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Research report

Detrimental effect of clomipramine on hippocampus-dependent learning in an animal model of obsessive-compulsive disorder induced by sensitization with d2/d3 agonist quinpirole

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HIGHLIGHTS

- Active place avoidance with reversal is a test of cognitive flexibility.
- Quinpirole-sensitized rats in an animal model of OCD display a flexibility deficit.
- Clomipramine added to quinpirole causes a severe learning deficit.
- Risperidone added to clomipramine and quinpirole rescues performance.

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ABSTRACT

Quinpirole (QNP) sensitization is one of the commonly used animal models of obsessive-compulsive disorder (OCD). We have previously shown that QNP-sensitized animals display a robust cognitive flexibility deficit in an active place avoidance task with reversal in Carousel maze. This is in line with numerous human studies showing deficits in cognitive flexibility in OCD patients. Here we explored the effect of clomipramine, an effective OCD drug that attenuates compulsive checking in QNP, on sensitized rats in acquisition and reversal performances in an active place avoidance task. We found that the addition of clomipramine to QNP-sensitization impairs acquisition learning to a degree that reversal learning could not be tested. In a hippocampal-independent two-way active avoidance task clomipramine did not have an effect on acquisition learning in QNP-treated rats; suggesting that the detrimental effect of clomipramine is hippocampus based. We also tested the effect of risperidone in QNP-sensitized animals, which is not effective in OCD treatment. Risperidone also marginally impaired acquisition learning of QNP-sensitized animals, but not reversal. Moreover, we explored the effect of the augmentation of clomipramine treatment with risperidone in QNP-sensitized rats- a common step in treating SRI-unresponsive OCD patients. Only under this treatment regime animals were unimpaired in both acquisition and reversal learning. Augmentation of SRI with neuroleptics therefore could be beneficial for improving cognitive flexibility, and possibly be considered a first line of treatment in patients with reduced cognitive flexibility.

1. Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder with a lifetime prevalence of 2–3%, [41] and is characterized by intrusive thoughts (obsessions) that are often accompanied by rigid, repetitive and time consuming behaviors (compulsions) [20,52]. At the present, the first line of treatment of OCD is administration of high doses of serotonin reuptake inhibitors (SRIs) [32]. SRIs are, however, ineffective in around 40–60% of patients [36]. Some of the patients unresponsive to the SRI treatment respond

Abbreviation: SRIs, serotonin reuptake inhibitors; CBT, cognitive-behavioral therapy; QNP, quinpirole; ACQ, acquisition session; REV, reversal session; ITI, inter-trial interval; CSE, conditioned stimulus escape; USE, unconditioned stimulus escape; PPX, pramipexole; VTA, ventral tegmental area; OFC, orbitofrontal cortex; DA, dopamine; PFC, prefrontal cortex.

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to complementary treatment with neuroleptics [7]. Of these, complementation with low doses of risperidone appears to be most effective [13]. However, the nature of this interaction is as yet unclear.

Numerous animal models of OCD have been developed (for review see [3]. Each of these models exemplifies different aspects of compulsive behavior (unfortunately, obsessive thoughts are impossible to measure). Mostly, rigid behavior such as stereotypical movements, ritual formation, incessant grooming and increased marble burying are considered to be compulsive behaviors analogous to those behaviors displayed by patients. Animals sensitized with the dopamine D2/D3 receptor agonist quinpirole show changes in behavior proposed as models of OCD; these include compulsive checking in an open-field arena [47], reduced spontaneous alternation in a T-maze [15] and contra-freeloading [11]. In all cases these behaviors are ameliorated by clomipramine – a tricyclic antidepressant that is very potent in treating OCD [47,11]. We have previously shown that animals treated with QNP also show reversal learning deficits [18]. Importantly, acquisition learning remained comparable to controls. Since there have been numerous reports of decreased cognitive flexibility in patients with OCD [12,34,25,27,8,16]; but see: [1,33] and patients with checking symptoms more often show cognitive flexibility deficits compared to patients with other symptom manifestations [35], we hypothesized that a D2 sensitization model could represent a subgroup of patients that display a deficit in cognitive flexibility along with OCD-symptoms [18].

The aim of the present study is to deepen our understanding of the link between OCD and cognitive flexibility. We examined two questions bearing on their suggestion that cognitive flexibility is altered in the model OCD preparation: (1) is the alteration in cognitive flexibility sensitive to drugs used in the clinical treatment of human OCD; and, (2) how do those drugs impact cognitive flexibility in a hippocampal-independent task such as two-way active avoidance learning.

