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# Fluoxetine prevents 8-OH-DPAT-induced hyperphagia in Fischer inbred rats

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ABSTRACT

Ovariectomized, Fischer rats were hormonally primed with 10 μg estradiol benzoate and 50 μg progesterone or were treated with the sesame seed oil vehicle. Food intake was measured 2 h and 24 h after treatment with 0.25 mg/kg of the 5-$HT_{1A}$ receptor agonist, (±)-8-hydroxy 2-(di-n-propylamino) tetralin (8-OH-DPAT), 5 mg/kg of the selective serotonin reuptake inhibitor, fluoxetine, or their combination. Consistent with prior studies, two hour food intake of rats given fluoxetine and 8-OH-DPAT did not differ from vehicle controls. 8-OH-DPAT-induced hyperphagia, evident at 2 h, was blocked by co-treatment with fluoxetine. However, in contrast to prior studies, 5 mg/kg fluoxetine, alone, had only modest effects on food intake. Differences in our experimental protocols and/or the strain of rat may account for the lower anorectic response to fluoxetine. Nevertheless, the absence of a significant response to fluoxetine, alone, coupled with the drug's attenuation of the hyperphagic effect of 8-OH-DPAT, leads to the suggestion that the behavioral response to the combined treatment is more complex than that of simple additivity. Consistent with this suggestion, 24 h food intake of rats given 8-OH-DPAT and fluoxetine was lower than that of vehicle or 8-OH-DPAT-treated rats.



## 1. Introduction

Fluoxetine (Prozac®) and other selective serotonin reuptake inhibitors (SSRIs) produce anorexia in humans and experimental animals (Caccia et al., 1992; Clifton et al., 1989; Clifton and Lee, 1997; Currie et al., 1998; Halford et al., 2007; Heisler et al., 1999). SSRI-induced anorexia is thought to result, at least in part, from blockage of the reuptake of serotonin (5-HT) into nerve terminals and consequent elevation of extracellular 5-HT (Caccia et al., 1992; Gobert et al., 1997; Halford et al., 2007; Hernandez et al., 1991; Lee and Clifton, 1992; Malagie et al., 1995; Tao et al., 2002; Trillat et al., 1998; Wong et al., 1995). Serotonin plays a major role in the regulation of food intake through both peripheral and central mechanisms (Blundell et al., 1995; Fujitsuka et al., 2009; Garfield and Heisler, 2009; Kaye, 2008) and includes the neurotransmitter's activity at multiple 5-HT receptors (Currie et al., 2002; Dalton et al., 2006; Garfield and Heisler, 2009; Hayes and Covasa, 2006; Heal et al., 2008; Heisler et al., 2006; Lam et al., 2008; Voigt et al., 2002; Xu et al., 2008). Elevations of extracellular 5-HT in regions innervated by 5-HT are correlated with decrements in food intake. Thus, activation of somatodendritic 5-$HT_{1A}$ autoreceptors will produce hyperphagia by reducing the release of 5-HT from nerve terminals (Dourish et al., 1986; Hutson et al., 1986, 1988). It is, therefore, not surprising that pretreatment with the 5-$HT_{1A}$ receptor agonist, (±)-8-hydroxy 2-(di-n-propylamino) tetralin (8-OH-DPAT), was reported to attenuate fluoxetine-induced anorexia (Currie et al., 2004; Currie et al., 1998).

The ability to reverse fluoxetine-induced anorexia has important implications since decrements in food intake may contribute to effects of fluoxetine on sexual dysfunction (Sarkar et al., 2008; Uphouse et al., 2006). Since SSRI-induced sexual dysfunction and eating dysfunction (e.g. nausea) are important contributors to patient noncompliance (Fujitsuka et al., 2009; Gregorian et al., 2002; Montgomery et al., 2002; Ueda et al., 2003; Werneke et al., 2006), further understanding of the responsible mechanisms would be important for the development of therapeutic interventions. The possibility that 5-$HT_{1A}$ receptor agonists could reduce the impact of fluoxetine on food intake is one such potential intervention. However, 8-OH-DPAT's ability to reverse fluoxetine-induced anorexia has been examined only in Sprague–Dawley rats, and systemic effects of 8-OH-DPAT on the response to fluoxetine have only been examined in Sprague–Dawley males (Currie et al., 2002). It is, therefore, important to assess the generality of these observations to another rat strain. In addition, since human females are the major consumers of antidepressant drugs (Grigoriadis and Robinson, 2007; Kessler et al., 1993; Montgomery et al., 2002; Solomon and Herman, 2009), more information is needed about the potential interaction between fluoxetine and the 5-$HT_{1A}$ receptor agonist in females.

