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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.

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