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Effect of antidepressants on striatal and accumbens extracellular dopamine levels

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Abstract

The effect of the selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor, fluoxetine (10 mg/kg s.c.), two tricyclic antidepressants, clomipramine (10 mg/kg s.c.) and imipramine (10 mg/kg s.c.), and vehicle on extracellular dopamine levels was studied in rat nucleus accumbens and striatum by in vivo microdialysis. Fluoxetine produced significant decreases in extracellular dopamine levels in both the nucleus accumbens and striatum (mean maximum percentage decrease: 58% and 57% of pre-drug baseline, respectively). In contrast, imipramine and clomipramine significantly increased extracellular dopamine in the striatum (148% and 150%, respectively) compared to the effect of vehicle alone (118%). These results suggest that the selective serotonin reuptake inhibitor, fluoxetine, and the tricyclic antidepressants, clomipramine and imipramine, affect dopaminergic activity in diverse ways and in a region-specific manner. Thus, the antidepressant effect of these drugs is unlikely to be related to their acute effects on dopaminergic neurotransmission. The differential effects of the selective serotonin reuptake inhibitor and tricyclic antidepressants on extracellular dopamine could account for other differences in their clinical and side effect profiles. Further studies of the chronic effects of the selective serotonin reuptake inhibitor and the tricyclic antidepressants on dopaminergic activity are required to elucidate the role of dopamine in the antidepressant effect.

Keywords: Fluoxetine; Clomipramine; Imipramine; Dopamine; 5-HT (5-hydroxytryptamine, serotonin); Extrapyramidal symptom; Antidepressant; Microdialysis, in vivo; Nucleus accumbens; Striatum; (Rat)

1. Introduction

There is considerable electrophysiological, behavioral and neurochemical evidence that chronic administration of tricyclic antidepressant drugs such as imipramine, clomipramine and amitriptyline increases brain serotonergic activity (Wilner, 1985; Heninger and Charney, 1987; Blier et al., 1987, 1988; Chaput et al., 1991). This is consistent with the hypothesis that diminished brain serotonergic activity is important to the etiology of major depression (Meltzer and Lowy, 1987; Delgado et al., 1989, 1990). However, it has also been suggested that dopamine is important for the pathogenesis of some aspects of depression (Randrup and Braestrup, 1977; Wilner, 1983; Jimerson, 1987). Both direct acting dopamine agonists, e.g., piribedil (Post et al., 1978) and bromocriptine (Theohar et al., 1981), and an indirect dopamine acting agonist, amphetamine (Silberman et al., 1981), have been reported to have antidepressant effects.

A role for the involvement of the dopamine system in the central action of tricyclic antidepressants has been suggested by numerous studies (DeMontis et al., 1990a,b; Brown et al., 1991; Scavone et al., 1992; Brown and Gershon, 1993) which show that chronic administration of these agents increases brain dopaminergic activity. For example, long-term treatment with tricyclic antidepressant produces: (1) an increase in the ability of apomorphine, a direct acting dopamine agonist, to stimulate locomotor activity and stereotyped behavior (Maj et al., 1984); and (2) an increase in the ability of the indirect acting dopamine agonist amphetamine to release dopamine (Brown et al., 1991; Nomikos et al., 1991). These studies suggest that tricyclic antidepressant may act, in part, by increasing the responsivity of postsynaptic dopamine D_2

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receptors and by enhancing the stimulated release of dopamine. The development of subsensitive presynaptic dopamine D_2 autoreceptors following tricyclic antidepressant administration, which could be expected to increase dopamine release, has also been demonstrated (Serra et al., 1979; Nielsen, 1986; Scavone et al., 1992; Allison et al., 1993; Pucilowski and Overstreet, 1993). Taken together, these considerations suggest that an activation of both serotonin (5-hydroxytryptamine, 5-HT) and dopamine systems may contribute to the therapeutic efficacy of antidepressants.

