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Differential Effects of Antidepressant Treatments on Fenfluramine-Induced Increases in Plasma Prolactin and Corticosterone in Rats

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AULAKH, C. S., J. ZOHAR, K. M. WOZNIAK, J. L. HILL, M. HAASS AND D. L. MURPHY. *Differential effects of antidepressant treatments on fenfluramine-induced increases in plasma prolactin and corticosterone in rats.* PHARMACOL BIOCHEM BEHAV **39**(1) 91–95, 1991.—Intravenous administration of 5-HT releasing agent, fenfluramine, to rats produced increases in plasma prolactin and corticosterone concentrations. Short-term or long-term treatment with either clorgyline or imipramine did not affect baseline levels of prolactin or corticosterone. On the other hand, short-term but not long-term lithium treatment significantly increased baseline levels of corticosterone but not of prolactin. Short-term treatment with lithium but not clorgyline or imipramine potentiated fenfluramine-induced increases in plasma prolactin but not corticosterone. On the other hand, long-term treatment with clorgyline but not imipramine or lithium attenuated fenfluramine's effect on plasma prolactin but not on corticosterone. These findings demonstrate differential effects of antidepressant treatments on fenfluramine-induced increases in plasma prolactin and corticosterone in rats and are consistent with several other clinical and animal studies demonstrating dissimilar actions of different antidepressant treatments on two different 5-HT-mediated neuroendocrine functions.

Fenfluramine Clorgyline Imipramine Lithium Rats Prolactin Corticosterone

BRAIN serotonin changes have been implicated in the etiology of affective illness and the mode of action of antidepressant and antimanic drugs (33, 39, 49). Due to the therapeutic lag between the initiation of antidepressant treatment and onset of clinical effects, animal studies of molecular mechanisms pertinent to antidepressant efficacy have concentrated on the adaptive changes in various aminergic neurotransmitter systems following long-term antidepressant treatment. Adaptive changes in the serotonergic neurotransmitter mechanism have been studied using behavioral, electrophysiological, neuroendocrine, and biochemical paradigms (56).

Fenfluramine is used as an anorexigenic agent in man since it reduces food intake without central nervous system stimulant side effects (17,46). Fenfluramine acts presynaptically to release serotonin. In rats, administration of fenfluramine produces increases in plasma prolactin (43,57) and corticosterone (14). Attenuation of the stimulatory effects of fenfluramine on corticosterone (47) and prolactin (44) secretion by prior depletion of serotonin concentration by either raphe lesions or by intraventricular injection of 5,7-dihydroxytryptamine (5,7-DHT) suggests that these effects are mediated by serotonin release.

In previous reports from this laboratory, we have observed differential effects of long-term antidepressant treatments on fenfluramine-induced versus m-chlorophenylpiperazine (m-CPP, a postsynaptic 5-HT_1 receptor agonist)-induced decreases in food intake and locomotor activity in rats (1, 3, 4, 9). Recently, we demonstrated attenuation and potentiation of m-CPP-induced increases in plasma prolactin but not corticosterone following long-term treatment with clorgyline (a selective MAO type A inhibiting antidepressant) and imipramine (a tricyclic antidepressant), respectively (2,5). In the present study, we used fenfluramine as a challenge agent to explore functional adaptational changes in the serotonergic neurotransmission involved in the secretion of prolactin and corticosterone following long-term

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treatment with imipramine, clorgyline and lithium in rats. Lithium has antimanic, antidepressant, and mood-stabilizing properties (42).

