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Research report

5-HT2C receptor involvement in the control of persistence in the Reinforced Spatial Alternation animal model of obsessive–compulsive disorder

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HIGHLIGHTS

- We examined spontaneous and mCPP-induced persistence in an OCD model.
- Acute 5-HT2A or 2C antagonism did not affect spontaneous persistence.
- mCPP-induced persistence was reduced by 5-HT2C but not 5-HT2A antagonism.
- Use of 5-HT2C antagonists may have therapeutic value in OCD.

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ABSTRACT

Objective: The serotonergic system is implicated in the pathophysiology of obsessive–compulsive disorder (OCD). However, the distinct role of serotonin (5-HT) receptor subtypes remains unclear. This study investigates the contribution of 5-HT2A and 5-HT2C receptors in the modulation of persistence in the reinforced spatial alternation model of OCD.
Methods: Male Wistar rats were assessed for spontaneous and pharmacologically induced (by *m*-chlorophenylpiperazine: mCPP) directional persistence in the reinforced alternation OCD model. Systemic administration of mCPP (non-specific 5-HT agonist, 2.5 mg/kg), M100907 (selective 5-HT2A receptor antagonist, 0.08 mg/kg), SB242084 (selective 5-HT2C receptor antagonist, 0.5 mg/kg) and vehicle was used. Experiment 1 investigated M100907 and SB242084 effects in animals spontaneously exhibiting high and low persistence during the early stages of alternation training. Experiment 2 investigated M100900 and SB242084 effects on mCPP-induced persistence.
Results: Under the regime used in Experiment 1, 5-HT2A or 5-HT2C receptor antagonism did not affect spontaneous directional persistence in either high or low persistence groups. In Experiment 2, 5-HT2C but not 5-HT2A receptor antagonism significantly reduced, but did not abolish, mCPP-induced directional persistence.
Conclusions: These findings suggest that 5-HT2C but not 5-HT2A receptors contribute to the modulation of mCPP-induced persistent behaviour, raising the possibility that the use of 5-HT2C antagonists may have a therapeutic value in OCD.

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1. Introduction

Obsessive–compulsive disorder (OCD) is an incapacitating psychiatric disorder with a lifetime prevalence of ≈ 2% [1–3]. OCD is characterized by recurrent persistent intrusive thoughts and impulses (obsessions), repetitive, seemingly purposeful actions (compulsions) and excessive anxiety. Clinical expression of OCD is heterogeneous in terms of symptomatology and co-morbid conditions, suggesting heterogeneity in the underlying pathology [4]. Although OCD pathophysiology remains unclear,

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accumulating evidence implicates contributions of the serotonergic and dopaminergic systems [5,6] and the cortico–striato–thalamo-cortical circuitry which includes the orbitofrontal cortex [4,7–9].

Serotonin (5-HT) involvement in OCD is mainly supported by the selective response of obsessive-compulsive symptoms to specific serotonin reuptake inhibitors (SSRIs) [10–12]. However, 40–60% of OCD patients are resistant to SSRIs [13,14] and may benefit from pharmacological augmentation treatments such as antipsychotics [13–15]. SSRI effectiveness has been associated with increased 5-HT neurotransmission in the orbitofrontal cortex [16].

Given that SSRI administration leads to changes in 5-HT neurotransmission, investigation of the contribution of distinct serotonin receptor subtypes in compulsive behaviour is important for the understanding of OCD pathophysiology as well as SSRI mechanism of action. In addition, it could provide useful information for the development of new anti-compulsive agents acting on specific 5-HT receptors. Recent evidence implicates 5-HT2 receptor families in OCD pathophysiology and the mediation of SSRI anti-obsessive action [17]. However the relevant literature presents a conflict.

One line of evidence suggests that 5-HT2A/2C agonism alleviates OC symptomatology, while antagonism promotes it. Intoxication with psychedelic drugs possessing potent 5-HT2A/2C agonist properties reportedly has favourable effects on OCD patients [18–21]. Furthermore, 5-HT2C receptor antagonism has been suggested to contribute to the generation of OC symptoms in patients with co-morbid psychiatric disorders, although not in patients with primary/pure OCD [22,23]. Interestingly, 5-HT2C knockout mice display compulsive-like behaviours [24]. Additionally, the 5-HT2 antagonist ritanserin reverses the therapeutic effect of fluvoxamine [25].