Recently, selective serotonin reuptake inhibitors such as fluoxetine (Wong et al., 1974, 1975; Lemberger et al., 1985; Benfield et al., 1986; Beasley et al., 1992) have been introduced as effective and safe antidepressants. Selective serotonin reuptake inhibitors have been shown to increase net serotonergic neurotransmission following chronic treatment, as is the case with tricyclic antidepressants (Hyttel, 1982; Beasley et al., 1992). Selective serotonin reuptake inhibitors may affect other neurotransmitters as well. For example, in one of the first patients treated with fluoxetine, it caused extrapyramidal symptoms and decreased cerebrospinal fluid homovanillic acid (HVA), suggesting it could decrease nigrostriatal dopaminergic activity in humans (Meltzer et al., 1979). Similar findings have been reported by others (Lipinski et al., 1989; Reccoppa et al., 1990; Mann and Kapur, 1991; Wirshing et al., 1992; Salzman et al., 1993; Dave, 1994; Scheepers and Rogers, 1994). These observations raise the question whether the selective serotonin reuptake inhibitors, like tricyclic antidepressants, increase brain dopaminergic activity, as has just been reported, or that the antidepressant effects of selective serotonin reuptake inhibitors and tricyclic antidepressant are not related to their dopaminergic effects.

To test these hypotheses, the present study was designed to investigate the effects of fluoxetine, a selective serotonin reuptake inhibitor, in comparison with those of two tricyclic antidepressants, imipramine and clomipramine, on extracellular dopamine in the nucleus accumbens and the striatum of awake, freely moving rats.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley albino rats (Zivic-Miller, PA, USA) weighing 200–300 g were used throughout the study. They were housed two per cage and maintained under a controlled 12–12 h light–dark cycle and a constant temperature of 22°C, with free access to food and water.

2.2. Drug challenge

Fluoxetine hydrochloride (10 mg/kg, Eli Lilly, Indianapolis, IN, USA), imipramine hydrochloride (10 mg/kg, Sigma) and clomipramine (10 mg/kg, Sigma) were dissolved in deionized water and administered parenterally (subcutaneous injection, s.c.).

2.3. Microdialysis procedure and dialysate analysis

The rats were anesthetized with a combination (intraperitoneal injection, i.p.) of xylazine (6 mg/kg, Rompun, Miles, KA, USA) and ketamine hydrochloride (70 mg/kg, Ketaset, Fort Dodge Lab., IA, USA) and mounted in a stereotaxic frame (David-Kopf). Two stainless guide cannula (21 gauge) with a dummy probe were fixed onto the cortex dorsal to both the striatum and the nucleus accumbens. Three to five days following cannulation, the dialysis probes were implanted into both the striatum and the nucleus accumbens in the same rat under anesthesia with methoxyflurane (Metofane, Pitman-Moore, IL, USA) and then connected to an infusion pump which 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) by a compact infusion pump (Model 22, Harvard) at a rate of 0.8 μl/min. The coordinates of each probe when implanted were A +0.5, L −4.0, V −5.5 for the striatum and A +2.0, L +1.5, V −7.5 mm for the nucleus accumbens, respectively, relative to bregma; incision bar level: −3.0 mm, according to the atlas of König and Klippel (1963). The exposed length of the probe membrane (AN69 HF, Hospal 310 μm, o.d., molecular cutoff 40 000) was 2 mm for the striatum and the nucleus accumbens. The day after implantation of the probes, dialysate samples were collected every 30 min. Samples were directly applied onto a high-performance liquid chromatography (HPLC) with electrochemical detection and analyzed for dopamine with an integrator (HP 3396A, Hewlett-Packard). After obtaining stable baseline values in the dialysate in at least three samples (within 10% of the mean baseline), vehicle (i.p.) and 30 min later, each drug (s.c.) was administered to the rats. The effect of the drug was followed for at least another 180 min. The location of the dialysis probes was verified at the end of each experiment by dissection of the brain.

Dopamine was separated on a stainless steel, reversed phase column (Ultracarb 3 μm C18, 2.0 × 100 mm, Phenomenex, Torrance, CA, USA) at 35°C maintained by a 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. Dopamine was detected by a dual glassy carbon working electrode (MF-1000, BAS) set at +0.60 V (LC-4C, BAS) vs. an Ag/AgCl reference electrode. The reagents used were analytical or HPLC grade.

2.4. Analysis of data

(1) The time-course effect of the drugs on extracellular levels of dopamine (Fig. 1 and Fig. 2 and Fig. 3): The mean pre-drug basal values were taken as 100% to compare the mean response of dopamine at the various time points after drug or vehicle. This is the most frequently used method to express microdialysis data. (2) The maximum percentage change: The maximum increase or decrease in extracellular levels of dopamine was expressed as a function of baseline value (100%) following drug challenge. This result describes the maximum response regardless of the difference in time-course effects.

Statistical differences were determined using a repeated measure analysis of variance (ANOVA) followed by the Scheffe's post-hoc pairwise comparison procedure wherever possible (StatView 4.02 for the Macintosh). A probability (P) of less than 0.05 was considered significant in this study.

