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Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: a potential model for obsessive compulsive disorder

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Abstract. Schedule-induced polydipsia was used to determine the effects of selective serotonin re-uptake inhibitors on adjunctive water consumption. Polydipsia was induced in food deprived rats by exposure to a fixed time feeding schedule (FT = 60 s) for 150 min per day for 22 days. Selected polydipsic rats consumed 3–4 times greater volume of water compared to food deprived control rats. Chronic administration of the selective serotonin re-uptake inhibitors fluoxetine and clomipramine (CMI) at 5 mg/kg per day and fluvoxamine at 10 mg/kg twice a day significantly decreased schedule-induced polydipsia (SIP) on day 15 and throughout the remainder of the study compared to control rats. The noradrenergic re-uptake inhibitor, desipramine (DMI), only decreased SIP behavior on day 1. The neuroleptic, haloperidol (0.03 and 0.1 mg/kg), and the benzodiazepine, diazepam (2.5 mg/kg), failed to alter SIP behavior. Since obsessive-compulsive disorder (OCD) and polydipsic behavior both involve excessive expression of a normal behavior, the polydipsia model may be relevant for the prediction of compounds useful in the treatment of OCD.

Key words: Schedule-induced polydipsia – Serotonin re-uptake inhibitors – Adjunctive behavior – Obsessive-compulsive disorder

Introduction

Food deprived rats exposed to a procedure in which food is delivered intermittently will drink large amounts of water if given the opportunity to do so. This behavioral phenomenon is termed scheduled-induced polydipsia and is an example of a more general class of behaviors termed adjunctive behaviors (Falk 1971; Pellon and Blackman 1992). The greatest polydipsic behavior is produced with a fixed time feeding schedule of less than or equal to 180 s and greater than or equal to 60 s (Falk 1971). This SIP behavior cannot be explained in terms of a physiological deficit due to water deprivation and despite extensive research, the nature of these behaviors remains uncertain (Falk 1971; Robbins and Koob 1980). Adjunctive behaviors have been cited as potential animal models for human compulsions (Pitman 1989).

Compulsive behaviors observed in patients with obsessive-compulsive disorder (OCD) have also been defined as excessive behaviors (Pitman 1989). To date, only selective serotonin re-uptake inhibitors such as fluoxetine, clomipramine (CMI), and fluvoxamine, attenuate these compulsive behaviors in OCD patients (Goodman et al. 1990a,b; Insel et al. 1990; Rapoport 1991). The purpose of the present investigation was to assess the effects of chronic administration of these serotonergic re-uptake inhibitors on SIP in rats. In addition, the norepinephrine re-uptake inhibitor, desipramine (DMI), the neuroleptic, haloperidol, and the benzodiazepine, diazepam, were evaluated in this paradigm.

Materials and methods

Immature male Wistar rats (Charles River) weighing 180–250 g were individually housed and maintained in accordance with the "NIH Guide to Care and Use of Laboratory Animals" (National Institute of Health Care Publications, No. 85–23, revised 1985) with a 12-h light; 12-h dark cycle and allowed free access to food and water. After at least a 1-week acclimation period the rats were placed on a restricted diet which maintained 80% of their free feeding body weight. To induce polydipsia, rats were placed in test chambers housed in sound attenuated boxes where a pellet dispenser automatically dispensed two 45 mg (Noyes) pellets on a fixed-time 60-s (FT-60 s) feeding schedule over a 150-min test session. Water was available at all times in the test chambers. After 4 weeks (Monday through Friday) of exposure to the FT-60 s feeding schedule, approximately 80% of the rats met a pre-determined criterion for water consumption (greater than 60 ml of water per session) and were considered to have polydipsic behavior. Rats ($n = 6$) were intraperitoneally (IP) administered vehicle or one of the following compounds daily 60 min prior to testing: fluoxetine (2.5 mg/kg and 5 mg/kg), CMI (5 mg/kg), DMI (5 mg/kg), haloperidol (0.03 and 0.1 mg/kg), or diazepam (2.5 mg/kg). Fluvoxamine (10 mg/kg) was administered twice daily due to its short duration of activity. Once dosing commenced, the rats were tested in the chambers once a week to assess SIP behavior. Water bottles were weighed before and after the 150-min test sessions to assess the volume (ml) of water consumed as a means of measuring SIP behav-

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ior. In addition, it was confirmed that the rats consumed all of the food pellets dispensed during the test session to assure that the compounds were specifically affecting polydipsia and not ingestive behaviors in general.