A second line of evidence suggests the opposite, i.e. that 5-HT2A/2C agonism exacerbates OC symptoms, while the therapeutic action of SSRIs is attributed to desensitization of 5-HT2C receptors. Administration of the non-specific 5-HT agonist m-clorophenylpiperazine (mCPP), which has high affinity for 5-HT2C and 5-HT2A receptors [26], reportedly exacerbates obsessive compulsive symptoms [25–30]. The pro-obsessive compulsive role of 5-HT2C receptor activation is also supported by findings showing that chronic treatment with SSRIs, the first line anti-OCD agents, leads to desensitization of 5-HT2C receptors [27–32]. Moreover, a hypersensitivity of 5-HT2 receptors has been reported in OCD patients [33]. In the animal literature, effects of 5-HT2 receptor subtype blockade or activation on persistent behaviour are also equivocal (see Discussion).

This conflict regarding the role of 5-HT2C and 5-HT2A receptors in OC symptomatology is reflected in current hypotheses on their therapeutic potential. Some authors propose that 5-HT2A or 5-HT2C agonism would have therapeutic effects in OCD [34–37]. Others suggest that 5-HT2A and/or 5-HT2C receptor antagonism may be therapeutic [38].

One reason for the inconsistencies regarding the role of 5-HT2 receptors in OC symptomatology may be that 5-HT2A and 5-HT2C receptors appear to have opposing functional and behavioural roles [39]. For example, 5-HT2C receptor agonists decrease, while 5-HT2C receptor antagonists increase dopamine (DA) release in the nucleus accumbens. Moreover, 5-HT2C receptor antagonists enhance DA release in the prefrontal cortex, while 5-HT2C receptor agonists are ineffective. In contrast, 5-HT2A receptor antagonists do not alter DA release in the nucleus accumbens or the prefrontal cortex, whereas systemic administration of a non-selective 5-HT2 receptor agonist increases DA release in the prefrontal cortex, an effect which is completely blocked by a selective 5-HT2A receptor antagonist. Overall, these results suggest that 5-HT2A and 5-HT2C receptors provide opposing stimulatory and inhibitory effects, respectively, in the mesolimbocortical dopaminergic system [48,49].

The possibility of opposing roles of 5-HT2A and 5-HT2C receptors has been investigated in inhibitory response control. 5-HT2C receptor antagonism (by SB242084) has been shown to enhance spatial reversal learning by reducing perseveration; in contrast, 5-HT2A receptor antagonism (by M100907) compromises it [39]. In conclusion, although 5-HT2A and 5-HT2C receptors share similar pharmacological profiles with a high degree of sequence homology (about 50% overall sequence identity), their antagonism produces different biochemical and behavioural actions. This discrepancy may be attributable to fundamental differences in signal transduction pathways of the two receptor subtypes [40,41].

The aim of the present study was to examine further the contribution of 5-HT2A and 5-HT2C receptors in persistent behaviour, using the reinforced spatial alternation model of OCD [42]. This model favours the view that 5-HT2A/2C agonism exacerbates OC symptoms. We have previously demonstrated that the non-specific 5-HT receptor agonist mCPP acts as a pharmacological challenge incrementing directional persistence in the model for 4–5 administration days [42], an effect which dissipates after prolonged mCPP administration [43]. This acute, pro-compulsive effect of mCPP might reflect the initial activation of certain 5-HT receptor subtypes, which are desensitized through chronic administration [27–32].

The present study aims to analyze further the pro-compulsive effect of mCPP by assessing the relative contribution of the 5-HT2A and 5-HT2C receptors therein. We examined the effects of specific 5-HT2A and 5-HT2C receptor antagonism on (a) the spontaneous persistence noted in early acquisition of reinforced alternation and (b) persistence induced pharmacologically by acute mCPP. Our hypothesis was that 5-HT2C antagonism, which reduces perseveration in spatial reversal learning [39], should moderate mCPP-induced persistence, whereas 5-HT2A receptor antagonism should spare it.

2. Methods

2.1. Animals

Male experimentally naïve Wistar rats (Pasteur Institute, Athens) aged 2–3 months and weighing 250–300 g on delivery were used. They were housed in triads under stable environmental conditions (23–25 °C, 12 h light–dark, lights on at 7:00 am) in the same animal room. After 10 days of habituation with water and food ad libitum (Standard Diet, 4RF18, Mucedola s.r.l., Italy), at which point the average weight was 290 g, they were put on a 23-h daily food deprivation schedule with free water. Animals were approximately 90% of free feeding weight at the onset of behavioural training.