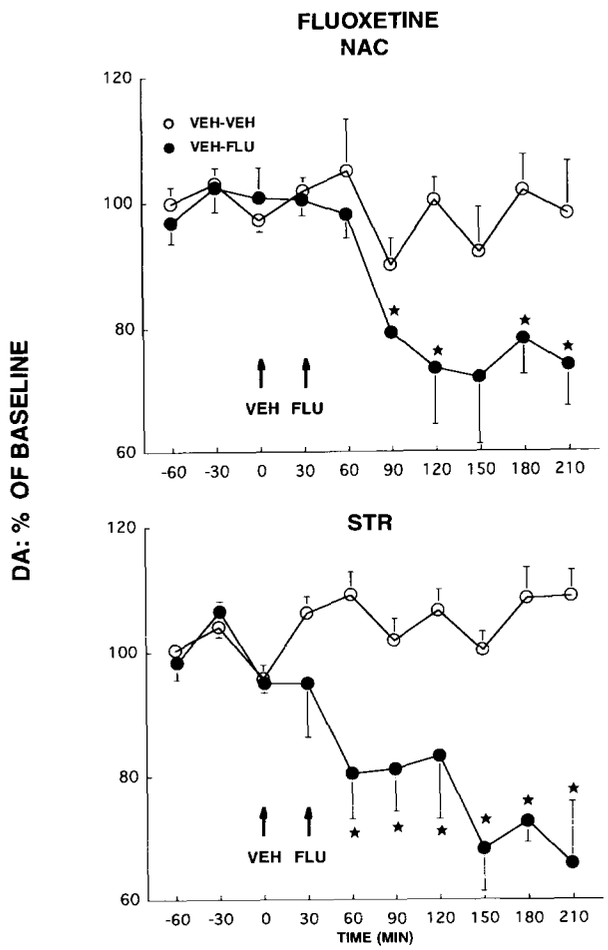

Fig. 1. The time course of the effect of single doses of fluoxetine (10 mg/kg s.c.) on in vivo extracellular dopamine levels in rat nucleus accumbens and striatum: vehicle (VEH, 1 ml/kg i.p.)-fluoxetine (FLU) (●) and VEH (1 ml/kg i.p.)-VEH (1 ml/kg s.c.) (○). Fluoxetine significantly decreased extracellular dopamine levels in both the nucleus accumbens and the striatum. Data are means ± S.E.M. (bars) of corresponding time points, expressed as percentages of the mean pre-drug baseline dopamine values (time −60, time −30 and time 0), as measured for each group (n = 6–7). Pre-drug baseline values are designated as 100% (time −60, time −30 and time 0). Significant differences between vehicle-vehicle and vehicle-fluoxetine are indicated: $^{*}P < 0.05$.