In recent reports, subchronic intraperitoneal (ip) treatment of intact, female Fischer inbred rats with 10 mg/kg fluoxetine had rapid effects on food intake as well as on reproductive cyclicity (Sarkar et al., 2008; Uphouse et al., 2006). Food intake was reduced 24 h following the first fluoxetine injection and vaginal cyclicity was disrupted.

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When vehicle-treated females were restricted to the same amount of lab chow that the fluoxetine-treated rats ate during each 24 h period, the food restriction was as effective as fluoxetine in blocking estrous cyclicity (Uphouse et al., 2006). However, with continued fluoxetine treatment, fluoxetine-treated rats recovered from the estrous cycle block within 12 to 16 days while pair-fed rats failed to do so. In contrast, when Sprague–Dawley females were treated with 10 mg/kg fluoxetine under conditions identical to experiments with Fischer females, estrous cycle disruption was modest in spite of a robust fluoxetine-induced decline in food intake (Maswood et al., 2008). These findings allowed the suggestion that Fischer and Sprague–Dawley females may differ in their response to fluoxetine.

Interestingly, the strain difference in the response to 8-OH-DPAT is reversed in that ovariectomized, hormonally primed Sprague–Dawley females are more sensitive than Fischer females to 8-OH-DPAT's ability to inhibit female rat sexual behavior (Uphouse et al., 2002). Since 8-OH-DPAT's ability to reduce effects of fluoxetine on food intake has only been studied in Sprague–Dawley rats, examination of the interaction between fluoxetine and 8-OH-DPAT on eating behavior would be especially important to assess in Fischer females.

In the following experiments, ovariectomized Fischer rats with and without hormonal priming were examined because (1) intraraphe 8-OH-DPAT was reported to attenuate fluoxetine-induced anorexia in Sprague–Dawley males and in ovariectomized females without hormonal priming, but not in intact Sprague–Dawley females (Currie et al., 1998); and (2) hormonally primed ovariectomized females have been reported to show lower 8-OH-DPAT-induced hyperphagia than ovariectomized rats without hormonal priming (Salamanca and Uphouse, 1992).

## 2. Materials and methods

### 2.1. Materials

Estradiol benzoate (EB), progesterone (P), sesame seed oil, the serotonin reuptake inhibitor, [±]-N-methyl-γ-[4-(trifluoromethyl)-phenoxy]benzenepropanamine (fluoxetine), and the 5-$HT_{1A}$ receptor agonist, (±)-8-hydroxy 2-(di-n-propylamino) tetralin (8-OH-DPAT), were purchased from Sigma-Aldrich Chemical Company (St. Louis, MO). Isoflurane (AErrane®) and suture materials were purchased from Henry Schein (Melville, NY). Food (8604 Harlan Teklad rodent diet) was purchased from Harlan Teklad (Madison, WI). All other supplies came from Fisher Scientific (Houston, TX).

### 2.2. Treatment of animals

Female, Fischer inbred rats (CDF-344) were purchased from Charles River Laboratories (Wilmington, MA). Upon arrival, rats were housed 2 or 3 per cage in polycarbonate shoebox cages (45.72×24.13×2.59 cm) in a housing room maintained at 25 °C and 55% humidity with a 12:12 h light–dark cycle (lights on from 12:00 am to 12:00 pm). Food and water were available *ad lib*. Approximately two weeks after arrival, the rats were bilaterally ovariectomized under AErrane® anesthesia as previously described (White and Uphouse, 2004). At least two weeks later, rats were singly housed for 7 days until the completion of the experiment. All procedures were in accordance with PHS policy and were approved by the IACUC at Texas Woman's University.

