration of 8-OH-DPAT leads to decrements in several aspects of performance on the 5CSRT (Carli and Samanin 2000), opposite behavioural effects have been noted depending on whether the drug was administered directly into the DRN or into their projection areas (File et al. 1996; Warburton et al. 1997; Meneses 1999).

Systemic administration of the 5-HT<sub>2A/2C</sub> receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) increases impulsivity and omissions and decreases accuracy on the 5CSRT (Koskinen et al. 2000). A selective 5-HT<sub>2A</sub> antagonist, such as M100907, which has a 300-fold greater affinity for 5-HT<sub>2A</sub> receptors over other receptor subtypes including 5-HT<sub>2C</sub> and  $\alpha_1$  receptors (Sorensen et al. 1993; Kehne et al. 1996), could therefore

enhance performance through decreasing impulsive responding and improving accuracy. Therefore, in this study, the contribution of post-synaptic 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors in mPFC to performance on the 5CSRT was investigated through intracerebral infusions of 8-OH-DPAT and M100907 in comparison with systemic administration of the two drugs.

## Materials and methods

### Subjects

Subjects were 26 male, Lister Hooded rats (Charles River, UK) weighing 300–320 g at the start of the experiment and were maintained on 14 g rat chow per day. Water was available ad libitum. Animals were housed in pairs under a reverse light cycle (lights on from 1900 hours until 0700 hours) and testing took place between 0900 hours and 1300 hours six days per week. All experiments were carried out in strict accordance with the UK Animals (Scientific Procedures) Act 1986.

### Behavioural apparatus

A detailed description of the nine-hole apparatus has been provided previously (Carli et al. 1983). Briefly, eight 25×25×25-cm nine-hole boxes (Paul Fray Ltd., UK) were used, each contained within a ventilated and sound-attenuated chamber and illuminated by a 3-W house light. Nine evenly spaced square holes (2.5×2.5×4 cm) containing a 3-W light were set into the curved aluminium wall at the rear of the box, 2 cm above the wire-grid floor. An infra-red beam located at the entrance to each hole enabled detection of nose-poke responses. Every other hole was blocked so that only five of the holes were accessible. A food magazine was located in the middle of the opposite wall into which food pellets could be dispensed (Noyes dustless pellets, 45 mg; Sandown Scientific, UK). An infra-red beam located horizontally across the entrance to the magazine allowed recording of entries into the magazine. The distance from the centre hole at the rear of the box and the magazine was 25 cm. The boxes were controlled by software written in BBC BASIC (Paul Fray Ltd, Cambridge, UK) running on an Acorn Archimedes series computer (Cambridge, UK).

### Behavioural training

Rats were trained on the 5CSRT to a stable level of performance as described previously (Granon et al. 2000). Briefly, subjects were trained to make nose-poke responses into holes upon brief illumination (0.5 s) of the light located therein. Animals received 5–6 sessions per week until a high level of stable performance was reached ( $\geq 80\%$  accuracy;  $\leq 20\%$  omissions). Each session consisted of 100 trials and lasted approximately 30 min. A correct response was rewarded with a food pellet, whereas an incorrect, premature or lack of response (omission) was punished by non-delivery of reward and a 5-s time-out period was imposed where the house light was extinguished. Repeated responding in any hole during the presentation of the light stimulus or during the limited hold period was classified as perseverative responding and, whilst monitored, was not punished.

### Surgery

Rats were anaesthetised with ketamine (Ketaset, 100 mg/kg i.m.; Vet Drug, Bury St, Edmunds, UK) and xylazine (Rompun 10 mg/kg i.m.; Vet Drug) and secured in a stereotaxic frame with the incisor bar set at –3.3 mm relative to the inter-aural line in a flat skull position. Bilateral 22-gauge, stainless-steel guide cannulae (Plastics

One, UK) were implanted in the prelimbic region of the prefrontal cortex (area Cg3; Zilles and Wree 1995) using standard stereotaxic techniques and secured to the skull using three bone screws and dental cement. The co-ordinates used were: anteroposterior +3.0 mm (from bregma), dorsolateral  $\pm$  0.7 mm dorsoventral -2.2 mm from dura (Paxinos and Watson 1998). Twenty-nine gauge obdurators flush with the end of the guide cannulae were inserted in the guide cannulae. The head assembly was protected by a plastic dust cap (Plastics One, UK). After surgery, animals were housed individually and had free access to food for 1 week prior to re-training on the 5CSRT.

#### Microinfusion procedure

Following re-establishment of stable post-operative performance over 15 sessions, rats were habituated to the infusion procedure with two mock infusions. Infusions were given on a 3-day cycle, starting initially with a baseline session. The following day the rats received a drug or vehicle infusion prior to testing on the 5CSRT. On the third day animals were not tested and remained in their home cages.