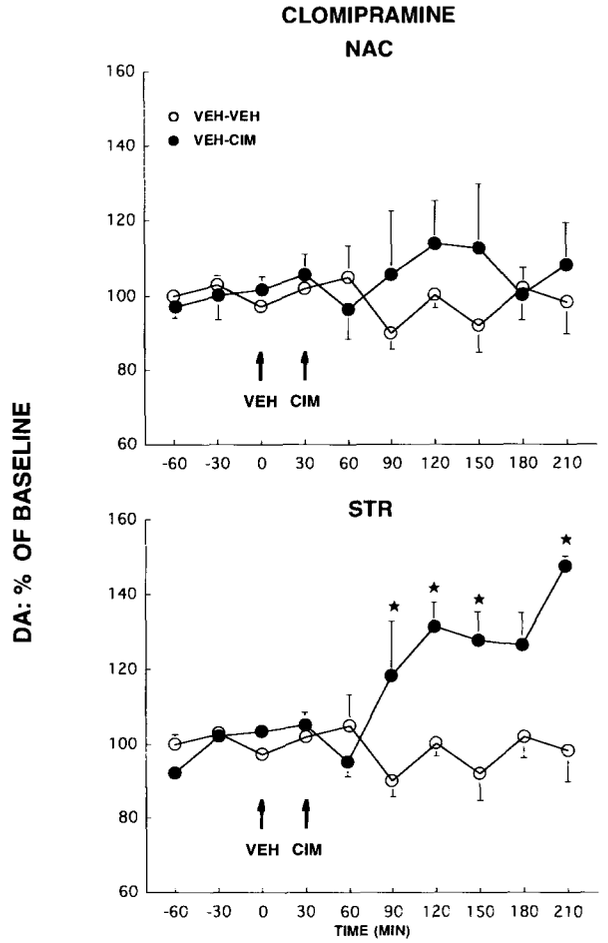

Fig. 2. The time course of the effect of single doses of clomipramine (10 mg/kg s.c.) on in vivo extracellular dopamine levels in rat nucleus accumbens and striatum: vehicle (VEH, 1 ml/kg i.p.)-clomipramine (CIM) (●) and VEH (1 ml/kg i.p.)-VEH (1 ml/kg s.c.) (○). Clomipramine significantly increased extracellular dopamine levels in the striatum, but had no effect in the nucleus accumbens. Data are means ± S.E.M. (bars) of corresponding time points, expressed as percentages of the mean pre-drug baseline dopamine values (time −60, time −30 and time 0), as measured for each group (n = 4–7). Pre-drug baseline values are designated as 100% (time −60, time −30 and time 0). Significant differences between vehicle-vehicle and vehicle-clomipramine are indicated: $^{*}P < 0.05$.

3. Results

As shown in Fig. 1 and Fig. 2 and Fig. 3, fluoxetine (10 mg/kg) produced significant decreases in extracellular dopamine in both the nucleus accumbens and the striatum, whereas clomipramine (10 mg/kg) and imipramine (10 mg/kg) produced significant increases in extracellular dopamine in the striatum but had no effect on extracellular dopamine in the nucleus accumbens.

(1) The time-course change (Fig. 1 and Fig. 2 and Fig. 3): fluoxetine (10 mg/kg), $F = 9.77$, $P = 0.0108$ for the nucleus accumbens and $F = 41.84$, $P = 0.0001$ for the striatum, compared to respective vehicle.

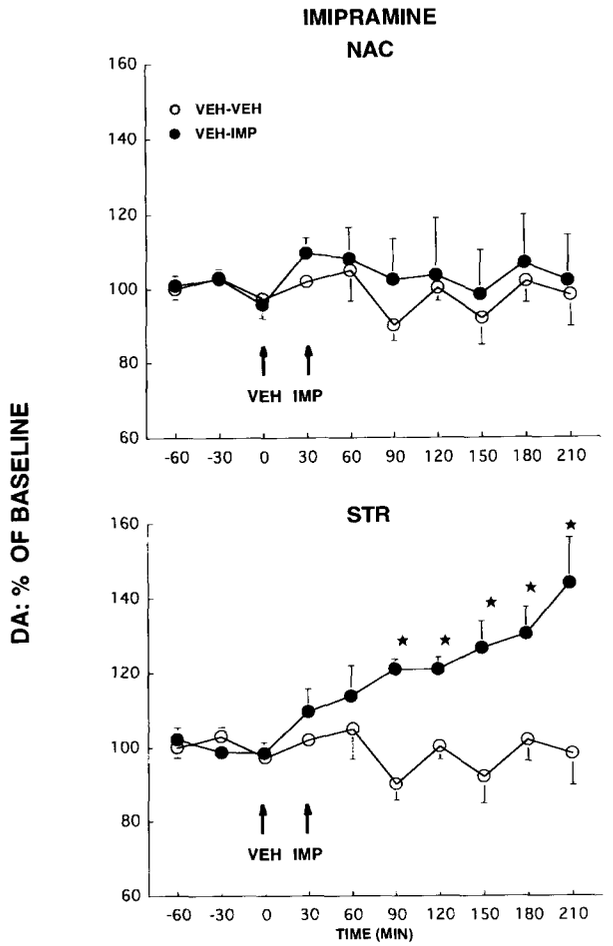

Fig. 3. The time course of the effect of single doses of imipramine (10 mg/kg s.c.) on in vivo extracellular dopamine levels in rat nucleus accumbens and striatum: vehicle (VEH, 1 ml/kg i.p.)-imipramine (IMP) (●) and VEH (1 ml/kg i.p.)-VEH (1 ml/kg s.c.) (○). Imipramine significantly increased extracellular dopamine levels in the striatum, but had no effect in the nucleus accumbens. Data are means ± S.E.M. (bars) of corresponding time points, expressed as percentages of the mean pre-drug baseline dopamine values (time −60, time −30 and time 0), as measured for each group ($n = 5$–7). Pre-drug baseline values are designated as 100% (time −60, time −30 and time 0). Significant differences between vehicle-vehicle and vehicle-clomipramine are indicated: $^{*}P < 0.05$.