2.2. Apparatus and behavioural procedure

2.2.1. Apparatus

The T-maze used stood 120 cm above the floor. The stem measured 90 × 10 cm, the first 20 cm acting as the start area, delineated by a guillotine door. The cross arm measured 140 × 10 cm and had two opaque reward cups 2 cm from each end. The reward used was cereal puffs. The maze was wiped clean with alcohol after each run.

2.2.2. Behavioural procedure

2.2.2.1. Pretraining. Animals were handled for a week, followed by a week of habituation to the loaded T-maze (5 min daily), during which they could explore and eat.

2.2.2.2. Baseline. Reinforced alternation acquisition was initiated. Each trial included two T-maze runs, with both food cups baited. Each animal was placed in the start area, back towards the closed door. In the first ('information') run, one arm was blocked by an obstacle, according to a daily pseudo-random sequence (four left and four right forced runs daily, maximum two consecutive ones in the same direction). The animal was returned to the start point after reaching the goal and consuming the reward. The obstacle was removed and the second ('choice') run began immediately. When all paws of the animal were in a lateral arm retracing was prevented. Choice of the arm opposite to the preceding forced arm was rewarded, persistence to the same resulted in non-reward with 10-s timeout. Animals were run in squads of three, returning to the holding box after each trial. The resulting inter-trial

interval was approximately 100 s. Initially, animals received two daily trials, then four and finally eight.

2.2.2.3. Drug administration phase. The behavioural procedure was identical to Baseline, with eight trials per day.

2.2.2.4. Data collection. The dependent variable recorded was a simple estimate of persistence towards one of the two response alternatives available. This Persistence Index (P-index), in its daily form, is the absolute value of the difference of daily right and left success rates [=|(daily LEFT correct choices/4)% − (daily RIGHT correct choices/4)%|]. A phase Persistence Index was also calculated for each experimental phase on the basis of cumulative errors to the left and right, transformed to left and right success rates, on the basis of the phase's opportunities for left and right correct choices. It was calculated as follows: Phase Persistence Index = |(phase LEFT correct choices/phase LEFT opportunities)% − (phase RIGHT correct choices/phase RIGHT opportunities)%. The phase Persistence Index offers more robust data, since directional persistence is best documented if chance daily preference fluctuations are allowed to cancel out over time. For both indices, spontaneous values of near-zero reflect low persistence tendency. It can be argued that the Persistence Index score is relatively independent of individual differences in learning or memory capacity, since errors due to those should be equally distributed to both directions, therefore cancel out if an animal shows no directional persistence [42,43].

2.3. Drugs

The following substances were administered intraperitoneally (30-gauge needle):

a. *m*-Chlorophenylpiperazine (mCPP; non-specific serotonin agonist, SIGMA 12,518-0, Lot S30984-365): a dose of 2.5 mg/kg was dissolved in 2.5 ml physiological saline [43].
b. The 5-HT2A receptor antagonist M100907 (R-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol, Solvay, Weesp, Netherlands) was dissolved in physiological saline and the pH adjusted to 6.25 using 0.1 M NaOH and 0.1 M HCl. The concentration of the substance was calculated as salt. The daily dose was 0.08 mg/kg, dissolved in 1 ml of the vehicle [39,44].
c. The 5-HT2C receptor antagonist SB242084 (6-cloro-5-methyl-1-[2(2methylpyridyl-3-oxy)-pyrid-5-ylcarbamoyl] indoline, SIGMA S8061, Lot 124K4600) was dissolved in 25 mM citric acid in 8% cyclodextrine in 0.9% physiological saline, and the pH was adjusted to 6.4 using 0.1 M NaOH and 0.1 M HCl). The concentration of the substance was calculated as salt. The daily dose was 0.5 mg/kg, dissolved in 1 ml of the vehicle [39,44].
d. Vehicle control injections: the experiments reported here would require three vehicle control conditions (saline, M100907 vehicle and SB242084 vehicle). A comparison of three groups receiving either saline ($n = 5$) or M100907 vehicle ($n = 5$) or SB242084 vehicle ($n = 4$) was carried out [1-way, repeated measures ANOVA; independent variable: Vehicle Type (M100907 vehicle, SB242084 vehicle, saline), repeated measure: Experimental Phase (Baseline vs. Drug phase)]. This indicated that the three groups did not differ in number of trials to criterion of reinforced alternation [$F(1,11) = 1.26$]. They also did not differ in Persistence Index scores (Vehicle Type main effect: $F(1,11) = 0.04$; Vehicle Type × Phase interaction: $F(2,11) = 0.25$). On the basis of these observations we combined the M100907 and SB242084 vehicle conditions into a single vehicle-control group in each experiment.

