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Differential effects of chronic imipramine and fluoxetine on basal and amphetamine-induced extracellular dopamine levels in rat nucleus accumbens

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Abstract

The effect of chronic treatment with the tricyclic antidepressant drug, imipramine (10 mg/kg per day), the selective serotonin (5-HT) reuptake inhibitor, fluoxetine hydrochloride (10 mg/kg per day), and vehicle, in drinking water for 24–28 days followed by 3–5 days withdrawal, on extracellular dopamine levels was studied in rat nucleus accumbens by in vivo microdialysis. Basal extracellular dopamine levels in the nucleus accumbens were increased after chronic imipramine (12.7 ± 1.5 fmol/20 μl per 30 min, $P = 0.019$), and moderately decreased after chronic fluoxetine (6.5 ± 0.6, $P = 0.047$), as compared to the vehicle controls (9.1 ± 0.7), determined by one-way analysis of variance (ANOVA). Repeated measure ANOVA indicated that the D-amphetamine sulfate (0.5 mg/kg, s.c.)-induced increase in extracellular dopamine levels in the nucleus accumbens was potentiated after chronic imipramine ($P = 0.002$), but unchanged after chronic fluoxetine ($P = 0.83$). The difference in the effect of amphetamine could be influenced by the significant differences in basal levels. However, these results were also confirmed by analysis of the net area under the curve (net-AUC) for a 180-min period (six samples): for chronic imipramine (337 ± 45 fmol/180 min, $P = 0.005$) and chronic fluoxetine (249 ± 38, $P = 0.57$), as compared to the vehicle controls (178 ± 29), determined by one-way ANOVA. We suggest that the effect of treatment with these agents on mesolimbic dopamine is unlikely to be involved in their shared antidepressant action, but may be relevant to other aspects of the therapeutic profile of these two drugs, e.g. the switch into mania which is more common after treatment with imipramine than fluoxetine and exacerbation of positive symptoms in patients with schizophrenia or schizoaffective disorder.

Keywords: Fluoxetine; Imipramine; Antidepressant; Amphetamine; Dopamine; Microdialysis; Nucleus accumbens; (Rat)

1. Introduction

Modulation of subcortical dopamine neurotransmission by antidepressant drugs could account for their clinical and side effect profiles, e.g. ability to cause psychotic and extrapyramidal symptoms (Meltzer et al., 1979; Coulter and Pillans, 1995). For example, the selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor antidepressant fluoxetine has been reported to acutely increase cortical extracellular dopamine levels without affecting extracellular dopamine levels in the nucleus accumbens (Jordan et al., 1994; Tanda et al., 1994; Clark et al., 1996). Similarly, tricyclic antidepressants such as imipramine, clomipramine, desipramine, and amitriptyline, as well as atypical antidepressants such as mianserin and maprotiline have also been reported to acutely increase cortical extracellular dopamine levels without affecting extracellular dopamine levels in the nucleus accumbens (Gresch et al., 1995; Kihara and Ikeda, 1995; Tanda et al., 1994, 1996b). Furthermore, striatal extracellular dopamine levels are reported to be increased by imipramine and clomipramine, but decreased by selective serotonin reuptake inhibitor such as fluoxetine, sertraline, paroxetine (Meltzer et al., 1993) and citalopram (Dewey et al., 1995), or unchanged by amitriptyline (Meltzer et al., 1993), desipramine (Pozzi et al., 1994; Gresch et al., 1995) and fluoxetine (Perry and Fuller, 1992; Maj et al., 1996). We have recently reported that imipramine (10 mg/kg, s.c.) and clomipramine (10 mg/kg, s.c.) increased extracellular dopamine levels

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in the striatum but not the nucleus accumbens, whereas fluoxetine (10 mg/kg, s.c.) decreased extracellular dopamine levels in both regions (Ichikawa and Meltzer, 1995). Taken together, these results suggest that the antidepressant effect of these drugs is unlikely to be related to the acute effects on the mesolimbic dopamine neurotransmission.

However, chronic studies in rodents may be more relevant to the therapeutic actions of antidepressant drugs since their therapeutic action is often delayed for 2–6 weeks. Chronic desipramine treatment is reported to potentiate the ability of amphetamine to increase extracellular dopamine levels in the nucleus accumbens but not the striatum, while leaving basal levels unaffected in either region (Nomikos et al., 1991). Chronic imipramine is also reported to potentiate the ability of cocaine to increase extracellular dopamine levels in the nucleus accumbens, but had no effect on basal levels (Rossetti et al., 1991). Fluoxetine is reported to have no effect on extracellular dopamine levels in the medial prefrontal cortex (Tanda et al., 1996a) or the nucleus accumbens (Clark et al., 1996), after chronic treatment. These results, collectively, suggest that tricyclic antidepressants may facilitate stimulated dopamine neurotransmission in the nucleus accumbens after chronic treatment.