METHOD

Male Wistar rats weighing approximately 250 g at the beginning of the study were used. The animals were housed six per cage and had free access to food and water. Under halothane anesthesia, the left femoral artery and vein were cannulated (PE 50, polyethylene tubing) in each animal, and the catheters were exteriorized subcutaneously at the back of the neck (22). For protection of the exteriorized cannulae, the animals were put into special jackets (Harvard Instruments) allowing the animals to freely move in their individual cage without twisting or damaging the catheter. After surgery, each animal was kept individually in a clear plastic cage with food and water freely available. Both the arterial and venous cannulae were flushed every day with heparinized saline to prevent blood clotting. Saline or fenfluramine hydrochloride (2.5 mg/kg) was injected intravenously (11:00–11:30 a.m.) at least 48 hours after the surgery. Separate groups of animals were used for short-term (2–3 days) and long-term (21–22 days) antidepressant studies. In the antidepressant studies, imipramine hydrochloride (5 mg/kg/day), clorgyline (1 mg/kg/day) or saline was subcutaneously administered continuously by means of osmotic minipumps (Alza Corporation) for 28 days; the pumps were reimplanted at 2 weeks. Each osmotic minipump was 2.5 cm long with a mean pumping rate of 0.49 μl/h and a mean fill volume of 193 μl. In the case of lithium, the animals were given rat chow (solid) containing lithium carbonate for 22 days. Plasma levels of lithium in rats maintained on this diet were 0.8 ± 0.07 mEq/l. Plasma levels of lithium were determined by atomic absorption spectroscopy. All the imipramine-treated, clorgyline-treated, lithium-treated, and saline-treated animals were challenged first with saline followed by a 2.5 mg/kg dose of fenfluramine, separated by 24 hours during both short-term (2–3 days) and long-term (21–22 days) antidepressant treatment. The selection of the moderate dose of fenfluramine was based on the previously published dose-response studies on plasma prolactin and corticosterone (15, 43, 55). Blood samples (1.5 ml) were drawn between 11:30–12:00 a.m. in each animal 30 minutes after saline or fenfluramine injection. Blood was collected in centrifuge tubes containing 0.5 ml of ethylenediaminetetracetic acid (EDTA). Following centrifugation, plasma samples were collected and stored at −70°C. The plasma concentrations of prolactin and corticosterone were measured by radioimmunoassays as described elsewhere (40,53).

Drugs

Imipramine hydrochloride (Sigma Chemical Co., St. Louis, MO), clorgyline hydrochloride (Research Biochemicals, Inc., Natick, MA) and d,l-fenfluramine hydrochloride (A.H. Robins Company, Richmond, VA) were all dissolved in saline. Doses of the drugs given in the text refer to the salt. The volume injected was 0.1 ml/100 g of body weight.

Statistical Analysis

These data were analyzed by repeated measures analysis of variance (GLM procedure, SAS Institute, Cary, NC). Significant effects were further characterized by one-way analysis of variance at each level of the repeated factor accompanied by a priori designed contrasts.

RESULTS

Short-term (3-day) or long-term (21-day) treatment with various antidepressants did not produce significant changes in baseline levels of prolactin (Fig. 1) or corticosterone (Fig. 2) as compared to saline treatment except for increased corticosterone levels in short-term lithium-treated animals (Fig. 2A).

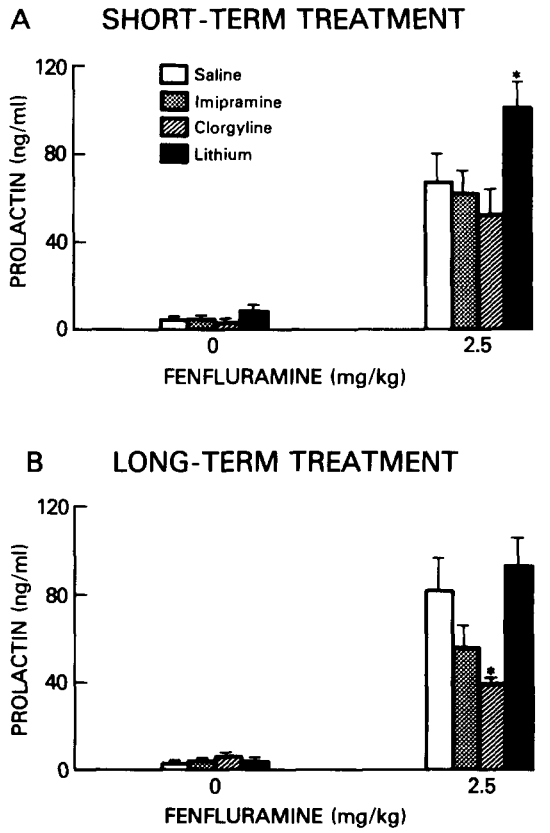

FIG. 1. Effect of short-term (3-day, A) and long-term (21-day, B) saline or antidepressant drug treatments on fenfluramine-induced increases in plasma prolactin (ng/ml) levels in rats. Values of antidepressant-treated animals significantly different from saline-treated animals are represented by $*p<0.05$.