2.4. Data collection and statistical analysis

The dependent variable recorded was a simple estimate of persistence towards one of the two response alternatives available. This Persistence Index (P-index), in its daily form, is the absolute value of the difference of daily right and left success rates [=|(daily LEFT correct choices/4)% − (daily RIGHT correct choices/4)%|]. When appropriate, a phase P-index was also calculated for the baseline and drug phases [=|(phase LEFT correct choices/phase LEFT opportunities) % − (phase RIGHT correct choices/phase RIGHT opportunities)% |]. In the drug-free state, near 0 values of both P-indices reflect low spontaneous persistence levels. The P-index is relatively independent of differences in learning or memory capacity, since errors due to those should be equally distributed to both directions, therefore expected to cancel out if an animal shows no directional persistence [42,43].

Analyses were carried out by the STATISTICA for Windows statistical package (2008, version 6.1 StatSoft Inc., Tulsa, OK, USA). Details on the statistical analysis are given in individual experiments.

3. Experiment 1: effects of specific 5-HT2A and 5-HT2C receptor antagonism on spontaneous directional persistence

The aim of this experiment was to examine the effects of specific 5-HT2A (M100907) and 5-HT2C (SB242084) receptor antagonists on spontaneously high and low directional persistence. As practical limitations precluded use of multiple doses, a single dose of established behavioural effectiveness for each substance was used [39,44].

3.1. Subjects

63 animals were subjected to reinforced alternation training. 48 of these were included in the experiment, following the screening procedure reported below.

3.2. Procedure

3.2.1. Baseline phase (5 days)

Animals were subjected to 5 days (40 trials) of drug-free alternation training, during which they were screened for spontaneous persistence on the basis of the daily P-index. 24 animals with the highest and 24 with the lowest P-index scores were included in the experiment. The remaining 15 animals showing medium levels of persistence were excluded (and were subsequently used in Experiment 2). Three high and three low persistence groups ($n = 8$) were then formed. The three high persistence groups were matched for P-index scores, as were the three low persistence groups. Three group pairs, each including a high and a low persistence group were formed. Each group pair was randomly allocated to one of three pharmacological conditions (Table 1).

3.2.2. Drug administration phase (1 day)

On training day 6, all animals received an intraperitoneal injection 30 min before behavioural training. The first group pair received M100907 (0.08 mg/kg), the second SB242084 (0.5 mg/kg); the third pair (vehicle control group) received injections of either M100907 ($n = 4$) or SB242082 ($n = 4$) vehicle (see Section 2.3a).

3.2.3. Post-drug washout phase (1 day)

On training day 7, animals continued alternation training without drug administration.

3.3. Statistical analysis

A two-way ANOVA with repeated measures was then carried out. The independent variables were (a) spontaneous directional persistence (high vs. low) and (b) drug treatment (vehicle vs. SB242084 vs. M100907). The repeated measures (Experimental Phase) included 3 levels: baseline (last day), drug administration (1 day) and post-drug washout (1 day). Data were subjected to a square root transform.

4. Experiment 2: effects of specific 5-HT2A and 5-HT2C receptor antagonism on pharmacologically induced directional persistence