Recent clinical studies reported that the manic switch in bipolar depressed patients occurred substantially more often with tricyclic antidepressants (11.2%) than with selective serotonin reuptake inhibitors (3.7%) or placebo (4.2%) (Peet, 1994). Henry et al. (1992) reported that among the unipolar and bipolar depressed patients, the risk of mania was significantly greater in the active control-treated patients (0.79%) compared to the placebo-treated patients (0.13%) whereas there was no significant difference in the incidence of mania between the selective serotonin reuptake inhibitor sertraline (0.39%)- and placebo-treated patients. Amphetamine is reported to be capable of inducing a significant switch from depression to mania in bipolar patients (Peet and Peters, 1995). Thus, it could be speculated that the ability of tricyclic antidepressants to facilitate mesolimbic dopamine neurotransmission by increasing basal and/or amphetamine-induced dopamine release, contribute, at least in part, to the mechanism(s) involved in the induction of the manic switch in patients with bipolar depression during tricyclic antidepressant treatment.

Antidepressant drugs are frequently given to schizophrenic patients who are experiencing depression. Specifically, tricyclic antidepressant drugs are known to produce an acute exacerbation of delusions and hallucinations as a sequelae to this (Siris et al., 1978; Plasky, 1991). This could also be related to increased dopaminergic activity in the nucleus accumbens. However, fluoxetine has been reported to improve negative symptoms without worsening positive symptoms of schizophrenic patients when added to antipsychotic drugs (Goff et al., 1995). Thus, it could also be hypothesized that fluoxetine produces less of an effect on mesolimbic dopaminergic activity after chronic treatment than does imipramine.

The present study was designed to test the hypothesis that chronic imipramine produces a facilitating effect on basal and amphetamine-induced increases in extracellular dopamine levels in the nucleus accumbens, whereas chronic fluoxetine produces a lesser effect on those measures.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley albino rats (Zivic-Miller, PA) weighing 180–200 g at the start of chronic treatment were used. They were housed two or three per cage and maintained in a controlled 12–12 h light–dark cycle and under constant temperature at 22°C, with free access to food and water.

2.2. Drugs

Rats received either fluoxetine hydrochloride (10 mg/kg per day, Eli Lilly, Indianapolis, IN) or imipramine hydrochloride (10 mg/kg per day, Sigma) in their drinking water (24–28 days), which was changed in light-proof drinking bottles twice a week. Doses of these two drugs in this chronic study were chosen based on a previous acute study (Ichikawa and Meltzer, 1995) which compared their acute effects. Those doses are in accord with other recent microdialysis studies (Rossetti et al., 1991; Clark et al., 1996; Tanda et al., 1996b), and it is possible to compare the results published by other investigators. Dosages used were corrected by weight and daily intake of water each time. Although the amount of drug each rat received could not be determined exactly, the variance in intake volume and body weight between groups was small and stable. Drugs were dissolved in deionized water and then diluted by tap water (vehicle). D-Amphetamine sulfate (0.5 mg/kg, s.c.) was administered to rats after 3–5 days drug withdrawal. In order to confirm non-significant effects of the vehicle injection to rats, vehicle was administered 30 min before D-amphetamine.

2.3. Microdialysis procedure and dialysate analysis

Rats were anesthetized with a combination (intraperitoneal injection) of xylazine (6 mg/kg) and ketamine hydrochloride (70 mg/kg) and mounted in a stereotaxic frame (David-Kopf). Two stainless guide cannula with a dummy probe were fixed onto the skull dorsal to the nucleus accumbens. Three to five days following cannulation, the dialysis probe was implanted into the nucleus accumbens under a slight anesthesia with methoxyflurane (Metofane) and then connected to an infusion pump which

Table 1
Basal extracellular levels of dopamine (mean ± S.E.M. fmol/20 μl per 30 min) in the nucleus accumbens (F (2, 18) = 11.08, $P < 0.001$) after 3–5 days withdrawal of chronic (24–28 days) treatment

	n	Dopamine	%	*P*
Vehicle	7	9.08 ± 0.74	100	
Fluoxetine (10 mg/kg per day)	7	6.51 ± 0.60	72	0.047
Imipramine (10 mg/kg per day)	7	12.7 ± 1.54	140	0.019

n, number of animals.
Differences between treatment and vehicle were determined by one-way ANOVA followed by Fisher's PLSD procedure.
P values vs. vehicle-treated controls.