Ovariectomized rats with and without hormonal priming were used in the study. For hormonal priming, rats were injected with 10 μg estradiol benzoate in the afternoon followed two days later with 50 μg progesterone (EP rats) at 9:00 am. Injections were delivered subcutaneously (sc) in 0.1 ml sesame seed oil. Ovariectomized rats without hormonal priming (OO rats) received sesame seed oil injections instead of the estradiol benzoate or progesterone. Rats were injected ip with saline (1 ml/kg) on the day of the injection with estradiol benzoate and on the following day in order to familiarize them with injections. On these two days, rats were also handled as previously described (Uphouse et al., 2009). These "sham" procedures were designed to simulate injection conditions that would take place on the day of the experiment.

On the day of the progesterone (or oil) injection, food was removed at 9:00 am (during the light portion of the light/dark cycle) and rats were weighed immediately before injection. At approximately 1:00 pm (1 h after lights off), rats were injected ip with 8-OH-DPAT (0.25 mg/kg) or saline. Ten minutes later, rats were injected ip with either 5 mg/kg fluoxetine or ultrapure water. Doses of 8-OH-DPAT and fluoxetine were based on our earlier studies (Guptarak et al., 2010; Salamanca and Uphouse, 1992) and those of Currie et al. (Currie et al., 2004; Currie et al., 1998). Four treatment groups were included in each of the EP and OO conditions: saline/water (vehicle group), 8-OH-DPAT/water (DPAT group), saline/fluoxetine (fluoxetine group), and 8-OH-DPAT/fluoxetine (DPAT/fluoxetine group). 8-OH-DPAT (dissolved in saline) and fluoxetine (dissolved in ultrapure water) were injected ip in a volume of 1 ml/kg.

Thirty minutes after the fluoxetine or water injection, a pre-measured quantity of food was returned to the cage and rats were left undisturbed. Two hours later, food was removed, weighed for assessment of 2 h food intake, and returned to the rat's cage. Twenty-four hours later, the remaining food was again weighed for assessment of 24 h food intake. Body weight was monitored on the morning of the progesterone/oil injection and at the conclusion of the 24 h food intake.

The complete experiment was conducted in three phases to restrict the portion of the light/dark cycle during which the experiment was conducted and to counterbalance across variables (within days): (1) EP rats were given each of the four treatments each day (24 rats), (2) OO rats were given each of the four treatments each day (26 rats), or (3) pairs of EP and OO rats were given identical treatments within days (14 EP and 15 OO rats; data from 1 EP rat was lost).

### 2.3. Statistical analysis

Food intake was evaluated by two-factor ANOVA with hormone and drug treatment as independent factors and 2 h or 24 h food intake as dependent factors. Body weight changes were compared with two-factor repeated measures ANOVA with pre and post treatment body weight as the repeated factor. Data were analyzed with SPSS version 15.0 or 17.0. Post-hoc comparisons were made with Newman–Keul's procedures (Zar, 1999).

## 3. Results

Effects of 8-OH-DPAT and fluoxetine on 2-h food intake are shown in Fig. 1. As expected, 8-OH-DPAT produced robust hyperphagia ($F_{1,71}=7.9$, $p\leq0.01$) and fluoxetine reduced food intake ($F_{1,71}=16.57$, $p\leq0.001$). However, the 5 mg/kg dose of fluoxetine had smaller effects on food intake than expected so that, within hormonal treatment, food intake of fluoxetine-treated rats was not significantly different from the vehicle controls ($p>0.05$). However, there was a significant interaction between 8-OH-DPAT and fluoxetine treatment ($F_{1,71}=3.06$, $p\leq0.05$) due to the attenuation of 8-OH-DPAT-induced hyperphagia by fluoxetine treatment.