4.1. Subjects

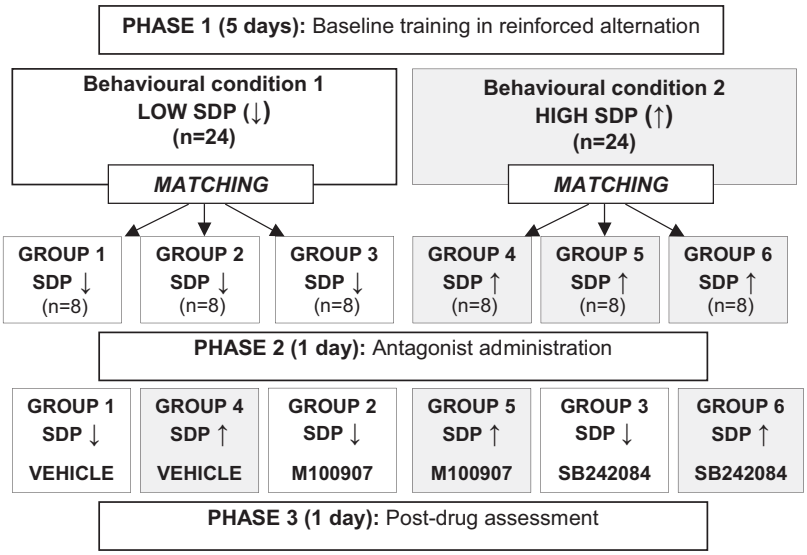
A cohort of 45 animals, comprising the 15 animals of medium spontaneous persistence excluded from Experiment 1, plus 30 additional animals, was used.

4.2. Procedure

4.2.1. Baseline phase

All animals were subjected to drug-free alternation training for 30 days (240 trials). At that point, 41 animals which had reached a performance criterion of 7/8 correct choices daily over 5 consecutive days were included in the experiment. Four animals were excluded as they did not reach Baseline criterion. Five animals were

Table 1
The design of Experiment 1. SDP = spontaneous directional persistence; ↓ = low, ↑= high.



used as a saline control group in order to ensure that M100907 vehicle and SB242084 vehicle did not have an effect on rewarded alternation acquisition (see Section 2.3d and Table 2, comparison of vehicle conditions). Given the stringent training criterion, all P-index scores approached 0 at the end of baseline. Therefore, matching for spontaneous persistence levels for subsequent allocation to the pharmacological treatment groups was based on earlier baseline scores (trials 1–80).

4.2.2. Drug phase

Two days of identical pharmacological treatment followed.

4.3. Pharmacological procedure (Table 2)

Four pharmacological treatment groups, matched for spontaneous persistence levels were used. Each received two injections, 60 and 30 min before behavioural testing. Group 1 (VEH + SAL, $n = 9$) received an injection of vehicle [vehicle M100907 ($n = 5$) and vehicle SB242084 ($n = 4$): see Section 2.3d and Table 2)], followed by an injection of normal saline. Group 2 (VEH + mCPP, $n = 9$) received a vehicle injection followed by an injection of mCPP; Group 3 (M100 + mCPP, $n = 9$) received an injection of M100907 followed by mCPP; Group 4 (SB + mCPP, $n = 9$) was injected with SB2420284 followed by mCPP.

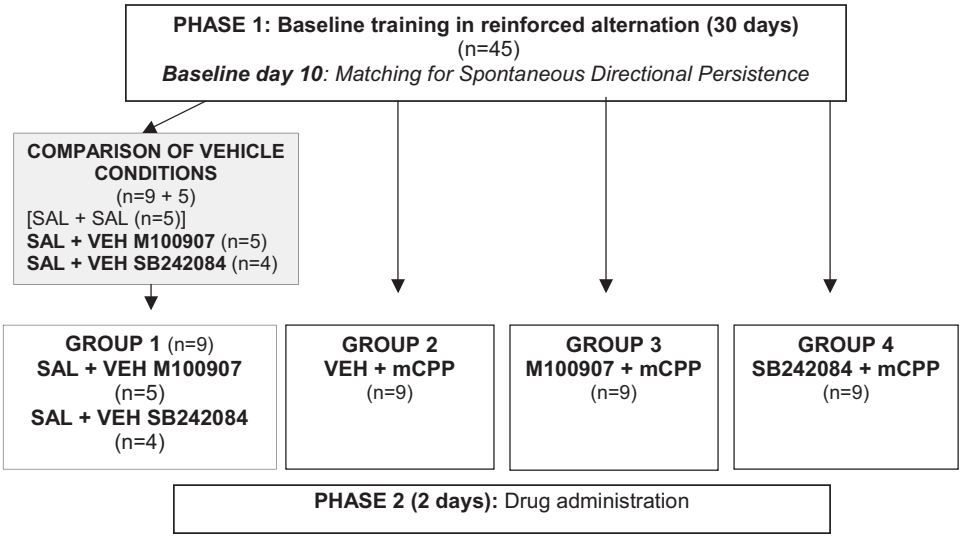
4.4. Statistical analysis

Data were analyzed by means of a 1-way repeated measures ANOVA. The independent variable was drug treatment (VEH + SAL, VEH + mCPP, M100907 + mCPP, SB242084 + mCPP) and the repeated measure was Experimental Phase (Baseline, Drug administration). Significant ANOVA effects were further explored through contrast testing.