In order to measure water consumption in non-polydipsic food deprived rats, a separate group of rats ($n=6$) was individually housed and received a single bolus (16 g) of food per day which maintained them at 80% of their free feeding body weight. The water bottles were weighed before and after the 150-min daily feeding sessions to assess the volume (ml) of water consumed as a means of measuring drinking.

The experimental data comparing the effects of chronic administration of compounds on SIP behavior were analyzed with the Mann Whitney *U*-Test.

Clomipramine HCl and desipramine HCl (Sigma), diazepam (Roche), fluoxetine HCl (Eli Lilly), fluvoxamine maleate (Solvay-Duphar), and haloperidol (Mc Neil) were either dissolved or suspended in distilled water plus 0.1 ml of Tween 80 and injected IP in a dosage volume of 1 ml/kg. The final volume was prepared to account for salt content and the dosage was expressed as 100% base.

Results

Chronic administration of the serotonin re-uptake inhibitors fluoxetine, CMI, and fluvoxamine caused no significant decrease in water intake in non-polydipsic food deprived rats over a 150-min session. In addition, there were no significant changes in locomotor activity (beam crossing) or weight following administration of these compounds compared to vehicle control. The polydipsic rats significantly increased their mean water intake to 63.2 ± 1.5 ml per session while the control rats averaged 17 ± 1.3 ml of water intake during the 150-min feeding session. The mean $\pm$ SE animal weight was 288 ± 15.8 on day 1 of dosing and 310 ± 17.7 on the final day of dosing.

Figure 1 shows the effects of chronic administration of fluoxetine on SIP behavior. Fluoxetine at 5 mg/kg significantly decreased SIP behavior compared to vehicle control from 63.5 and 62.5 ml to 35 and 37.3 ml on days 15 and 22, respectively. Fluoxetine at 2.5 mg/kg did not significantly attenuate SIP behavior at any time throughout the study. Chronic administration of a 10 mg/kg dose resulted in hypophagia and prevented accurate measurement of SIP behavior.

Figure 2 compares the effective doses of CMI, fluvoxamine, and DMI on SIP behavior in rats. CMI at 5 mg/kg significantly decreased SIP behavior from 60.7 and

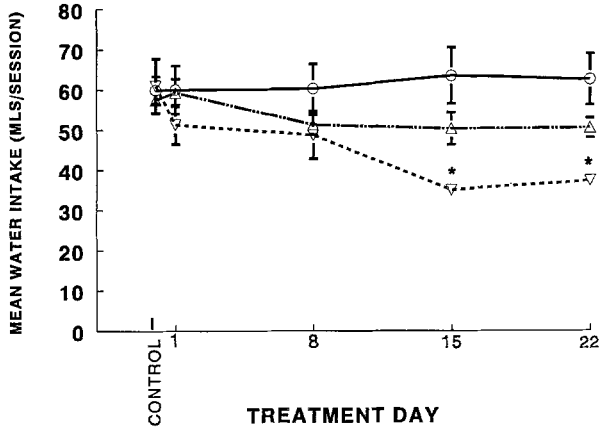

Fig. 1. Effects of fluoxetine (2.5 and 5 mg/kg, IP) or vehicle on the mean water intake ($\pm$ SEM) of polydipsic rats. Drugs were administered daily for 22 days with a 60-min pretreatment on test days. Control data are represented for the day prior to the commencement of dosing. $N=6$ animals per group. $^*P<0.05$ compared to vehicle control. (○ – ○) Vehicle; (△ – ··· – △) fluoxetine 2.5 mg/kg; (▽- - -▽) fluoxetine 5 mg/kg