For prolactin (Fig. 1), during short-term antidepressant treatment, there was a significant, $F(1,18)=117.78$, $p<0.001$, fenfluramine drug effect, a significant, $F(3,18)=3.48$, $p<0.05$, antidepressant treatment effect but nonsignificant, $F(3,18)=2.46$, $p>0.05$, drug × treatment interaction. Further analysis revealed that fenfluramine-induced increases in prolactin in short-term lithium-treated animals, but not in animals receiving other antidepressants, differed significantly, $F(1,18)=4.71$, $p<0.05$, from those of saline-treated animals (Fig. 1A). During long-term antidepressant treatment, there was a significant, $F(1,16)=127.38$, $p<0.001$, fenfluramine drug effect, a significant, $F(3,16)=4.33$, $p<0.05$, antidepressant treatment effect as well as a significant, $F(3,16)=5.32$, $p<0.01$, drug × treatment interaction. Further analysis revealed that fenfluramine-induced increases in prolactin were less in long-term clorgyline-treated animals but were not different in other antidepressant-treated animals compared to saline-treated animals, $F(1,16)=6.0$, $p<0.05$ (Fig. 1B).

For corticosterone (Fig. 2), during short-term antidepressant treatment, there was a significant, $F(1,17)=48.0$, $p<0.001$, fenfluramine drug effect, a significant, $F(3,17)=4.79$, $p<0.05$, antidepressant treatment effect but nonsignificant, $F(3,17)=0.73$, $p>0.05$, drug × treatment interaction. Further analysis

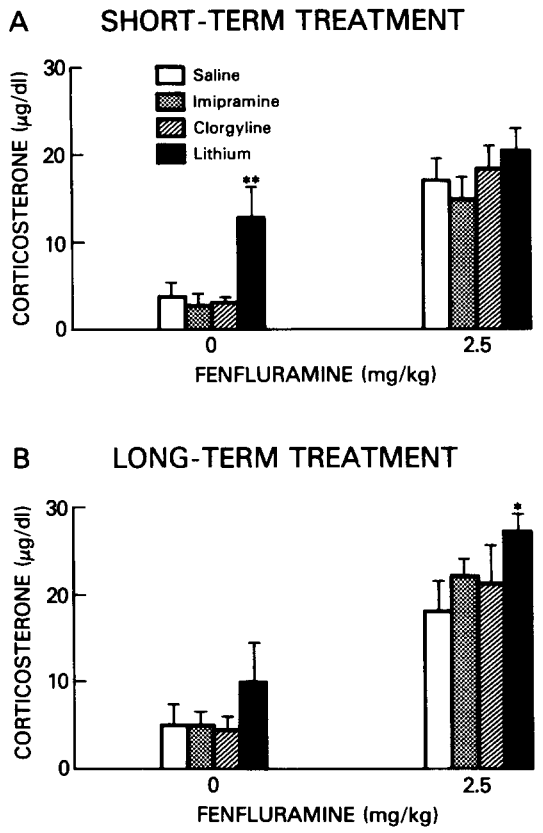

FIG. 2. Effect of short-term (3-day, A) and long-term (21-day, B) saline or antidepressant drug treatments on fenfluramine-induced increases in plasma corticosterone (µg/dl) levels in rats. Values are expressed as means ± S.E.M. from 5–6 animals. Values of antidepressant-treated animals significantly different from saline-treated animals are represented by $*p<0.05$; $**p<0.01$.