OO rats ate significantly more than EP rats ($F_{1,71}=8.01$, $p\leq0.01$) but did not differ from EP rats in their response to the drug treatments. Within hormonal groups, 8-OH-DPAT significantly increased food intake relative to the vehicle control [8-OH-DPAT vs vehicle for EP and OO rats, respectively, $q_{71,2}=3.67$ and 3.67, $p\leq0.05$)] and fluoxetine reduced the response to 8-OH-DPAT (for EP and OO rats, respectively, $q_{71,2}=4.69$ and 5.53, $p\leq0.05$). 8-OH-DPAT plus fluoxetine-treated rats did not differ from either the vehicle

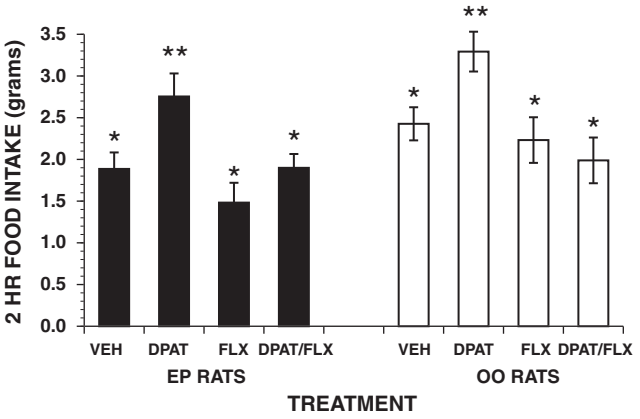


**Fig. 1.** Two hour food intake in EP and OO rats. Ovariectomized rats were hormonally primed with 10 μg estradiol benzoate followed by 50 μg progesterone (EP rats) or received control injections with sesame seed oil (OO rats). Data are the mean ± S.E. 2 h food intake for vehicle-treated rats (VEH), rats injected with 0.25 mg 8-OH-DPAT (DPAT), rats injected with 5 mg/kg fluoxetine (FLX), and rats injected with 5 mg/kg fluoxetine and 0.25 mg/kg 8-OH-DPAT (DPAT/FLX). For EP and OO rats, N's for vehicle, 8-OH-DPAT, fluoxetine, and 8-OH-DPAT/fluoxetine, respectively, were 10, 9, 10, 10 and 9, 9, 11, 11. *Indicates significant difference from rats treated only with 8-OH-DPAT. **Indicates significant difference from vehicle-treated rats.

control ($q_{71,2}$ and $q_{71,3}$ for EP and OO rats, respectively, = 1.78 and 1.06, $p > 0.05$) or from rats treated with fluoxetine, alone (all $p > 0.05$).

Twenty-four hours after treatment (Fig. 2), significant effects of hormone ($F_{1,71} = 7.07$, $p \leq 01$) and fluoxetine ($F_{1,71} = 23.39$, $p \leq 0.001$), but not 8-OH-DPAT ($F_{1,71} = 3.27$, $p \geq 0.05$), were still present. Food intake of rats given 8-OH-DPAT plus fluoxetine was significantly less than rats treated only with 8-OH-DPAT (for EP and OO rats, respectively, $q_{71,4} = 4.94$ and 4.58, $p \leq 0.05$) or the vehicle control (for EP and OO rats, respectively, $q_{71,3} = 4.71$ and 3.63, $p \leq 0.05$).

Body weight was relatively unaffected by the experimental treatments (data not shown). Although OO rats had slightly greater body weight (respectively for EP and OO rats, mean ± S.E. = 158.6 ± 1.38 and 164.1 ± 1.37, $F_{1,71} = 8.14$, $p \leq 0.01$), none of the other main effects were significant (all $p > 0.05$). There was, however, an interaction between pre and post-treatment body weight and fluoxetine treatment ($F_{1,71} = 5.17$, $p \leq 0.05$). In water-treated rats, body weight was roughly equivalent before and after treatment (respectively, 161.0 ± 1.42 and 161.2 ± 1.4) while fluoxetine-treated rats showed a slight decrease in body weight (respectively 162.0 ± 1.34 and 161.2 ± 1.34).