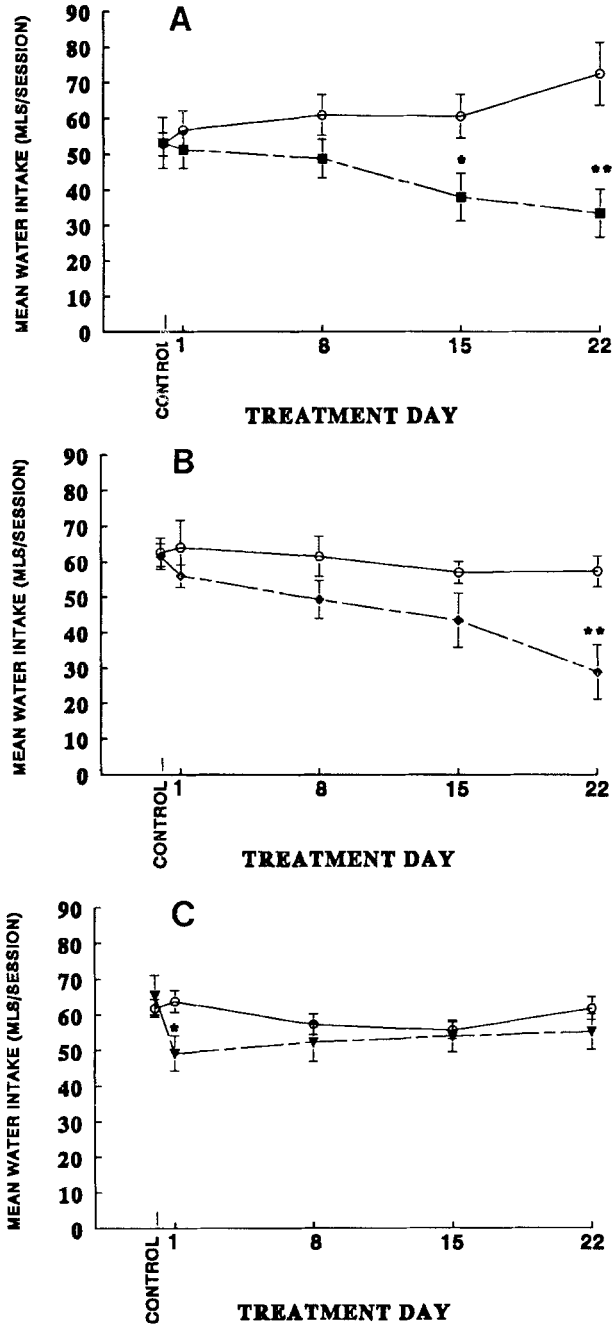

Fig. 2A–C. Effects of **A** clomipramine (5 mg/kg, IP), **B** fluvoxamine (10 mg/kg, IP) and **C** desipramine (5 mg/kg, IP) mean water intake ($\pm$SEM) in polydipsic rats. Drugs were administered once daily (except for fluvoxamine which was dosed twice daily) for 22 days with a 60-min pretreatment on test days. Control data are represented for the day prior to the commencement of dosing. $N=6$ animals per group. $^*P<0.05$, $^{**}P<0.01$ compared to vehicle control. (○ – ○) Vehicle; (■ – – – ■) CMI 5 mg/kg; (◆ – – – ◆) fluvoxamine 10 mg/kg; (▼ – – – ▼) DMI 5 mg/kg

72.6 ml to 38 and 33.5 ml on days 15 and 22, respectively, compared to vehicle control. Fluvoxamine at 10 mg/kg significantly reduced SIP behavior compared to vehicle control from 57.3 ml to 28.8 ml on day 22. DMI at 5 mg/kg only significantly decreased SIP behavior on day 1. This effect was attenuated by day 8 and for the remainder of the study.

Haloperidol at 0.03 and 0.1 mg/kg and diazepam at 2.5 mg/kg failed to have any effect on SIP behavior in rats.

Discussion

Although several classes of compounds have been tested for their ability to attenuate polydipsic behavior, the effects of chronic administration of selective serotonin re-uptake inhibitors have not been investigated. The present results show that administration for 15–22 days of the serotonin re-uptake inhibitors fluoxetine, CMI and fluvoxamine consistently resulted in a significant reduction of SIP behavior. The noradrenergic re-uptake inhibitor, DMI, only reduced SIP behavior on day 1 of administration. The neuroleptic, haloperidol, and the benzodiazepine, diazepam, failed to alter SIP behavior at the doses tested.

Previous investigations have produced conflicting results in SIP after the administration of a number of different classes of compounds such as amphetamine, haloperidol and diazepam. A number of reports have shown that the acute administration of amphetamine caused a decrease in SIP behavior (Sanger 1977; Kuribara and Tadokoro 1980). Additional studies showed that amphetamine also decreased water consumption in water deprived rats (Sanger and Corfield-Sumner 1979). On the other hand, chronic administration of amphetamine induced excessive drinking behavior in rats similar but not identical to SIP behavior (Rowland et al. 1981). The acute administration of haloperidol also decreased SIP behavior in rats but significant sedation was observed, as measured by a decrease in lever pressing (Snodgrass and Allen 1987). It has been observed that subcutaneous administration of diazepam (0.25 mg/kg) resulted in a significant decrease in SIP behavior without decreases in lever pressing (Kuribara and Tadokoro 1980). More recently, investigators have observed that a 1 mg/kg (IP) dose of diazepam did not significantly decrease panel pressing and did not decrease SIP behavior; however, doses which produced significant decreases in panel pressing (3.0–5.0 mg/kg) also significantly decreased SIP behavior (Mittleman et al. 1988). In addition, other studies have shown that after oral administration of diazepam (5, 10, and 15 mg/kg) SIP behavior was not affected, even though there was a significant decrease in lever pressing (Canon and Lippa 1977). The discrepancies between these previous studies and the present investigation may be due to differences in experimental protocols such as acute versus chronic dosing regime, drug pretreatment time, and active behavior required for food reward. Some of the previous studies required rats to panel press in order to obtain a food-reward with an FT-60 s feeding schedule. The present paradigm employed automatic delivery of food pellets on a FT-60 s feeding schedule without requiring lever/panel pressing. Since it has been demonstrated that lever/panel pressing was not necessary for the induction of SIP behavior (Falk 1971), sedative compounds which decrease an animal's ability to lever/panel press may actually decrease the food the rat receives and as a consequence decrease water consumption. Therefore, a reduction in lever pressing which may prolong pellet delivery time past 180 s would result in a weak behavioral condition which would not sustain an adjunctive behavior such as SIP. As a result, lever pressing in order to attain food reward rather than automatic delivery on an FT feeding schedule may produce conflicting results when sedative compounds such as diazepam are administered.

