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Ritualistic Chewing Behavior induced by mCPP in the rat is an animal model of Obsessive Compulsive Disorder

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ABSTRACT

Obsessive Compulsive Disorder (OCD) is characterized by recurrent, anxiety-producing thoughts accompanied by unwanted, overwhelming urges to perform ritualistic behaviors. Pharmacological treatments for this disorder (serotonin uptake inhibitors) are problematic because there is a 6–8 week delayed onset and half of the patients do not adequately respond. The present study evaluated whether Ritualistic Chewing Behaviors (RCBs) induced by the serotonin agonist mCPP in the rat is a behavioral model for OCD. The effects upon the RCBs induced by mCPP (1 mg/kg) were evaluated following treatments with either the serotonin antagonist mianserin (3 mg/kg), the dopamine antagonist haloperidol (1 mg/kg), the GABA modulator diazepam (10 mg/kg), or the serotonin uptake inhibitors clomipramine and fluvoxamine (15 mg/kg). The response to mCPP was blocked by acute treatment with mianserin, but not with acute haloperidol or diazepam. Further experiments revealed that the effects of mCPP were blocked by chronic, but not acute, treatment with clomipramine and fluvoxamine. A time-course demonstrated that 14 days of chronic treatment were required for blockade of the mCPP-evoked response.

The current study demonstrates that mCPP-evoked RCBs may be a rodent model for OCD that can be used to predict the clinical efficacy and time course of novel OCD treatment. Future investigations may be able to use the current model as a tool for bench-marking corresponding changes in other measures of neurological activity that may provide insight into the mechanisms underlying OCD.

1. Introduction

Obsessive Compulsive Disorder (OCD) is a severe, chronic neurological condition that affects 2–3% of the population (Karno et al., 1988; Ruscio et al., 2010; Weissman et al., 1994). Patients diagnosed with OCD experience recurrent, anxiety-producing thoughts that the patient cannot inhibit or ignore. Patients also engage in time-consuming, repetitive and intentional behaviors or mental acts (American Psychiatric Association, 2000). Although the exact pathology of OCD is undetermined, neural imaging studies of OCD patients evidence abnormalities of cortico-basal ganglia-thalamic circuits (for a review see Saxena and Rauch, 2000).

The most successful pharmacological approach to alleviation of OCD symptoms involves drugs which inhibit the uptake of serotonin, either selectively or non-selectively (McDougle et al., 1993; Piccinelli et al., 1995; Pigott and Seay, 1999). Monotherapy with psychoactive drugs lacking serotonergic properties, such as the norepinephrine uptake inhibitor desipramine (Goodman et al., 1990; Hoehn-Saric et al., 2000; Zohar and Insel, 1987), GABA receptor modulators (Bandelow et al., 2008; Hollander et al., 2003a) and dopaminergic receptor antagonists (reviews by Math and Janardhan Reddy, 2007; Sareen et al., 2004) are ineffective in treating OCD. Alleviation of OCD symptoms with serotonin uptake inhibitors, however, is associated with a number of shortcomings. Only 40–60% of OCD patients are effectively treated by the pharmaceuticals (Foa et al., 2005; Koran et al., 1996; March et al., 1998; Riddle et al., 2001) and treated patients only experience a 30–48% mean reduction in symptom score on the Yale–Brown Obsessive Compulsive Scale (Clomipramine Collaborative Group, 1991; Foa et al., 2005; Freeman et al., 1994; Hollander et al., 2003b). Moreover, there is a significant delay before symptom attenuation. Typically, patients require 6–8 weeks of administration to attain an initial response and 10 or more weeks to attain a maximal response (March et al., 1998; Math and Janardhan Reddy, 2007). Finally, relapse following discontinuation of serotonin uptake inhibitor therapy is common (Catapano et al., 2006; Pato et al., 1988; Simpson et al., 2006).