5. Results and discussion

We have previously shown that acute administration of mCPP induces persistence in the reinforced spatial alternation model

Table 2
The design of Experiment 2. SAL: normal saline; VEH: vehicle.



of OCD, in spontaneously high but not low persisters [42,43]. This effect is analogous to the transient symptom exacerbation reported after acute mCPP administration to untreated OCD patients [45–49]. In our model, as in OCD, this detrimental effect of mCPP was blocked by pretreatment with an SSRI [42,46,50], but not by pretreatment with agents with no specific therapeutic action on OCD (tricyclic antidepressants or benzodiazepines).

5-HT2A and 5-HT2C receptors have been implicated in the pathophysiology of OCD and in the mechanism mediating the therapeutic effect of SSRIs in this disorder. However, it is currently unclear whether activation or blockade of these receptors has an anti-compulsive effect [51,52]. Hence the present study focussed on 5-HT2A and 5-HT2C receptor subtype involvement in the mechanism of spontaneous and mCPP-induced persistence.

In Experiment 1, a 2-way repeated measures ANOVA confirmed a significant main effect of spontaneous directional persistence [high vs. low: $F(1,42) = 91.98$, $p < 0.001$]. Neither pharmacological phase (baseline vs. drug administration vs. washout) nor drug treatment (5-HT2A antagonist M100907 vs. 5-HT2C antagonist SB242084 vs. vehicle) produced significant main effects [respectively: $F(2,84) = 1.85$; $F(2,42) = 0.88$]. Interactions were also non-significant ($0.42 > p > 0.95$). Therefore, blockade of 5-HT2A or 5-HT2C receptors did not affect the spontaneous directional persistence noted in early reinforced alternation training (Fig. 1).

This lack of effect should be treated with caution, as it could be attributed to the single dose of antagonists used in this experiment. It is possible that more prolonged administration of 5-HT2A or 5-HT2C antagonists might have influenced spontaneous persistence. Indeed previous studies have shown that chronic but not acute administration of 5-HT2C receptor antagonists enhanced reversal learning by decreasing perseverative responding. Similarly, it was chronic 5-HT2A receptor antagonism that led to impoverished performance by increasing perseveration [39]. If not driven by the duration of 5-HT2A and 5-HT2C antagonist administration, the observed differences between the present study and that of Boulougouris et al. [53] could be attributed to the discrete nature of the two behavioural paradigms. Perseveration in the form of spontaneous directional persistence may have a different neurobiological basis than perseveration in reversal learning and may reflect different aspects of OCD [52]. In fact, perseverative responding during reversal learning has been challenged as an animal model of OCD: although it appears to offer face and construct validity (lesions to the orbitofrontal cortex impair reversal learning performance: [53,54]), its predictive validity is low [beneficial response to desipramine and atomoxetine [55]).

In Experiment 2, a 1-way repeated measures ANOVA yielded significant main effects of Drug Group and Experimental Phase [respectively: $F(3,32) = 6.30$, $p < 0.002$ and $F(1,32) = 117.6$, $p < 0.0001$; Fig. 2]. The significant interaction [$F(3,32) = 8.21$, $p < 0.0003$] was examined by contrast testing following a Bonferroni criterion ($0.05/6 = 0.0083$). Between-group contrasts for the baseline phase revealed that the four groups did not differ ($0.70 > p > 0.20$). For the drug phase, between group contrasts showed the following: (a) The M100907 + mCPP group significantly differed from the VEH + SAL controls [$F(1,32) = 17.73$, $p = 0.0002 < 0.0083$], but not from the VEH + mCPP group [$F(1,32) = 1.70$, $p < 0.20$]. Therefore 5HT2A antagonism did not reduce the impact of mCPP challenge on directional persistence. (b) In contrast, the SB242084-mCPP group did not significantly differ from the VEH + SAL controls [$F(1,32) = 6.62$, $p = 0.015 > 0.0083$], but showed significantly lower persistence than the VEH + mCPP group [$F(1,32) = 8.66$, $p = 0.006 < 0.0083$]. Therefore 5HT2C blockade offered partial protection from mCPP challenge. The fact that 5-HT2C but not 5-HT2A receptor antagonism alleviated the mCPP