delivers modified Dulbecco's phosphate-buffered saline solution (NaCl 138 mM, Na_2HPO_4 8.1 mM, KCl 2.7 mM, KH_2PO_4 1.5 mM,, MgCl 0.5 mM, $CaCl_2$ 1.2 mM, pH = 7.4) at a rate of 0.8 μl/min. Co-ordinate of the probe with 2 mm exposed dialyzing surface of the membrane (AN69 HF, Hospal) when implanted is $A + 2.0$, $L + 1.5$, $V - 7.5$ mm for the nucleus accumbens, relative to bregma; incision bar level: −3.0 mm, according to the atlas of Paxinos and Watson (1986). The day after implantation, dialysate samples were collected every 30 min into microcentrifuge tubes. Samples (24 μl/30 min) were directly applied onto a high-performance liquid chromatography (HPLC) with electrochemical detection with a 20 μl sample loop, and analyzed for dopamine with an integrator (HP 3396A, Hewlett-Packard).

Dopamine was separated on a stainless steel, reversed phase column (Ultracarb 3 μm C_{18}, 2.0 × 100 mm, Phenomenex, Torrance, CA) at 35°C maintained by column heater and temperature controller (LC-22C, BAS). The mobile phase consisted of 32 mM citric acid anhydrous and sodium acetate 54.3 mM containing EDTA-2Na (50 mg/l) and octyl sodium sulfate (50 mg/l, Kodak) adjusted to pH 4.2 with concentrated phosphoric acid, and 5% (v/v) methanol. With a mobile phase flow rate of 0.25 ml/min, the sample run was less than 10 min. Dopamine was detected by a dual glassy carbon working electrode

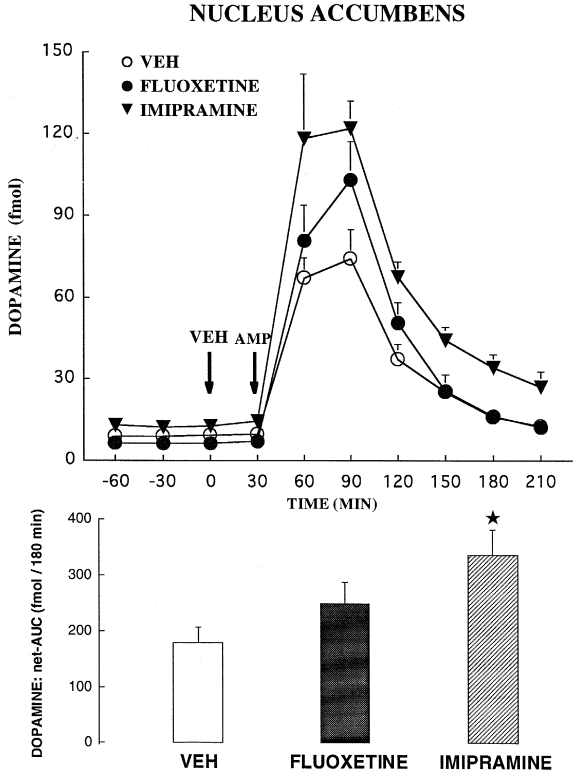

Fig. 1. The time course effect of chronic treatment with vehicle (VEH), fluoxetine (10 mg/kg per day) or imipramine (10 mg/kg per day) on amphetamine (AMP) (0.5 mg/kg, s.c.)-induced increase in extracellular dopamine levels in rat nucleus accumbens. Repeated measure ANOVA or one-way ANOVA for the net-AUC, followed by Fisher's PLSD procedure, indicated that chronic imipramine significantly potentiated AMP-induced increase in extracellular dopamine levels in the nucleus accumbens, whereas chronic fluoxetine had no significant effect. Significance: ★, $P < 0.05$ compared to the vehicle controls.

(MF-1000, BAS) set at +0.60 V (LC-4C, BAS) vs. Ag/AgCl reference electrode. Reagents used were analytical or HPLC grade. After obtaining stable baseline values in the dialysate such that a percentage of standard error of the three consecutive dopamine values (S.E.M.) in the dialysate differed less than 10% of the mean values, each drug or vehicle was administered s.c. to the rats. The effect of the drug was followed at least another 180 min. The location of the dialysis probes were verified at the end of each experiment by dissection of the brain.

The procedures applied in these experiments were approved by the Institutional Animal Care and Use Committee (IAUAC) of Case Western Reserve University in Cleveland, OH, where we completed this study.