2. Material and methods

2.1. Animals

Adult male Long-Evans rats from the Instituteís breeding colony (Institute of Physiology, CAS, Czech Republic) were used with starting body weights of 300–350 g. Animals were housed two to three per cage. Standard laboratory food and water was supplied ad libitum. Animals were housed at 22 °C and humidity of 50% and a 12/12 light/dark regime with the light phase beginning at 6am. All experiments were conducted during the light phase. Ten days of handling/habituation preceded the commencement of the experiment. All animal procedures were approved by the local Animal Care Committee and complied with the Animal Protection Act of the Czech Republic and EU directive 2010/63/EC.

2.2. Drug treatment

There were six treatment groups used in experiment 1–a quinpirole-treated group (QNP, n = 15); a saline treated control group (SAL, n = 10); a group receiving quinpirole and clomipramine (QNP + CMI, n = 11); a group receiving quinpirole and risperidone (QNP + RIS, n = 11); a group receiving quinpirole and a combination of clomipramine and risperidone (QNP + CMI + RIS, n = 11); and a group receiving only clomipramine (CMI, n = 9). Risperidone was not tested alone as its effects on active place avoidance performance have been described previously by our group [9]. In experiment 2 there were SAL, CMI, QNP and QNP + CMI treatment groups. For administration of all pharmaceuticals animals were retrieved from the home cage, injected, and returned back to home cage until commencement of experiment. CMI (10/mg/kg) and RIS (0.25 mg/kg) were administered 90 min and QNP (0.5 mg/kg) 30 min before the introduction of animals into the testing apparatus (Carousel maze). All groups received 3 injections and groups that did not have a scheduled administration of a drug received saline solution instead in a volume appropriate for their body weight. QNP was dissolved in saline; RIS was dissolved in a drop of acetic acid and diluted with saline (final pH 3.0); (CMI was dissolved in saline). CMI was administered intraperitoneally and RIS and QNP were given subcutaneously. For administration of all pharmaceuticals animals were retrieved from their home cage, injected, and returned back to home cage until the time of placement into the testing apparatus.

For experiment 2, there were 4 groups: a saline control group (SAL, n = 7); QNP (n = 6); QNP + CMI (n = 6); CMI (n = 6). Prior to experiment, animals received 10 administrations of QNP, CMI or both in their home cages. Other things were the same as in Experiment 1.

2.2.1. Active place avoidance with reversal on carousel – experiment 1

Active place avoidance with reversal in a Carousel maze is an established tool [44,50,45,46,37] to explore spatial learning, cognitive coordination and cognitive flexibility and is hippocampus-dependent [24]. We previously found that QNP selectively impairs reversal learning in this task [18].

The Carousel maze is an elevated metallic platform that rotates 1 revolution/min. Part of this platform can be assigned as a to-be-avoided sector, where, upon entering, the animal receives a mild electric shock. This electric shock is adjusted individually to elicit an escape response (AC, 50 Hz, 0.2–0.6 mA), and is administered automatically at 1200-ms intervals up to the time the animal leaves the sector. The to-be-avoided sector is directly imperceptible and stable in the coordinates of the room while the platform rotates constantly at 1 revolution/min. To avoid this sector successfully, the animal has to move in a counter-rotational direction to avoid being dragged into the sector. A camera placed above the arena samples animal movements at a frequency of 25 Hz (the camera detects an infrared light-emitting diode (LED) attached to the back of the animal on a small rubber jacket). In addition to LED, the animal has a subcutaneous needle attached to the nape of the neck that is connected to a current source, to deliver the mild electric shock across the grounded floor. This conditioning procedure has been previously shown to be effective and safe for the animals [10,44]. The analog signal from the overhead infrared camera was digitized using a DT-3155 card (Data Translation, USA) in the Tracker program (Biosignal Group, USA) and transformed into a set of coordinates. From these, locomotion and number of errors (entrances into to-be-avoided sector) were extracted for behavioral analysis.

2.2.2. Behavioral procedure in active place avoidance with reversal

The experimental procedure used here can be divided into three principal phases – habituation, acquisition and reversal. This same procedure has already been used to test cognitive flexibility deficits in QNP-treated rats [18]. In short, the experiment began with 10 sessions of habituation to the arena (every other day). Habituation was 30 min long (as are the subsequent acquisition and reversal phases) and there was no defined to-be-avoided sector. Arena was rotating during habituation. During this habituation phase (which is also the sensitization phase for rats treated with QNP), all groups received their assigned drug treatments as described under “Drug treatment”, a regimen that continued for the following acquisition and reversal learning phases (see Fig. 1A).

Habituation was followed by five acquisition sessions (ACQ1–ACQ5; 30 min every other day). During acquisition the to-