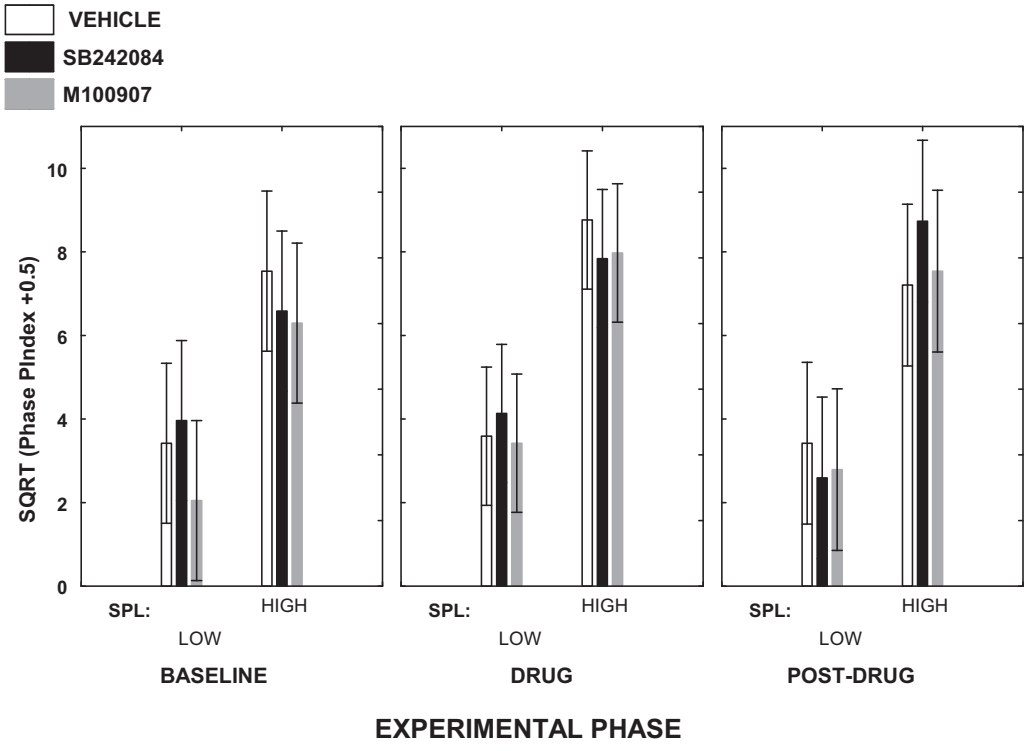


Fig. 1. Experiment 1 examined the effects of 5-HT2A and 5-HT2C receptor antagonism (with M100907 and SB242084 respectively) on spontaneous directional persistence in T-maze alternation. The main effect of Spontaneous Directional Persistence (SPL, high vs. low) was significant [$F(1,42) = 91.98$, $p < 0.001$]. Pharmacological Phase (baseline vs. drug administration vs. washout) and Drug Treatment (M100907 vs SB242084 vs vehicle control) main effects and interactions were not significant. Data are square root transformed daily Persistence Index (P-index) scores, shown as means ± 95% confidence intervals.