2.4. Analysis of data

Statistical differences are determined using one-way or repeated measure analysis of variance (ANOVA) followed by the Fisher's PSLD (protected least significant difference) post hoc pairwise comparison procedure (StatView® 4.02 for the Macintosh). A probability, P, of less than 0.05 is considered significant in this study. All results are given as mean ± S.E.M. and expressed as absolute net increase which is calculated from each absolute level over each pre-drug basal value, or as net area under the curve (net-AUC) which is calculated from the absolute net increase for a 180-min period after amphetamine or vehicle (six samples) over each mean value of pre-drug basal levels.

3. Results

3.1. Basal extracellular dopamine levels (Table 1)

As shown in the Table 1, one-way ANOVA revealed that significant difference between treatments was observed in the nucleus accumbens. Post hoc comparison indicated that chronic imipramine significantly increased basal extracellular dopamine levels in the nucleus accumbens, but chronic fluoxetine significantly decreased them, compared to the vehicle controls.

3.2. Amphetamine-induced extracellular dopamine levels (Fig. 1)

Repeated measure ANOVA (treatment × time) ($F(2, 18) = 8.73$, $P = 0.002$) followed by post hoc comparison indicated that chronic imipramine ($P = 0.002$), but not chronic fluoxetine ($P = 0.83$), significantly potentiated amphetamine-induced increases in extracellular dopamine levels, as compared to the vehicle controls. Similarly, analysis of the net-AUC (one-way ANOVA: $F(2, 18) = 5.90$, $P = 0.011$) followed by post hoc comparison indicated a significant effect of chronic imipramine (337 ± 45 fmol/180 min, $P = 0.005$), but not chronic fluoxetine (249 ± 38 fmol/180 min, $P = 0.57$), as compared to the vehicle controls (178 ± 29 fmol/180 min).

4. Discussion

The present study demonstrated that chronic imipramine treatment (10 mg/kg per day, for 24–28 days) increased basal extracellular dopamine levels in the nucleus accumbens ($P = 0.019$). Although the significance is marginal ($P = 0.047$), chronic fluoxetine (10 mg/kg per day, for 24–28 days) decreased basal extracellular dopamine levels to 72% of the vehicle controls (Table 1). Clark et al. (1996) (5 mg/kg, i.p. once a day for 20 days followed by one day drug washout) and Tanda et al. (1996a) (10 mg/kg, i.p. once a day for 14 days followed by one day drug washout) reported no significant effect of chronic fluoxetine treatment on basal extracellular dopamine levels in the nucleus accumbens. Gardier et al. (1994) reported that chronic administration of fluoxetine (5, 10 and 15 mg/kg, i.p. twice a day for 21 days followed by 1–14 days withdrawal) produced a decrease in tissue dopamine concentrations in the nucleus accumbens one day after the last treatment, which recovered to the control levels two days later. Gardier et al. (1994) also reported that, in accord with the results of tissue dopamine concentrations, the plasma and brain concentrations of fluoxetine and norfluoxetine quickly decreased after discontinuation of the chronic treatment. However, the half life of fluoxetine is reported to be 2–4 days for the parent drug and 7–15 days for its active metabolite norfluoxetine (Preskorn, 1994). The difference in the pharmacokinetics of fluoxetine due to the design of chronic studies, e.g. administration routes, may affect the basal extracellular dopamine levels. Thus, it is possible that certain amount of fluoxetine remains in the brain even 3–5 days after its discontinuation in this study and decreases basal extracellular dopamine levels. This is consistent with our previous report that fluoxetine acutely decreases extracellular dopamine levels in the nucleus accumbens and the striatum (Ichikawa and Meltzer, 1995).

The significant increase after chronic imipramine in extracellular dopamine levels in the nucleus accumbens observed in this study is not consistent with previous findings from Rossetti et al. (1991) who reported that chronic imipramine treatment (20 mg/kg, i.p. once a day for 21 days followed by two days drug washout) had no significant effect on basal extracellular dopamine levels in the nucleus accumbens. Methodological differences could account for the discrepant findings of Rossetti et al. (1991) and present results. For example, we treated rats at the dose of 10 mg/kg per day in drinking water for 24–28 days followed by 3–5 days drug withdrawal. Rossetti et al. (1991) used higher doses of imipramine (20 mg/kg, i.p.) vs. 10 mg/kg in drinking water in this study which may

be less than the dose of 10 mg/kg, i.p in the brain. Furthermore, Rossetti et al. (1991) used transverse type dialysis probe which may dialyze both the core and shell region of the nucleus accumbens, whereas we used the concentric type probe which may mostly dialyze the shell region. Chronic imipramine treatment does not affect basal striatal extracellular dopamine levels (Ichikawa et al., unpublished data). Dopaminergic activity of the core region of the nucleus accumbens and the striatum may respond similarly to some drugs (Deutch et al., 1993).