revealed that during short-term antidepressant treatment, there was no significant difference between the saline-treated animals and any of the three antidepressant-treated animals in response to fenfluramine challenge. However, the baseline values of lithium-treated animals were significantly, $F(1,17)=8.76$, $p<0.01$, higher than those of saline-treated animals (Fig. 2A). During long-term antidepressant treatment, there was a significant, $F(1,14)=54.58$, $p<0.01$, fenfluramine drug effect, a nonsignificant, $F(3,14)=2.76$, $p=0.08$, antidepressant treatment effect and a nonsignificant, $F(3,14)=0.23$, $p>0.05$, drug × treatment interaction. Further analysis revealed that the values of long-term lithium-treated animals were significantly, $F(1,14)=7.28$, $p<0.05$, higher than those of saline-treated animals (Fig. 2B).

DISCUSSION

The demonstration of enhanced secretion of prolactin and corticosterone following intravenous administration of fenfluramine in the present study is consistent with previous reports using intraperitoneal (IP) administration of fenfluramine (15, 43, 47). Fenfluramine acts presynaptically to release serotonin, an effect thought to mediate fenfluramine-induced behavioral and neuroendocrine changes. There is a variety of evidence suggesting a stimulatory role for the serotonergic mechanism in the secretion of prolactin (31) and corticosterone (14).

Long-term but not short-term treatment with clorgyline, which is an MAO type A inhibiting antidepressant (38), was found to significantly attenuate fenfluramine-induced increases in plasma prolactin but not corticosterone. In a previous report from this laboratory, we demonstrated attenuation of m-chlorophenylpiperazine (m-CPP)-induced increases in plasma prolactin but not corticosterone or growth hormone following similar long-term clorgyline treatment (5). m-CPP is a postsynaptic serotonergic receptor agonist (24). Fenfluramine-induced prolactin release is mediated by stimulation of serotonergic receptors since pretreatment with the serotonergic receptor antagonist metergoline attenuates fenfluramine-induced (43) increases in plasma prolactin. Thus one possible explanation for the attenuated prolactin response to fenfluramine may be development of functional subsensitivity of 5-HT receptors mediating prolactin release following long-term clorgyline treatment. A direct role of dopamine (DA) in attenuating fenfluramine's effect on prolactin seems unlikely since similar long-term clorgyline treatment does not have any significant effect on dopamine levels in the rat cortex (5), [^{3}H] spiroperidol binding or stereotypy (30). Various investigators have reported adrenergic innervation and a high density of β-adrenoceptors to be present in the corpus striatum (12,28) on DA neurons (45). Thus it could be argued that decreases in β-adrenoceptor number induced by similar long-term clorgyline treatment (10) might alter DA receptor-mediated responses. Alternatively, clorgyline-induced changes in serotonergic system might alter DA receptor-mediated responses: apomorphine-induced stereotypy has been reported to be increased or decreased by impairment or enhancement of serotonergic function (35). It is of note that unlike attenuation of fenfluramine's effect on plasma prolactin, similar long-term clorgyline treatment accentuates fenfluramine-induced anorexia without any effect on locomotor activity (3).

Long-term or short-term treatment with the tricyclic antidepressant imipramine did not have any significant effect on fenfluramine-induced increases in either plasma prolactin or corticosterone. Biochemical studies have shown that fenfluramine has to be taken up by the 5-HT uptake mechanism into the presynaptic neuron in order to produce release or depletion of serotonin since pretreatment with 5-HT uptake inhibitors of the tricyclic type, such as clomipramine, prevents the decrease in 5-HT caused by fenfluramine (18). In a previous report from this laboratory, we demonstrated attenuation of fenfluramine-induced anorexia following similar long-term but not short-term treatment with imipramine (4). The failure of long-term imipramine treatment to attenuate fenfluramine's effect on plasma prolactin may be explained by the fact that long-term imipramine treatment also produces functional supersensitivity of 5-HT receptors mediating prolactin release. Thus long-term but not short-term imipramine treatment potentiates the direct effects of the 5-HT receptor agonist, m-CPP, on plasma prolactin (2). Other investigators have demonstrated potentiation of the prolactin releasing effects of 5-HT precursors following long-term administration of tricyclic antidepressant drugs both in rodents (34) and humans (7).