During infusions, the rats were gently restrained whilst the obdurators were removed and a 29-gauge bilateral injector extending 1.5 mm beyond the length of the guide cannulae was inserted. One microlitre of solution was then infused for 2 min. The injector was left in place for 1 min to allow the drug to diffuse in the local vicinity of the injector tip. The injector was then removed and the obdurator replaced. Rats were then put directly into the operant chambers and the 5CSRT started immediately. All infusions were given in the behavioural testing room, and the task was started for each animal as soon as it was placed in the test chamber.

#### *Experiment 1: effect of intra-mPFC infusions of 8-OH-DPAT and M100907 on performance of the 5CSRT*

One group of rats ( $n=14$ ) received infusions of vehicle (phosphate-buffered saline, PBS) or 8-OH-DPAT (10 ng/ $\mu$ l, 30 ng/ $\mu$ l or 100 ng/ $\mu$ l per side) according to a Latin Square design based on a previously reported study (Warburton et al. 1997). The second group ( $n=11$ ) received infusions of vehicle (0.9% saline) or M100907 (30 ng/ $\mu$ l, 100 ng/ $\mu$ l or 300 ng/ $\mu$ l per side) according to a Latin square design. The parameters for the task were identical to those used in training.

#### *Experiment 2: effect of intra-mPFC infusions of 8-OH-DPAT and M100907 on 5CSRT performance with short stimulus duration*

The behavioural task was altered to increase its attentional demands. The stimulus duration was shortened from 0.5 s to 0.125 s. Performance after vehicle infusions was compared with that after either one dose of 8-OH-DPAT ( $n=14$ , 100 ng/ $\mu$ l) or M100907 ( $n=11$ , 300 ng/ $\mu$ l) according to a counterbalanced design. Doses were selected that significantly affected performance in experiment 1. Animals were kept in the same groups as for experiment 1. In order to ascertain whether the effects of 8-OH-DPAT were due to activation of 5-HT<sub>1A</sub> receptors, the group was split into two sub-groups, with animals receiving either systemic injections of WAY100635 or PBS 10 min prior to each infusion.

#### *Experiment 3: effect of systemic 8-OH-DPAT and M100907 on 5CSRT performance*

After all the infusions had been completed, the effects of systemic injections of 8-OH-DPAT and M100907 were investigated. Animals were kept in the same groups as for experiment 1. At least 7 days elapsed between the last infusion and the start of the systemic drug study, during which time the rats were not tested.

Systemic injections were given in a separate room from that in which behavioural testing took place. Drug administration again followed a Latin square design. Animals receiving 8-OH-DPAT received two injections per drug session. The first injection of either PBS or WAY100635 (0.3 mg/kg) was given subcutaneously. Ten minutes after the first injection, subjects received an intraperitoneal injection of either PBS (1 mg/ml) or 8-OH-DPAT (0.03, 0.1 or 0.3 mg/kg). Animals receiving M100907 were given one intraperitoneal injection per drug session of saline, 0.03, 0.1 or 0.3 mg/kg M100907. At least 10 min after 8-OH-DPAT or M100907 administration, animals were carried through to the testing room, placed in the operant chambers and the task started.

#### Drugs

8-OH-DPAT (Sigma, UK) and WAY100635 (Wyeth Research, UK) were dissolved in PBS and made up fresh on each test day. M100907 (Solvay, Weesp, The Netherlands) was dissolved in saline and the pH adjusted to 6.25 using 0.1 M NaOH and 0.1 M HCl. A stock solution (0.3 mg/ml) was prepared and aliquoted before being frozen at -80°C. On each infusion day, one aliquot was defrosted and diluted to give the range of concentrations required. Concentrations of 8-OH-DPAT and M100907 were calculated as the salt form, and concentrations of WAY100635 calculated as the free base, in keeping with previous reported use (Gundlach et al. 1997; Warburton et al. 1997). Systemic injections of drug were given in a volume of 1 ml/kg.

#### Histology

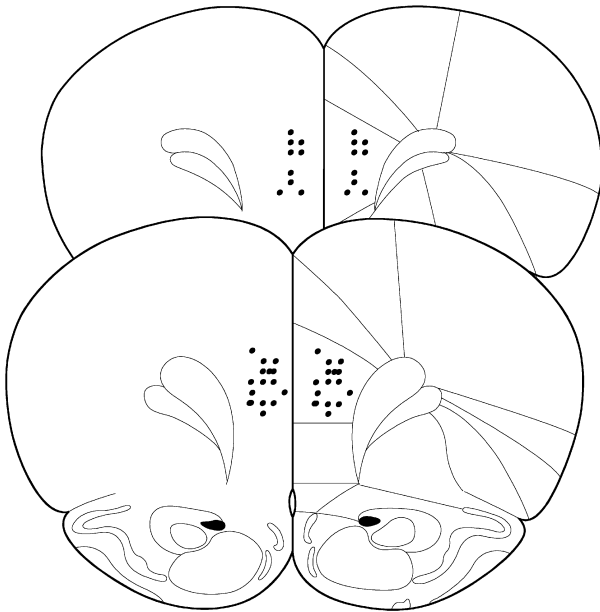
Following the completion of the experiment, subjects were anaesthetised with a lethal dose of sodium pentobarbitone (Euthal, 200 mg/ml, Genus Express, UK) and perfused transcardially with 0.01 M PBS followed by 4% paraformaldehyde. The brains were removed and post-fixed in paraformaldehyde. Prior to being cut, the brains were transferred to 20% sucrose in 0.2 M phosphate buffer and left overnight. Coronal sections were cut at 60  $\mu$ m on a freezing microtome and stained with Cresyl violet. Cannulae locations were mapped onto standardised sections of the rat brain (Paxinos and Watson 1998).