Clomipramine (10 mg/kg) and imipramine (10 mg/kg), $F = 0.41$, $P = 0.54$ and $F = 0.41$, $P = 0.54$ for the nucleus accumbens, respectively, $F = 23.70$, $P = 0.0009$ and $F = 26.21$, $P = 0.0003$ for the striatum, respectively, compared to each vehicle.

(2) Maximum percentage change over each pre-drug baseline value (100%), mean ± S.E.M.: fluoxetine (10 mg/kg), 58 ± 8% $F = 49.83$, $P < 0.01$ for the nucleus accumbens and 57 ± 10% $F = 62.49$, $P < 0.01$ for the striatum, respectively, compared to each vehicle (118 ± 6% for the nucleus accumbens and 118 ± 3% for the striatum, respectively). Clomipramine (10 mg/kg) and imipramine (10 mg/kg), 126 ± 13% $F = 0.35$, $P = 0.57$ and 120 ± 11% $F = 0.04$, $P = 0.84$ for the nucleus accumbens, respectively, and 148 ± 3% $F = 48.29$, $P < 0.01$ and 150 ± 9% $F = 12.12$, $P < 0.01$ for the striatum, respectively, compared to each vehicle (118 ± 6% for the nucleus accumbens and 118 ± 3% for the striatum, respectively).

4. Discussion

The major findings of this study are that fluoxetine (10 mg/kg) produced significant decreases in extracellular dopamine in both the nucleus accumbens and the striatum, whereas clomipramine (10 mg/kg) and imipramine (10 mg/kg) produced significant increases in extracellular dopamine in the striatum but had no effect on extracellular dopamine in the nucleus accumbens (Fig. 1 and Fig. 2 and Fig. 3). These results are in agreement with a previous study in the striatum reported by Meltzer et al. (1993) which showed that fluoxetine (10 mg/kg), sertraline (5 mg/kg), and paroxetine (10 mg/kg) produced significant decreases in extracellular dopamine in the striatum, whereas citalopram (10 mg/kg) had no effect on extracellular dopamine in the striatum. In sharp contrast, imipramine (10 mg/kg) and clomipramine (10 mg/kg) produced significant increases in extracellular dopamine in the striatum. Amitriptyline (10 mg/kg) had no effect on extracellular dopamine in the striatum.

4.1. Effect of imipramine and clomipramine

The increase in extracellular dopamine in the striatum following imipramine and clomipramine (Fig. 2 and Fig. 3) is consistent with the hypothesis that tricyclic antidepressants increase net dopaminergic activity (see Introduction). The lack of an effect of clomipramine and imipramine on extracellular dopamine in the nucleus accumbens is in agreement with previous microdialysis reports (Di Chiara and Imperato, 1988; Tanda et al., 1994), but is not in agreement with the results of Rossetti et al. (1993),

who reported that acute imipramine (10 mg/kg i.p.) significantly increased extracellular dopamine in the ventral striatum (limbic area). There are no reports which suggest a direct effect of imipramine and clomipramine on dopamine receptors or dopamine uptake sites ($K_i = 5.1$ μM and 1.8 μM, respectively), except for the relatively weak affinity of clomipramine for dopamine D_2 receptors ($K_d = 190$ nM) (Richelson and Nelson, 1984; Richelson and Pfenning, 1984). Inhibition of dopamine reuptake by imipramine and clomipramine could be attributable to the increase in extracellular dopamine. However, it seems unlikely since the dopamine reuptake inhibition activity of both drugs is weak, $K_i = 5.1$ μM for imipramine and 1.8 μM for clomipramine, respectively, and the tricyclic antidepressant amitriptyline ($K_i = 2.3$ μM) (Richelson and Pfenning, 1984) had no effect on extracellular dopamine (Meltzer et al., 1993). Collectively, these results suggest that the mechanism by which clomipramine and imipramine produce increases in striatal extracellular dopamine is unlikely to be involved in a direct effect on dopamine neurons and is possibly mediated by an effect on 5-HT neurons since imipramine and clomipramine are serotonin reuptake inhibitors, $K_i = 42$ nM for imipramine, 5.4 nM for clomipramine and 12 nM for fluoxetine (Richelson and Pfenning, 1984).