The present study evaluated whether behavioral effects of the serotonin receptor agonist m-chlorophenylpiperazine (mCPP) in the rat can serve as an animal model of OCD with predictive validity. A valid animal model of OCD would provide an invaluable research tool for the exploration of the neurophysiology underlying OCD and the development of

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new avenues of treatment. Although a number of animal models have been proposed to reflect certain aspects of OCD (reviews by Albelda and Joel, 2012; Joel, 2006; Korff and Harvey, 2006), no single model has been widely adopted. In the current study, mCPP-induced effects were selected for evaluation because mCPP exacerbates symptoms of obsession in untreated OCD patients (Erzegovesi et al., 2001; Hollander et al., 1992; Pigott et al., 1991; Zohar and Insel, 1987). In contrast, mCPP does not elicit obsessive symptoms in OCD patients who have been successfully treated with a serotonin uptake inhibitor (Hollander et al., 1991; Zohar et al., 1988). Additionally, mCPP-induced effects were selected for evaluation because mCPP is known to be anxiogenic in rats. Behavioral studies report that rats given mCPP demonstrate decreased exploration, locomotion, ingestion and social interaction (Kennett et al., 1989; Kennett and Curzon, 1988; Lucki et al., 1989; Wallis and Lal, 1988). Neurophysiological studies report that systemic mCPP activates anxiety-related loci in the rat brain, such as the thalamus, structures of the basal ganglia, and the prefrontal, cingulate and orbitofrontal cortices (De Deurwaerdere and Chesselet, 2000; Hackler et al., 2007; Singewald et al., 2003; Stark et al., 2006). These structures directly correspond to brain areas of OCD patients exhibiting abnormal activity (Baxter, 1995; Benkelfat et al., 1990; Busatto et al., 2000; Lacerda et al., 2003; Rauch et al., 1994).

In the current study, behavioral effects of mCPP in rats were assessed by quantifying the expression of a particular type of mouth movement designated as a "Ritualistic Chewing Behavior" (RCB; Winkler et al., 2006). The ability of mCPP-induced RCBs to predict the successfulness of OCD treatments was evaluated by examining the effects of clomipramine and fluvoxamine, two effective therapies for OCD (Clomipramine Collaborative Group, 1991; Goodman et al., 1989; Jenike et al., 1990). In addition, the dopamine receptor antagonist haloperidol and the GABA receptor modulator diazepam, ineffective therapies for OCD, were evaluated for their effects upon RCBs evoked by mCPP.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (Harlan, Indianapolis, IN) weighing from 120 to 400 g were used for these studies. Rats were housed in pairs in a temperature-controlled (22 °C) animal colony room with a 12 hour light–dark cycle and given free access to food and water. Animals were acclimated to housing, handling, and observational conditions for at least 10 days prior to participation in experimental studies. Animal housing and experimental protocols were in compliance with the guidelines of the National Research Council (1996, 2003), as well as the University of Tennessee at Chattanooga's Institutional Use and Care of Animals Committee.

2.2. Drugs

Clomipramine hydrochloride, mCPP (1-[3-chlorophenyl]piperazine) hydrochloride, haloperidol, mianserin hydrochloride, and diazepam were attained from Sigma Aldrich, (St. Louis, MO). Fluvoxamine maleate was donated by Solvay Pharmaceuticals (Marietta, GA). Drug solutions were prepared using 0.9% NaCl (saline) such that doses were delivered at 1 ml/kg body weight. Fluvoxamine was prepared by adding 2–3 drops of Tween-80 to the dehydrated drug prior to mixing with 0.9% NaCl. Drug doses refer to weight of the salt.