#### Data analyses

All analyses were conducted using SPSS for Windows (version 9.0; SPSS, Chicago, IL). Seven variables were analysed: the percentage of correct responses made (number of correct responses + number of incorrect responses/total correct and incorrect responses); percentage of responses omitted (number of omissions/total number of correct, incorrect and omitted responses); percentage of premature responses (number of premature responses/total number of trials), latency to make a correct response, latency to collect reward, perseverative responses and the total number of trials completed per session. Variables that were expressed as a percentage were subjected to an arcsine transformation in order to limit the effect of an artificially imposed ceiling (i.e. 100%). Baseline behavioural data were analysed using analysis of variance (ANOVA) with one within-subjects factor—day (seven daily test sessions). Results of drug studies were analysed using ANOVA with one repeated-measures factor—drug. If any analyses produced a significant effect of drug, mean values for individual doses were compared post-hoc to vehicle control values via paired sample *t*-tests.

## Results

All of the injector tips were located in the prelimbic cortex (Cg3, Zilles and Wree 1995) as shown in the schematic diagram (Fig. 1).



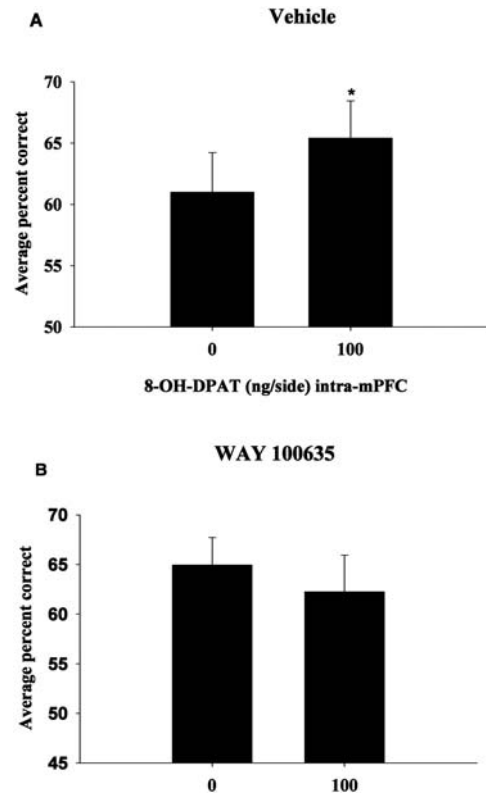
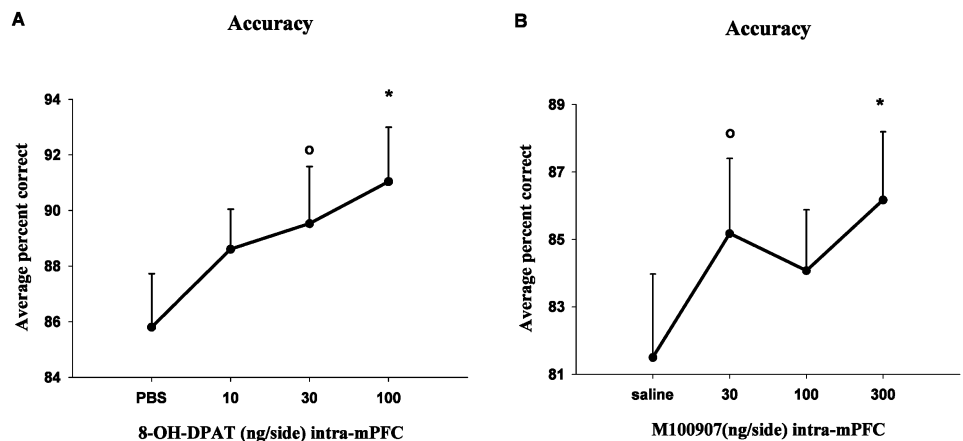
**Fig. 1** Schematic diagrams showing the location of injector tips in the prelimbic cortex (Paxinos and Watson 1998; *upper section* +3.7 mm, *lower section* +3.2 mm forward of bregma)

#### Effect of intra-mPFC infusions of 8-OH-DPAT and M100907 on performance of the 5CSRT

Infusions of 8-OH-DPAT into the prelimbic PFC produced a significant dose-dependent increase in the percentage of correct responses made as determined by a main effect of drug ( $F_{3,39}=3.454$ ,  $P<0.026$ ; Fig. 2A). The greatest effect was obtained with the highest dose, 100 ng/ $\mu$ l (paired samples  $t$ -tests comparing vehicle infusion with drug infusion:  $t=-2.518$ ,  $P<0.026$ ), whereas the intermediate dose produced a significant effect only at the  $P<0.10$  level ( $t=1.790$ ,  $P<0.097$ ). There were no significant changes in any of the other measures of performance, nor did the vehicle injection significantly affect performance relative to baseline.