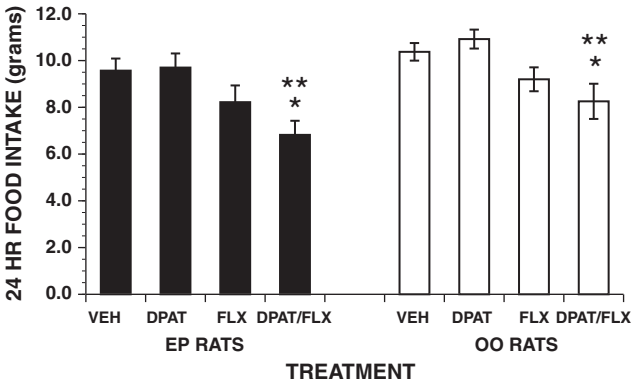


**Fig. 2.** Twenty-four hour food intake in EP and OO rats. Ovariectomized rats were hormonally primed with 10 μg estradiol benzoate followed by 50 μg progesterone (EP rats) or received control injections with sesame seed oil (OO rats). Data are the mean ± S.E. 24 h food intake for vehicle-treated rats (VEH), rats injected with 0.25 mg 8-OH-DPAT (DPAT), rats injected with 5 mg/kg fluoxetine (FLX), and rats injected with 5 mg/kg fluoxetine and 0.25 mg/kg 8-OH-DPAT (DPAT/FLX). For EP and OO rats, N's for vehicle, 8-OH-DPAT, fluoxetine, and 8-OH-DPAT/fluoxetine, respectively, were 10, 9, 10, 10 and 9, 9, 11, 11. *Indicates significant difference from rats treated only with 8-OH-DPAT. **Indicates significant difference from vehicle-treated rats.

## 4. Discussion

A major objective of the study was to determine if 8-OH-DPAT would attenuate effects of fluoxetine in Fischer female rats and if hormonal priming would attenuate this effect of 8-OH-DPAT. Findings are generally consistent with previous reports in that rats treated with both 8-OH-DPAT and fluoxetine showed 2 h food intake comparable to that of control rats (Currie et al., 2004; Currie et al., 1998). However, while fluoxetine reduced food intake in both EP and OO rats, food intake of fluoxetine and vehicle-treated rats were not significantly different. Moreover, in contrast to prior findings (Salamanca and Uphouse, 1992), there was no interaction between the effects of hormonal priming and the hyperphagic response to 8-OH-DPAT.

The latter observation may result from the lower levels of hormonal priming (10 μg estradiol benzoate and 50 μg progesterone) used in the current study compared to that reported by Salamanca and Uphouse (1992) (25 μg estradiol benzoate and 500 μg progesterone) since both estradiol benzoate and progesterone can reduce the effect of 5-$HT_{1A}$ receptor activation (Bethea et al., 2002; Jackson and Uphouse, 1998; Truitt et al., 2003). However, the explanation for an absence of anorexia after fluoxetine is less obvious.

The absence of a significant decline in food intake following 5 mg/kg fluoxetine was surprising since, in previous experiments with Sprague–Dawley or Wistar rats, a dose of 5 mg/kg, or lower, of fluoxetine did reduce 2 h food intake (Carlini et al., 2007; Currie et al., 2004; Currie et al., 1998). We have shown robust anorexia in regularly cycling Fischer females following 10 mg/kg fluoxetine (Uphouse et al., 2006) so Fischer females may require doses higher than 5 mg/kg fluoxetine before anorexia is statistically apparent. This would be consistent with other work in Fischer females where disruption of female sexual behavior was modest after an acute treatment with 5 mg/kg fluoxetine but clearly evident following 10 mg/kg (Guptarak et al., 2010). However, in prior experiments (Guptarak et al., 2010; Uphouse et al., 2006), food was not removed during fluoxetine treatment. In the current study, food removal on the morning of the experiment could have partially attenuated the anorectic effects of fluoxetine.

However, anorectic effects of 5 mg/kg fluoxetine have been reported following food restriction during the first 2 h of the dark cycle (Heisler et al., 1999) or even after 24 h food restriction (Hagan et al., 1997). It is important, though, that in each of these experiments, rats had been conditioned to eat specialized and/or highly palatable diets rather than the usual rat pellets used in the current study. When male Sprague–Dawley rats were conditioned to eat a palatable wet mash diet for 2 h/day (with food pellets available 22 h/day), food intake during the 2 h experiment was considerably higher (8–10 fold) than that of the current study. The higher food intake of control rats might be expected to amplify effects of fluoxetine. Therefore, the relatively low food intake of control Fischer rats may have contributed to the apparent lack of efficacy of fluoxetine. However, 5 mg/kg fluoxetine reduced food intake of Wistar rats under conditions of even lower food intake than seen in the present study (Carlini et al., 2007). Therefore, the explanation for the absence of a substantial decline in food intake after fluoxetine treatment is unknown. However, while the precise explanation is not clear, variations in experimental protocols and/or rat strain likely account, in part, for different outcomes in the current and prior studies.