4.2. Effect of fluoxetine

Fluoxetine, like sertraline and paroxetine, but not citalopram, as previously reported by Meltzer et al. (1993), produced a significant decrease in extracellular dopamine in the nucleus accumbens and the striatum (Fig. 1). These findings are not consistent with the results of Perry and Fuller (1992) and Tanda et al. (1994), who reported that fluoxetine, at the same dose studied here (10 mg/kg), did not decrease extracellular dopamine in the nucleus accumbens and the striatum. Further studies are needed to reconcile these differences.

Although the significance of the decrease in extracellular dopamine in the nucleus accumbens produced by fluoxetine is currently unclear, the ability of fluoxetine to decrease extracellular dopamine in the striatum may be relevant to the acute extrapyramidal symptoms produced by fluoxetine in humans, which suggests that nigrostriatal dopaminergic activity may be inhibited following acute fluoxetine administration (Meltzer et al., 1979, see the Introduction). They may also contribute to the reported ability of paroxetine and sertraline to increase haloperidol-induced dystonia and parkinsonism in monkeys (Korsgaard et al., 1985). Fluoxetine and the other selective serotonin reuptake inhibitors, sertraline and paroxetine, have not been reported to have any significant affinity for dopamine receptors or dopamine uptake sites (fluoxetine $K_i = 1.6$ μM) (Richelson and Nelson, 1984; Richelson and Pfenning, 1984; Benfield et al., 1986; Beasley et al., 1992; Maj and Moryl, 1992) and no significant in vivo affinities for any of 5-HT receptor subtypes (Wong et al., 1991). The effect of fluoxetine is to selectively inhibit the reuptake of 5-HT into 5-HT neurons, leading to an increase in extracellular 5-HT (reviewed by Fuller, 1994). It is possible that the increase in extracellular 5-HT produced by fluoxetine has an inhibitory effect on dopamine release in both the striatum and the nucleus accumbens, most likely due to stimulation of 5-HT receptors (Westfall and Tittermay, 1982; Hetey and Drescher, 1986; Muramatsu et al., 1988; Ugedo et al., 1989). Stimulation of 5-HT_{1A} receptors (Hjorth and Auerbach, 1994) as well as 5-$HT_{2A/2C}$ receptors by 1-(2,5-dimethoxy-4-iodophenyl)-aminopropane (DOI) produces a decrease in the firing rate in 5-HT cells of the dorsal raphe nucleus (Chaput et al., 1986; Sprouse and Aghajanian, 1987; Wright et al., 1990), which, in turn, may decrease the A9 or A10 dopamine activity, leading to a decrease in dopamine synthesis and release in terminal regions (DeSimoni et al., 1987; Yoshimoto and McBride, 1992).

However, it should be noted that direct application of 5-HT into the nucleus accumbens via a dialysis probe has been reported to increase accumbal extracellular dopamine, an effect which was attenuated by co-application of either pindolol, a relatively non-specific 5-$HT_{1A/1B}$ receptor antagonist, LY53,857, a specific 5-HT_2 receptor antagonist, or MDL7222, a specific 5-HT_3 receptor antagonist (Parsons and Justice, 1993). Benloucif and co-workers (Benloucif and Galloway, 1991; Benloucif et al., 1993) and others (Blandina et al., 1988, 1989; Galloway et al., 1993) also reported that local application of 5-HT and various agonists of 5-HT receptor subtypes, including the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), produced increases in [^{3}H]dopamine or extracellular dopamine in the striatum. These results contrast with the effects of systemic administration of fluoxetine, sertraline and paroxetine reported in this study and in a previous study (Meltzer et al., 1993). The net increase in extracellular 5-HT in neuron terminals produced by systemic administration of these reuptake inhibitors may be insufficient to stimulate the 5-HT-mediated increase in extracellular dopamine in neuron terminals since selective serotonin reuptake inhibitors typically do not produce the 5-HT syndrome or 5-HT receptor-mediated behaviors, signs of excessive stimulation of the serotonergic system, at the doses studied (Fuller, 1994).

In conclusion, systemic administration of fluoxetine, a selective serotonin reuptake inhibitor, produced a significant decrease in extracellular dopamine in both the nucleus accumbens and the striatum, whereas sys-

temic administration of the tricyclic antidepressants clomipramine and imipramine increased extracellular dopamine in the striatum but not in the nucleus accumbens. The differences between these selective serotonin reuptake inhibitors and tricyclic antidepressants in the ability to alter brain dopaminergic activity in a region-specific manner could contribute to the discrepant clinical profiles among antidepressants and imply that dopamine, at least with regard to acute effects, is unlikely to be related to their antidepressant effects.

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