Infusions of M100907 into prelimbic cortex also produced a selective increase in the percentage of correct

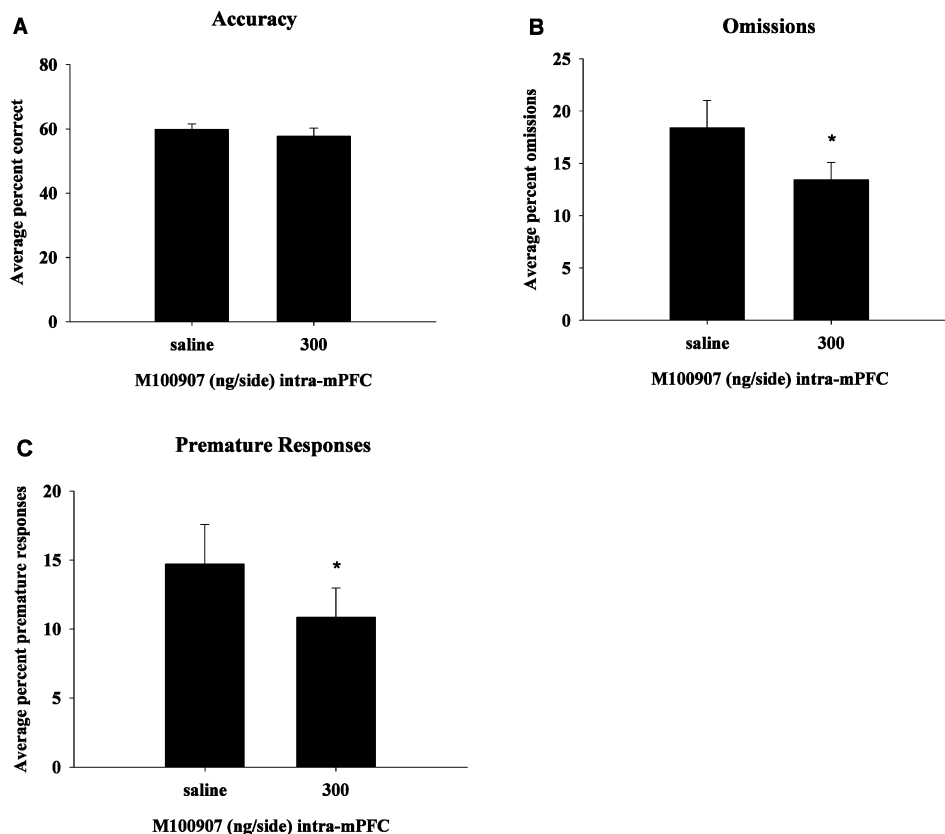
**Fig. 2** Effects of intra-medial prefrontal cortex (mPFC) infusions of phosphate-buffered saline (PBS), 10, 30 and 100 ng/ $\mu$ l per side 8-OH-DPAT (A) and saline 30, 100 and 300 ng/ $\mu$ l per side M100907 (B) on the percentage of correct responses on the standard five-choice serial reaction time task (5CSRT; stimulus duration =0.5 s). Values shown are mean and SEM. \* $P<0.05$  vs vehicle,  $oP<0.1$  vs vehicle



**Fig. 3** Effects of vehicle [phosphate-buffered saline (PBS), A] or WAY 100635 (0.3 mg/kg, B) pretreatment on the effects of intra-medial prefrontal cortex (mPFC) infusions of 8-OH-DPAT (0, 100 ng/ $\mu$ l per side) on the percentage of correct responses on the five-choice serial reaction time task (5CSRT) when the stimulus duration was reduced to 0.125 s. Values shown are mean and SEM. \* $P<0.05$  vs vehicle

responses made as indicated by a main effect of drug ( $F_{3,30}=3.021$ ,  $P<0.045$ , Fig. 2B). Again, the greatest increase in accuracy was found at the highest dose (paired samples  $t$ -test:  $t=3.590$ ,  $P<0.005$ ). No other behavioural variable was significantly affected, nor did the vehicle injection significantly affect performance relative to baseline.