It has been demonstrated that chronic administration of serotonin re-uptake inhibitors reduce food intake in non-food deprived rats (Wong et al. 1988; Clifton et al. 1989; Willner et al. 1990). The present paradigm used food deprived rats maintained at 80% of their free feeding body weight and chronic administration of the serotonin re-uptake inhibitors at doses which reduced SIP behavior did not induce hypophagia in these rats. However, at higher doses of these compounds hypophagia was observed, preventing an accurate measure of SIP behavior. Therefore, these serotonin re-uptake inhibitors selectively decreased SIP behavior while not affecting food intake in food deprived rats.

Previous studies in rats have shown that chronic administration of serotonin re-uptake inhibitors such as fluoxetine results in a functional down regulation of somatodendritic 5-HT_{1A} autoreceptors (Blier et al. 1987; Welner et al. 1989). In addition, electrophysiological studies have demonstrated that chronic administration of these compounds results in increased firing of neurons in the dorsal raphe nucleus and increased 5-HT transmission due to this functional down regulation of the somatodendritic autoreceptors (Blier et al. 1988). In a proposed model for OCD where spontaneous alternation behavior was disrupted by 8-OH-DPAT, chronic administration of fluoxetine attenuated 8-OH-DPAT-induced disruption of this behavior, possibly by down regulating the somatodendritic 5-HT_{1A} receptors (Yadin et al. 1991). Lesch et al. (1991) have also demonstrated that OCD patients given chronic fluoxetine had significantly attenuated ipsapirone-induced hypothermia, indicating a functional hyporesponsivity of the 5-HT_{1A} receptors. However, there was no direct correlation between this hyporesponsivity of the 5-HT_{1A} receptors and improvement of the OCD symptoms with the fluoxetine treatment. The relevance of this functional down regulation of 5-HT_{1A} receptors has yet to be fully determined.

To date, selective serotonin uptake inhibitors only partially improve the symptomatology of OCD (Rapoport 1991); thus, other neurotransmitter dysfunctions may be implicated. Patients with dopaminergic related disorders such as Tourette's syndrome (Frankel et al. 1986; Pauls et al. 1986; Delgado et al. 1990), Huntington's disease (Rapoport 1991) and postencephalic Parkinson's disease (Wise and Rapoport 1989) have a high incidence of obsessive compulsive symptoms, suggesting that OCD may involve a dysfunction of both

serotonergic and dopaminergic transmission. The symptomatology of these disease states has been related to dysfunction in the basal ganglia, an area rich in serotonergic and dopaminergic innovation (Wise and Rapoport 1989). More direct evidence shows that discrete lesions of the basal ganglia produced psychological changes that resembled obsessional illness (Laplane et al. 1984), and brain imaging studies showed that the caudate nuclei had increased metabolism in OCD patients compared to controls (Baxter 1987). Anecdotal reports suggest that haloperidol alone may improve some symptomatology in patients with obsessive-compulsive neurosis (O'Regan 1970), or have no effect in patients with primary OCD symptoms (Hussain and Ahad 1970). To date, the combined treatment of serotonin re-uptake inhibitors and neuroleptic agents has produced varying results, but with some reports showing improvement in symptomatology (Goodman et al. 1990a; McDougle 1990). All of these results suggest that OCD is a heterogenous disease.

In conclusion, SIP behavior induced by the present paradigm may be analogous to the compulsive behaviors observed in OCD (Insel 1988; Pitman 1989). Both the adjunctive behaviors in rats and clinical symptoms of OCD in man can be attenuated by chronic administration of selective serotonin re-uptake inhibitors, suggesting that the present paradigm may serve as an animal model to predict compounds which may be efficacious for some of the symptoms of OCD.

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