2.3. Experimental protocol

2.3.1. Ritualistic Chewing Behaviors

Ritualistic Chewing Behaviors (RCBs) were defined as: "any non-directed, repetitive chewing or gaping mouth movement. Smaller movements, such as oral tremors and tongue darting, were recorded as a single RCB if three or more distinct movements were observed in a continuous bout. A one second pause in a repetitious bout sequence separated individual RCBs. Larger movements, such as vacuous gaping, were counted individually as a RCB" (Winkler et al., 2006). This characterization of oral behaviors was developed because previous depictions of rodent oral dyskinesia presented in the literature (e.g. Eberle-Wang et al., 1996; Neisewander et al., 1994) proved to lack enough detail for reliable quantification and reproducibility among observers of this behavior in our research laboratory.

RCBs were assessed in experimental studies 15–25 min following mCPP administration. Preliminary data (n = 15) indicated that 44% of the total number of RCBs observed 0–30 min following mCPP administration occurred during this time period. During behavioral observations, each rat was individually placed into clear 3-gallon round plastic bowl set upon a rotating platform.

2.3.2. Dose response of mCPP

The number of RCBs exhibited after a subcutaneous (s.c.) injection was evaluated in rats receiving mCPP at either 0 mg/kg (0.9% saline), 0.5 mg/kg, 1.0 mg/kg, 2 mg/kg, or 4 mg/kg. Over consecutive days, rats were administered a single dose once a day in a randomized order. Each rat received a single exposure to each dose. Behavioral observers were blind to the identity of the injection.

2.3.3. Acute pretreatment with psychotherapeutic agents

Over consecutive days, rats were injected intraperitoneally (i.p.) once a day with one of the following pretreatments in randomized order: 1.0 mg/kg haloperidol, 3.0 mg/kg mianserin, 10.0 mg/kg diazepam, 15.0 mg/kg clomipramine, 15.0 mg/kg fluvoxamine, or 1.0 ml/kg 0.9% saline. One group of rats (n = 12) received pretreatments with haloperidol, mianserin, or saline. The other group of rats (n = 13) received with pretreatments with diazepam, clomipramine, fluvoxamine, or saline. Behavioral observers were blind to the identity of the pretreatment drug. Five minutes following the pretreatment injection, animals were administered 1.0 mg/kg s.c. mCPP. The expression of RCBs following the mCPP injection was assessed.

Selection of the doses of haloperidol and diazepam in the current study was based upon doses of these drugs used in prior studies to evidence that the expression of "OCD-like" behavioral effects are not attenuated by single administration of these pharmacological agents (Bilkei-Gorzo et al., 1998; Joel et al., 2004; Tsaltas et al., 2005; Woods et al., 1993).

2.3.4. Repeated treatment with serotonin uptake inhibitors

On Day 1, RCBs following an injection of 1.0 mg/kg s.c. mCPP were assessed. On Days 2–27, separate groups of rats were injected once daily with either 15.0 mg/kg i.p. clomipramine (n = 23), 15.0 mg/kg i.p. fluvoxamine (n = 16), or 1.0 ml/kg i.p. 0.9% saline (control rats, n = 22). Behavioral observers were blind to the identity of the daily injections given on Days 2–27. On Day 28, the number of RCBs exhibited after an injection of 1.0 mg/kg s.c. mCPP was evaluated.

Determination of the doses of clomipramine and fluvoxamine selected for the current study was based upon doses of these drugs used in prior studies that significantly reduced the expression of "OCD"-like behavioral effects following a repeated administration protocol (Bantsiele et al., 2009; Joel et al., 2004; Ulloa et al., 2004; Woods et al., 1993).

2.3.5. Time course of clomipramine's effect

On Day 1, RCBs following 1.0 mg/kg s.c. mCPP were assessed. Separate groups of rats were injected once daily with either 15.0 mg/kg i.p. clomipramine (n = 8) or 1.0 ml/kg i.p. 0.9% saline (n = 8) for 28 days. RCBs following an injection of 1.0 mg/kg s.c. mCPP were assessed on Days 8, 15, 22, and 29 of treatment. Injections of mCPP were given at least 22 h after the prior day's injection with clomipramine or saline. Daily injections of clomipramine or saline were given at least 6 h after the day's earlier mCPP injection.