**Fig. 4** Effects of intra-medial prefrontal cortex (mPFC) infusion of saline and 300 ng/ $\mu$ l per side M100907 on the percentage of premature responses (A), omissions (B) and correct responses (C) on the five-choice serial reaction time task (5CSRT) when the stimulus duration was reduced to 0.125 s. Values shown are mean and SEM. \* $P$ <0.05 vs vehicle



Effect of intra-mPFC infusions of 8-OH-DPAT and M100907 on 5CSRT performance with short stimulus durations

Decreasing the stimulus duration significantly decreased accuracy by approximately 40% ( $F_{1,10}=90.180$ ,  $P$ <0.0001), increased the latency to make a correct response by almost 20 ms ( $F_{1,10}=6.105$ ,  $P$ <0.033), increased omissions ( $F_{1,10}=5.673$ ,  $P$ <0.044) and also increased the number of premature responses made by over 50% ( $F_{1,10}=13.613$ ,  $P$ <0.004) relative to performance using a stimulus duration of 0.5 s.

Once again, infusions of 8-OH-DPAT (100 ng/ $\mu$ l) produced a small but significant increase in the percentage of correct choices made ( $F_{1,6}=7.797$ ,  $P$ <0.031; Fig. 3A), but did not significantly affect any other variable. Furthermore, this increase in accuracy was not seen in those animals pretreated with WAY100635 ( $F_{1,6}=1.140$ , N.S.), indicating that the 8-OH-DPAT-mediated enhancement of performance was due to a selective action at the 5-HT<sub>1A</sub> receptor (Fig. 3B). WAY 100635 by itself had no effect on any behavioural variable examined.

Administration of 300 ng/ $\mu$ l M100907 into the prelimbic cortex did not affect accuracy under this set of task parameters ( $F_{1,10}<1.6$ , N.S.; Fig. 4A). However, intra-cortical drug administration did reduce premature responding ( $F_{1,10}=6.084$ ,  $P$ <0.033, Fig. 4B) and decreased omissions ( $F_{1,10}=18.859$ ,  $P$ <0.001, Fig. 4C) relative to

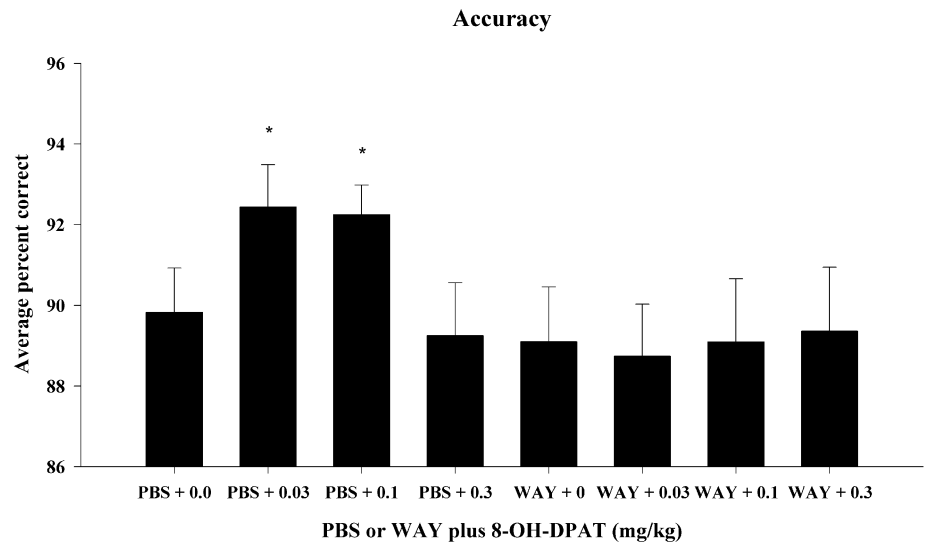
saline infusions. No other variable was significantly affected by M100907 administration, nor did the vehicle injection significantly affect performance relative to baseline.