Fischer and Sprague–Dawley females differ in the dose of 8-OH-DPAT required to produce several 5-$HT_{1A}$ receptor-mediated behaviors (Uphouse et al., 2002). For example, subcutaneous treatment with 0.1 mg/kg 8-OH-DPAT essentially eliminated female sexual behavior and elicited flat body posture in hormonally-primed Sprague–Dawley females while smaller effects were seen in Fischer females (Uphouse et al., 2002). Both of these behaviors depend on activation of 5-$HT_{1A}$

receptors in terminal fields rather than at 5-HT cell bodies (Jacobs and Klemfuss, 1975; Tricklebank et al., 1984) responsible for 8-OH-DPAT-induced hyperphagia. Serotonin's reduction in food intake is thought to include the neurotransmitter's interaction with 5-HT receptors in regions terminal to 5-HT neurons (Simansky, 1996) where 8-OH-DPAT can produce hypophagia rather than hyperphagia (Steffens et al., 2010). If Fischer females are less sensitive than Sprague–Dawley females to the behavioral consequences of 5-$HT_{1A}$ activation in these brain areas, Fischer females might be expected to be less vulnerable to fluoxetine-induced anorexia.

The 5 mg/kg dose of fluoxetine, alone, also failed to significantly reduce 24 h food intake. It is, therefore, interesting that 24 h food intake was suppressed in rats that received both 8-OH-DPAT and fluoxetine, evidencing an apparent 8-OH-DPAT enhancement of the effects of fluoxetine. Since 8-OH-DPAT has a short half-life (Mason et al., 1995; Yu and Lewander, 1997), it is unlikely that the lower 24 h food intake reflects a direct effect of 8-OH-DPAT on the response to fluoxetine. Fluoxetine and its metabolite, norfluoxetine, by contrast, have half-lives, respectively of approximately 5 and 15 h (Caccia et al., 1990). Therefore, prior treatment with 8-OH-DPAT may have initiated adaptive changes that amplified effects of fluoxetine or its metabolite. For example, the combination of 8-OH-DPAT and fluoxetine could accelerate somatodendritic 5-$HT_{1A}$ receptor desensitization**.** Consistent with this possibility, 8-OH-DPAT plus fluoxetine enhanced desensitization of somatodendritic 5-$HT_{1A}$ receptors as measured by the ability of 8-OH-DPAT to reduce 5-HT levels in the hypothalamus (Shalom et al., 2004). In addition, 8-OH-DPAT's initial reduction of fluoxetine's elevation of extracellular 5-HT is followed by a rebound response (Tao et al., 2002). Consequently, extracellular 5-HT in the hypothalamus after 8-OH-DPAT plus fluoxetine may exceed that of the vehicle controls. Such desensitization of somatodendritic 5-$HT_{1A}$ receptors should enhance anorectic effects of fluoxetine as seen in the 24 h food intake.

These findings confirm prior reports that food intake of rats treated with 8-OH-DPAT and fluoxetine does not differ from the vehicle control (Currie et al., 2004; Currie et al., 1998) and is the first report of 24 h food intake after the treatment with this drug combination. Given the hyperphagic effects of 8-OH-DPAT and anorectic effects of fluoxetine, an additive effect of the two compounds on food intake is a reasonable explanation for the absence of anorexia following treatment with both drugs. However, in the current study, a dose of fluoxetine that failed to reduce food intake prevented 8-OH-DPAT from increasing food intake. This finding allows the interpretation that the interaction between the two drugs on food intake may not be one of simple additivity.

These findings also illustrate the importance of examining multiple strains in the response to pharmacological manipulations. The Fischer strain, while less often used in the pharmaceutical literature, may prove to be a valuable model system for the study of antidepressant-induced side effects. With its higher anxiogenic profile, Fischer rats may more clearly illuminate the behavioral consequences of pharmacological interventions in individuals that are vulnerable to the development of mood disorders.

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