Potentiation of fenfluramine's effect on plasma prolactin in short-term (3-day) lithium-treated animals in the present study is consistent with a previous study demonstrating enhanced prolactin responses to 5-hydroxytryptophan (5-HTP) and 5-MeODMT in 4-day lithium-treated rats (34). Failure of long-term lithium treatment to potentiate fenfluramine's effect on plasma prolactin in the present study is consistent with a clinical report in which long-term lithium treatment did not affect fenfluramine-induced prolactin secretion in manic depressive patients as well as healthy subjects (36). Glue et al. (20) demonstrated potentiation of L-trytophan's effect on plasma prolactin in normal subjects following 4-day as well as 20-day lithium treatment. In the case

of corticosterone, our findings are consistent with two earlier clinical reports demonstrating potentiation of fenfluramine (37) and 5-HTP's (32) effects on cortisol in manic depressive patients following long-term lithium treatment. Several earlier studies have shown that lithium treatment enhances synthesis and/or turnover of brain serotonin (13,26). In addition, long-term lithium treatment also decreases postsynaptic 5-HT_1 and 5-HT_2 receptor densities (23,51). This may explain failure of long-term lithium treatment to potentiate fenfluramine's effect on plasma prolactin in the present study. Alternatively, enhanced synthesis of dopamine in the brain or an increased activity of tuberoinfundibular dopaminergic neurons following long-term lithium treatment (21) may account for long-term versus short-term lithium treatment consequences.

In the present study, none of the three antidepressants affected baseline prolactin levels following either short-term or long-term treatment. Our data are consistent with previous reports using subchronic (2 weeks) treatment with imipramine and clorgyline (11,16). However, it is noteworthy that acute administration of much higher doses (10 or more times than used in the present study) of several MAO inhibitors have been reported to increase and decrease baseline plasma prolactin levels (8,25).

Administration of lithium has been reported to lower baseline prolactin levels in some studies (21,48) but not others (6,50). We did not observe any significant effect of either short-term or long-term lithium treatment on baseline prolactin levels. However, plasma corticosterone levels were found to be significantly higher in short-term lithium-treated animals relative to controls. Lithium has been reported to act directly on anterior pituitary cells to stimulate the release of ACTH (58). Adaptational changes in various aminergic neurotransmitter mechanisms (41,52) may be responsible for failure of long-term lithium treatment to maintain enhanced baseline plasma corticosterone levels in the present study.

The demonstration of a differential effect of antidepressant treatments on 5-HT agonist-induced increases in plasma prolactin and corticosterone in the present study is consistent with a variety of clinical and animal studies. Thus long-term treatment with tricyclic antidepressants potentiates L-tryptophan-induced increases in prolactin (7) but attenuates 5-hydroxytryptophan-induced increases in cortisol (32) in depressed patients. In animal studies, long-term imipramine treatment potentiated m-CPP-induced increases in plasma prolactin but not corticosterone (2). In another study, long-term clorgyline treatment attenuated m-CPP-induced increases in plasma prolactin but not corticosterone levels, whereas short-term clorgyline treatment attenuated m-CPP's effect on plasma corticosterone but not on prolactin levels (5). One possible explanation for this differential effect may be that different 5-HT receptor subtypes may be involved in mediating prolactin and corticosterone release and, furthermore, these different 5-HT receptor subtypes may be affected differentially following antidepressant treatment. Several investigators have suggested that serotonergic regulation of corticosterone secretion is mediated by 5-HT_{1A} receptors (19, 27, 29) with a possible involvement of 5-HT_2 receptors (27). On the other hand, regulation of prolactin secretion has been suggested to be mediated by 5-HT_{1B} receptors (54). Alternatively, adaptational consequences of long-term treatment with various antidepressants may not be equal throughout the brain and may depend more specifically on changes induced within the brain areas influencing that particular paradigm, including changes in other interactive neurotransmitter systems.

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