Effect of systemic 8-OH-DPAT and M100907 on 5CSRT performance

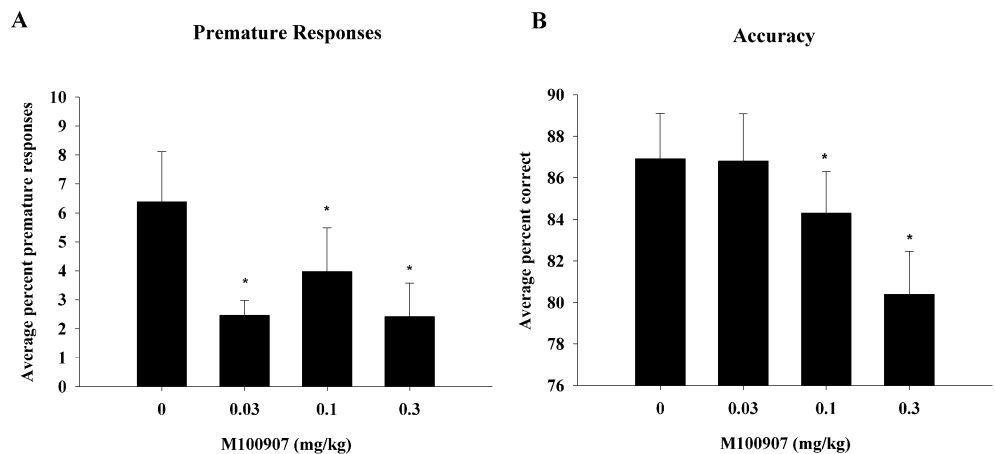
Systemic administration of the two lowest doses of 8-OH-DPAT (0.03 mg/kg and 0.1 mg/kg) produced a significant increase in the percentage of correct trials (Fig. 5), as determined by a main effect of drug ( $F_{7,35}=2.718$ ,  $P$ <0.023). Post-hoc  $t$ -tests revealed significant differences at dose levels of 0.03 mg/kg ( $t=-2.459$ ,  $P$ <0.030) and 0.1 mg/kg ( $t=-2.247$ ,  $P$ <0.044) relative to vehicle injections. This drug effect was absent when the animals were given WAY100635 prior to the injection of 8-OH-DPAT. WAY 100 635 itself had no effect on any behavioural measure tested. Furthermore, no effect was seen with the higher dose of 8-OH-DPAT (0.3 mg/kg).

All doses of M100907 tested significantly reduced premature responding as indicated by a main effect of drug ( $F_{3,30}=3.225$ ,  $P$ <0.041; Fig. 6) followed by paired sample  $t$ -tests comparing each injection against baseline to establish the source of the significant difference (0.03 mg/kg:  $t=-4.442$ ,  $P$ <0.002; 0.1 mg/kg:  $t=-3.616$ ,  $t=0.007$ ; 0.3 mg/kg:  $t=-4.593$ ,  $P$ <0.002).

**Fig. 5** Effects of systemic administration of phosphate-buffered saline (PBS) and 0.03, 0.1 and 0.3 mg/kg 8-OH-DPAT (i.p., 1 ml/kg) preceded by injections of either PBS or 0.3 mg/kg WAY100635 (s.c., 1 ml/kg) on the percentage of correct responses on the standard five-choice serial reaction time task (5CSRT; stimulus duration =0.5 s). Values shown are mean and SEM. \* $P$ <0.05 vs vehicle



**Fig. 6** Effects of i.p. injections of phosphate-buffered saline (PBS) and 0.03, 0.1 and 0.3 mg/kg M100907 (i.p., 1 ml/kg) on the percentage of premature responses (A) and correct responses (B) on the standard five-choice serial reaction time task (5CSRT; stimulus duration =0.5 s). Values shown are mean and SEM. \* $P$ <0.05 vs vehicle



However, there was also a significant main effect of drug on accuracy ( $F_{3,30}=3.760$ ,  $P<0.021$ ). In contrast to the effect of intra-mPFC administration, paired sample  $t$ -tests revealed that 0.3 mg/kg significantly reduced accuracy ( $t=-2.658$ ,  $P<0.024$ ). The higher doses also increased the latency to make a correct response, and the number of omissions made, although these effects fell short of significance (data not shown).

## Discussion

This investigation is the first to demonstrate enhanced performance of a task assessing visuospatial attention and impulsivity following direct administration of the selective 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT and the selective 5-HT<sub>2A</sub> antagonist M100907 into the mPFC. The effects of 8-OH-DPAT were blocked by administration of the selective 5-HT<sub>1A</sub> receptor antagonist WAY 100635, demonstrating that the effects of 8-OH-DPAT were due to selective activation of 5-HT<sub>1A</sub> receptors in the mPFC. Furthermore, the contributions of 5-HT<sub>1A</sub> and 5-

HT<sub>2A</sub> receptors in mPFC on task performance were dissociable. Although both drugs improved attentional performance, antagonism of 5-HT<sub>2A</sub> receptors had the additional effect of reducing high baseline levels of impulsive responding and decreasing omissions. These data demonstrate that serotonergic modulation of prefrontal cortical functioning via 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors can enhance attention and impulse control, a finding which could be relevant for the mechanism by which atypical antipsychotics relieve cognitive deficits in schizophrenia (Ichikawa and Meltzer 1999; Meltzer and McGurk 1999; Meltzer et al. 1999; McGurk and Meltzer 2000).

Converging lines of evidence implicate serotonergic systems in the regulation of different forms of impulsive behaviour (Linnoila et al. 1983; Soubrié 1986; Evenden 1999a, 1999b; Mobini et al. 2000), including impulsivity as assessed on the 5CSRT (Harrison et al. 1997a). Recent experiments using in vivo microdialysis in conjunction with performance of a simplified version of the 5CSRT have revealed a positive relationship between 5-HT release in the mPFC and impulsive responding (Dalley

et al. 2002). This finding is compatible with evidence that systemic administration of the 5-HT<sub>2A/2C</sub> agonist DOI increases premature responding on the 5CSRT (Koskinen et al. 2000; Koskinen and Sirvio 2001), whereas the 5-HT<sub>2A/2C</sub> antagonist ketanserin decreases premature responding following intra-mPFC and systemic administration (Ruotsalainen et al. 1997; Passetti et al. 2003). Therefore, the ability of M100907 to decrease impulsive responding may be due to a reduction in the tonic activation of 5-HT<sub>2A</sub> receptors in the mPFC.