Caution should be taken into consideration whenever basal extracellular dopamine levels are compared in microdialysis experiments. Dialysate concentrations of dopamine per se may be affected by factors other than pharmacological effects, e.g. in vivo recovery rate of the dialysis probe for extracellular dopamine. These differences could also cause a significant difference in basal levels between treatment groups.

Chronic imipramine, but not chronic fluoxetine treatment, potentiated the ability of amphetamine to increase extracellular dopamine levels in the nucleus accumbens, as demonstrated by both analyses of the time-course effects and the net-AUC. The significant difference in the time-course effects could be influenced by the imipramine-induced increase in basal extracellular dopamine levels. However, this seems unlikely since analysis of the net-AUC, which is not affected by the difference in basal values, produced the same results. Fluoxetine has not been reported to have any significant affinity for dopamine receptors or dopamine uptake sites ($K_i = 2.9$ μM) and no significant in vivo affinities for any of 5-HT receptor subtypes (see the review from Wong et al., 1995). The effect of fluoxetine is to selectively inhibit the reuptake of 5-HT ($K_i = 20$ nM) into 5-HT neurons, leading to an increase in extracellular 5-HT levels. Imipramine is also a serotonin reuptake inhibitor ($K_i = 41$ nM) and has minimal effect on dopamine uptake sites ($K_i = 11$ μM). Thus, mechanisms other than a direct effect on dopaminergic or serotonergic neurons may be important (Beasley et al., 1992; Brown and Gershon, 1993) to explain the difference between imipramine and fluoxetine. For example, the IC_{50} values for histamine$_1$ receptors are 30 nM for imipramine and 1900 nM for fluoxetine, respectively (see the review from Wong et al., 1995). The K_i values of imipramine and fluoxetine for norepinephrine uptake inhibition are reported to be 14 and 250 nM, respectively. Carboni et al. (1990) reported that blockade of norepinephrine uptake sites leads to an increase in extracellular dopamine levels, suggesting dopamine reuptake by the norepinephrine transporter. More importantly, down-regulation of β_1-adrenoceptors and decreased production of norepinephrine-stimulated cAMP in rat frontal cortex may be the most highly replicated finding produced by chronic tricyclic antidepressants such as imipramine, but not selective serotonin reuptake inhibitors (Beasley et al., 1992; Dennis et al., 1994; Duncan et al., 1994; Goodnough and Baker, 1994). Chronic selective serotonin reuptake inhibitors are reported to increase β_1-adrenoceptors in rat striatum (Pälvimäki et al., 1994) but are not changed by chronic imipramine (Duncan et al., 1994). Nomikos et al. (1991) reported that chronic treatment with desipramine (5 mg/kg, i.p. twice a day for 21 days with 3 days washout), a selective and potent norepinephrine uptake inhibitor (K_i = 0.6 nM) (see the review from Wong et al., 1995), potentiated the ability of amphetamine (1.5 mg/kg s.c.) to increase extracellular dopamine levels in the nucleus accumbens, but had no effect on basal levels. These results, collectively, suggest a potential involvement of adrenergic mechanisms in facilitation of the amphetamine-induced mesolimbic dopamine neurotransmission after chronic imipramine treatment. The increase in basal extracellular dopamine levels in the nucleus accumbens after chronic imipramine could be mediated by the mechanism(s) differing from adrenergic neurons. Interestingly, however, most studies investigated mainly cortical and, to a lesser extent, striatal β_1-adrenoceptors, but not the nucleus accumbens β_1-adrenoceptors, presumably due to technical problems. Thus, it remains to be determined whether and how the effect of tricyclic and selective serotonin reuptake inhibitor antidepressants on adrenergic neurons in the nucleus accumbens affects mesolimbic dopamine neurotransmission.

5. Conclusions

In summary, chronic imipramine increased and chronic fluoxetine decreased basal extracellular dopamine levels in the nucleus accumbens while chronic imipramine, but not chronic fluoxetine, potentiated amphetamine-induced increase in extracellular dopamine levels in the nucleus accumbens. Facilitation of mesolimbic dopamine neurotransmission due to chronic imipramine, but not fluoxetine, may reflect differences in clinical effects between imipramine and fluoxetine.

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