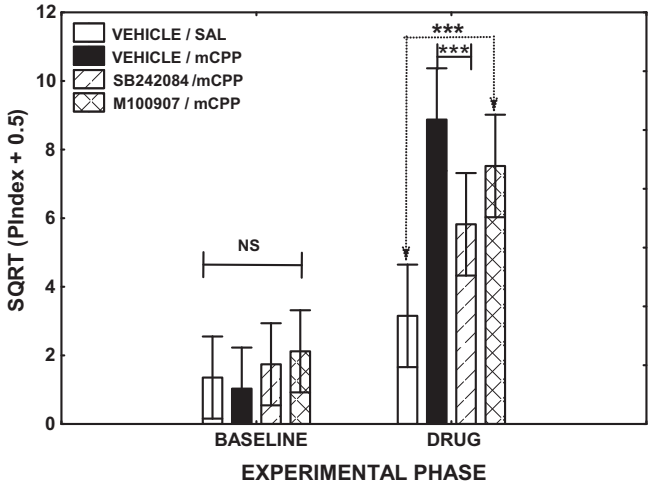


Fig. 2. Experiment 2 examined the effects of 5-HT2A and 5-HT2C receptor antagonism (with M100907 and SB242084 respectively) on mCPP-induced directional persistence in T-maze alternation. Between-group contrasts following the significant Drug × Phase interaction [$F(3,32) = 8.21$, $p = 0.0003$] revealed no difference during baseline. In the drug phase (a) the group receiving mCPP after M100907 (M100907/mCPP) differed from controls receiving vehicle and saline (VEHICLE/SAL; $p = 0.0002$] but not from vehicle and mCPP controls (VEHICLE/mCPP); (b) the group receiving mCPP after SB242084 (SB242084/mCPP) did not differ from VEHICLE/SAL but was significantly less persistent than VEH/mCPP [$p = 0.006$]. Therefore, 5HT2C but not 5HT2A antagonism offered partial protection from mCPP challenge. Data are square-root transformed Persistence Index (P index) scores (means ± 95% confidence intervals).

effect suggests involvement of the 5-HT2C receptor in mCPP-induced persistence and, by extension, possibly in the control of compulsive behaviour.

It should be mentioned at this point that drug responses in the two experiments reported here are not directly comparable, due to methodological differences. The first experiment evaluated spontaneous persistence, a behaviour which dissipates early in training and must, by necessity, be studied very early on in training. In contrast, the second experiment studied pharmacologically induced persistence. This phenomenon examines mCPP-induced re-emergence of persistence, it must therefore be examined after spontaneous persistence has completely dissipated by extensive training. The design of the current experiments does not allow the examination of a possible interaction between duration of training and antagonist response.

5-HT2C receptors are concentrated in corticolimbic structures, such as the frontal cortex, basal ganglia, hippocampus, amygdala and ventral tegmental area [56,57]. OCD is characterized by a dysfunction in cortico–thalamic-striatal circuits [58]. Thus, the preferential action of 5-HT2C receptor antagonists in corticolimbic structures implicated in the pathophysiology of OCD, may explain their therapeutic effect presented herein.

Reflecting the conflict presented in human literature, animal studies using various models of compulsive behaviour have produced conflicting results regarding the specific role of 5-HT2A and 5-HT2C receptors in the modulation of persistent behaviour. Flaisher-Grinberg et al. [51] reported that 5-HT2C but not 5-HT2A receptor antagonism selectively decreased 'surplus' lever-pressing in the signal attenuation model of OCD. These findings are compatible with ours. Other converging findings include reduction of stress-induced marble burying in mice by the mixed melatonin agonist/5-HT2C antagonist agomelatine, which has established antidepressant and anxiolytic effects in clinical populations [59], and promotion of compulsive grooming by 5-HT2C receptor activation in the compulsive grooming OCD model [60,61]. At odds with these and our present findings, 5-HT2C receptor activation attenuated compulsive behaviour in the OCD models of marble-burying and schedule-induced polydipsia in rats [62], while 5-HT2C receptor blockade increased compulsive drinking in the polydipsia model [36].

The observed inconsistencies may be attributable to the different 5-HT ligands used in the above studies or confounding factors associated with the non-specific (e.g. sedative) effects of 5-HT2C agonists [63]. Alternatively, a possible interpretation of the conflict may be that different expressions of compulsive behaviour may have different biological substrates. Similarly, the differential effect of 5-HT2C receptor antagonism on spontaneous versus mCPP-induced persistence could reflect the existence of different neurobiological mechanisms underlying these behaviours. In a recent review Albelda and Joel [52] offer the stimulating proposition that differences between models could be viewed as reflecting different aspects of OCD rather than arbitrary aspects not related to OCD. They also propose that the mCPP-induced persistence model, along with the signal attenuation and neonatal clomipramine models may be relevant to OCD patients in whom overactivation or hypersensitivity of 5-HT2C receptors plays a role in compulsive behaviours.

6. Conclusions

The aim of the present study was to examine the relative contributions of 5-HT2A and 5-HT2C receptors to persistent behaviour in the spatial reinforced alternation animal model of OCD. This assessment could contribute to the delineation of the potential of these receptors as drug targets for future anti-compulsive drug treatments. mCPP-induced perseveration in this animal model was not influenced by 5-HT2A antagonism, but was significantly attenuated by the pre-administration of a 5-HT2C antagonist. This finding may be relevant to the pathophysiology of OCD and suggests a potential role for 5-HT2C receptors in future treatment strategies for this disorder.

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