However, other behavioural effects of M100907, such as improved accuracy, may result from the channelling of endogenous 5-HT towards other receptors such as the 5-HT<sub>1A</sub> or 5-HT<sub>2C</sub> subtypes. Improvements in accuracy were observed following intra-mPFC but not systemic doses of M100907. This discrepancy may be due to differences in the concentration of M100907 in the mPFC and other areas of the brain following the different routes of administration. The behavioural effects of intra-mPFC administration of selective agents at the 5-HT<sub>2C</sub> receptor are currently unknown but would be of considerable interest, especially in light of recent evidence implicating the 5-HT<sub>2C</sub> receptor in regulation of impulse control and cocaine self-administration (Fletcher et al. 2002; Rocha et al. 2002).

In addition to increasing premature responding, serotonergic lesions of the DRN also improve discriminative performance on the 5CSRT (Harrison et al. 1997b), presumably by reducing 5-HT function in certain forebrain regions. Systemic administration of 8-OH-DPAT, which also decreases forebrain 5-HT release in the cortex (Bonvento et al. 1992), improved accuracy, an effect that was antagonised by WAY100635 (present study). However, in a previous study, systemic 8-OH-DPAT has been reported to reduce accuracy on the 5CSRT, as well as increase omissions and premature responses (Carli and Samanin 2000). Although both studies used similar doses of 8-OH-DPAT, the different behavioural effects may be explained by a different route of administration (intra-peritoneal, present experiment; subcutaneous, Carli and Samanin 2000). Thus, following i.p. administration, brain concentrations of 8-OH-DPAT are reportedly lower than following subcutaneous administration (Fuller 1987; Perry and Fuller 1989). This phenomenon has been cited by other authors as a possible explanation for the often contradictory behavioural effects of 8-OH-DPAT (Cole 1994) and implies that 8-OH-DPAT may exhibit a biphasic dose–response function with respect to effects on discriminative accuracy.

Increases in accuracy were also seen in the present study following intra-mPFC infusions of 8-OH-DPAT, an effect which was again blocked by WAY100635, suggesting that activation of 5-HT<sub>1A</sub> receptors in the mPFC results in pharmacologically and behaviourally specific improvements in attentional performance. Of course, it remains possible that some or all of the behavioural effects of 8-OH-DPAT were mediated outside the mPFC due to diffusion of the drug from the infusion site. However, this explanation is at variance with evidence

from other studies showing dissociable behavioural effects of this compound when administered into closely neighbouring regions such as the DRN and MRN (File et al. 1996).

Effects of 5-HT<sub>2A</sub> receptor antagonists on attentional selection were predicted following reports of the disruptive effects of 5-HT<sub>2</sub> receptor agonists on the 5CSRT (Carli and Samanin 1992; Koskinen et al. 2000) and from the iontophoretic application of M100907 into primate prefrontal cortex during a working memory task (Williams et al. 2002). Although intra-mPFC M100907 reduced the spatial tuning of prefrontal pyramidal cells, the authors suggest that, under more realistic conditions where animals have to attend to a range of relevant and irrelevant stimuli, antagonism at the 5-HT<sub>2A</sub> receptor would potentially enhance performance by reducing distractibility. In contrast to the data collected here with M100907, a previous experiment found no effect on accuracy on the 5CSRT following intra-mPFC infusions of the 5-HT<sub>2A/2C</sub> receptor antagonist ketanserin (Passetti et al. 2003). This discrepancy may be due to a different spectrum of pharmacological activity, particularly since M100907 has only a limited affinity for the 5-HT<sub>2C</sub> receptor (Sorensen et al. 1993; Kehne et al. 1996).

There is strong evidence for a functional interaction between 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors. For example, administration of the 5-HT<sub>2A</sub> receptor antagonists ICI 180,809 and ritanserin potentiates the 5-HT behavioural syndrome produced by systemic administration of 8-OH-DPAT (Backus et al. 1990; Sharp et al. 1990), and 8-OH-DPAT is reported to inhibit head twitching behaviour induced by systemic administration of the 5-HT<sub>2A/2C</sub> agonist DOI (Berendsen and Broekkamp 1990; Darmani et al. 1990; Dursun and Handley 1993). Data gathered using electrophysiology and microiontophoresis indicate that 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors are co-localised on a population of pyramidal cells in PFC (Araneda and Andrade 1991). Whereas 5-HT<sub>2A</sub> receptor agonists depolarise the cell membrane, 5-HT<sub>1A</sub> agonists lead to hyperpolarisation. Intra-mPFC M100907 potentiates the decrease in firing rate of cortical pyramidal neurons observed after local 8-OH-DPAT administration, indicating that 5-HT<sub>1A</sub> agonists and 5-HT<sub>2A</sub> antagonists produce interactive effects on cellular excitability in this region (Ashby et al. 1994).

Electrophysiological and neuroanatomical data indicate that both 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors are involved in regulating a feedback projection from the mPFC to the DRN (Hajos et al. 1999; Casanovas et al. 1999) through a glutamate-dependent mechanism (Scruggs et al. 2000; Celada et al. 2001; Martin-Ruiz et al. 2001). Activation of 5-HT<sub>1A</sub> receptors or antagonism of 5-HT<sub>2A</sub> receptors in the mPFC is thought to decrease activity of serotonergic neurons in the DRN through this projection. As mentioned previously, lesions of the DRN produce a significant improvement in accuracy on the 5CSRT (Harrison et al. 1997b) as does intra-mPFC administration of 8-OH-DPAT and M100907 (present study), suggesting that downregulating DRN activity and thereby altering sero-

tonergic modulation of the frontal cortex could contribute to the drug-induced enhancement of attentional performance, potentially via interactions with the glutamatergic system (Aghajanian and Marek 1999a, 1999b).

In addition, substantial evidence now implicates the cortical cholinergic system in attentional processing (Everitt and Robbins 1997; Sarter and Bruno 2000), including 5CSRT performance (Muir et al. 1993, 1994; Passetti et al. 2000; Dalley et al. 2001; McGaughy et al. 2002), and numerous studies indicate that serotonin negatively modulates the cholinergic system in the central nervous system (Samanin 1978; Gillet et al. 1985; Maura et al. 1989; Bianchi et al. 1990; Siniscalchi et al. 1990). Systemic administration of 8-OH-DPAT increases mPFC acetylcholine (ACh) (Consolo et al. 1996; Ichikawa et al. 2002a), an effect which is not abolished by lesions of the serotonergic system, indicating that the increase in ACh is due to activation of post-synaptic 5-HT<sub>1A</sub> receptors (Consolo et al. 1996). Since post-synaptic 5-HT<sub>1A</sub> receptors do not appear to be present on cholinergic terminals (Quirion et al. 1985; Harel-Dupas et al. 1991), the increase in ACh release induced by 8-OH-DPAT is presumably mediated by a multisynaptic mechanism, possibly involving dopaminergic terminals in this region.

This hypothesis is consistent with evidence that the increase in mPFC ACh release following systemic 8-OH-DPAT administration is blocked by D<sub>1</sub> receptor antagonists, indicating a critical role for DA acting at D<sub>1</sub> receptors (Consolo et al. 1996), and also with reports that both systemic and intra-mPFC administration of 8-OH-DPAT increase mPFC levels of DA (Arborelius et al. 1993; Tanda et al. 1994; Gobert 1998; Sakaue et al. 2000), an effect which is potentiated by M100907 (Ichikawa et al. 2001). It is also compatible with evidence that systemic administration of D<sub>1</sub> agonists leads to an increase in ACh release in mPFC (Day and Fibiger 1993; Steele et al. 1997), and the local administration of D<sub>1</sub> agonists into the mPFC has previously been shown to enhance attentional function on the 5CSRT (Granon et al. 2000). Therefore, it is possible that the increase in attentional performance observed after intra-mPFC infusions of 8-OH-DPAT and M100907 could be due to an increase in cortical ACh release mediated by 5-HT-DA interactions at 5-HT<sub>1A</sub> and D<sub>1</sub> receptors.

Future experiments could test this hypothesis by observing whether this attentional enhancement is blocked by administration of D<sub>1</sub> receptor antagonists or scopolamine. Consistent with this hypothesis, it has been suggested that the ability of atypical antipsychotics to preferentially increase mPFC DA (Moghaddam and Bunney 1990) and ACh release (Ichikawa et al. 2002b) may contribute to their amelioration of cognitive dysfunction in schizophrenia (Moghaddam and Bunney 1990; Meltzer and McGurk 1999; Tandon 1999). The increases in mPFC DA release hypothetically occur via activation of the 5-HT<sub>1A</sub> receptor as a result of the blockade of 5-HT<sub>2A</sub> and D<sub>2</sub> receptors (Rollema et al. 1997; Ichikawa et al. 2001).

In summary, data presented here demonstrate that serotonergic modulation of mPFC can both increase attentional selectivity and decrease impulsivity via 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors, potentially via interactions with both the cholinergic and dopaminergic systems. Such mechanisms may contribute to the ability of atypical anti-psychotics to improve cognitive function in schizophrenia. Further investigation into the role of mPFC 5-HT receptors in regulating monoaminergic function could lead to improved treatments for neuropsychiatric disorders.

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