SYNAPSE 23:125–131 (1996)

Effect of Acute and Chronic Fluoxetine on Extracellular Dopamine Levels in the Caudate-Putamen and Nucleus Accumbens of Rat

ROBERT N. CLARK, CHARLES R. ASHBY, JR., STEPHEN L. DEWEY, P. VEERARAGHAVAN RAMACHANDRAN, AND ROBERT E. STRECKER

Department of Psychiatry and Behavioral Sciences, and Department of Psychology, State University of New York at Stony Brook, Stony Brook, New York 11794 (R.N.C., R.E.S.), Department of Pharmaceutical Sciences, Saint Johns University, Jamaica, New York 11439 (C.R.A.), Department of Chemistry, Brookhaven National Laboratory, Upton, New York 11973 (S.L.D.), and H.C. Brown Laboratory of Chemistry, Purdue University, West Lafayette, Indiana 47907 (P.V.R.)

KEY WORDS Microdialysis, Striatum, DOPAC, HVA, 5HIAA, Cocaine, Serotonin, SSRI, Rat, Antidepressants

ABSTRACT Recent studies indicate that an increase in serotonergic (5-HT) activity in the nucleus accumbens (NAc) produces an increase in dopamine (DA) release, providing a possible mechanism for the involvement of DA in the therapeutic action of selective serotonin reuptake inhibitor (SSRI) antidepressants. However, acutely administered fluoxetine (2.5, 5.0, or 10.0 mg/kg, i.p.) failed to elevate extracellular levels of DA, or its metabolites in the NAc or caudate-putamen (CP). In fact, the highest dose produced a small (20%) decrease in DA levels in the NAc. Extracellular levels of the 5-HT metabolite 5HIAA were consistently decreased at all doses of fluoxetine in both structures. Since SSRIs generally require several weeks of treatment to be effective clinically, a second experiment examined the effect of chronic administration of fluoxetine. Chronic (21 day) daily treatment with 5 mg/kg had no effect on NAc basal levels of DA, DA metabolites, or 5HIAA, relative to a saline-treated control group. Finally, pretreatment with fluoxetine appeared to slightly enhance the elevation of NAc DA induced by an injection of cocaine (10 mg/kg, i.p.), an effect that was not quite significant ($P < .06$). In conclusion, the 5-HT-induced facilitation of NAc DA neurotransmission described in the literature may not be relevant to the therapeutic action of fluoxetine.

INTRODUCTION

Fluoxetine (Prozac), a prototypical selective serotonin reuptake inhibitor (SSRI), has been widely used in the treatment of depression and, more recently, for both obsessive compulsive disorder and bulimia (Wong et al., 1995). Compounds of this class are selective and potent in the inhibition of neuronal uptake of 5-HT, and have very weak effects on norepinephrine (NE) or dopamine (DA) uptake (Wong et al., 1995). Nonetheless, the precise central nervous system (CNS) action responsible for the therapeutic effect of fluoxetine is uncertain and could involve an indirect interaction of 5-HT with other neurotransmitters, such as DA. For example, several recent studies indicate that 5-HT and 5-HT agonists facilitate the release of DA in the nucleus accumbens (reviewed in Parson and Justice, 1993).

In contrast to the effect in the nucleus accumbens, the facilitation of 5-HT neurotransmission in the striatum has been shown to have an inhibitory effect on DA release and turnover (reviewed in Baldessarini et al., 1992). Further, Perry and Fuller (1992) found that a dose of 10 mg/kg fluoxetine produced a fourfold increase in striatal extracellular 5-HT levels and no change in striatal DA levels. In fact, it has been suggested that the extrapyramidal side effects, including parkinsonism, that have been associated with SSRI treatment could be due to a reduction of DA activity in the striatum (Baldessarini et al., 1992; Lipinski et al., 1989; Meltzer et al., 1979). Thus, while DA neurotransmission in the striatum is associated with extrapyramidal motor func-

Received August 12, 1995; accepted in revised form October 6, 1995.

Address reprint requests to Robert Strecker, Harvard Medical School, Neuroscience Research Group, 151C, Brockton VA Medical Center, 940 Belmont St., Brockton, MA 02401. Email: strecker@warren.med.harvard.edu

This work was presented in part at the 25th Annual Society for Neuroscience meeting in San Diego, CA (Abstracts Vol. 21, p. 371, 1995).

tion and parkinsonism, DA in the nucleus accumbens (NAc) and frontal cortex has been proposed to be involved in the central mediation of reinforcement/reward, and possibly depression and the mechanism of action of antidepressants (Kapur and Mann, 1992).

The present study tested the possibility that fluoxetine could have different effects on DA release in the striatum and nucleus accumbens. In addition, since fluoxetine is reported to require 10 to 14 days of treatment to relieve symptoms in depressed patients, the present study also examined the effect of chronic fluoxetine treatment (21 day) on extracellular DA levels in the NAc.

MATERIALS AND METHODS

Male Sprague-Dawley rats (Taconic Farms, Germantown, NY) weighing 250–350 g were maintained on a 12-hour light-dark cycle (lights on at 7:00 a.m.) and were housed in groups of two with food and water available ad libitum. All procedures in this experiment strictly adhered to Federal, State, and University guidelines concerning the use of animals in research.

Microdialysis procedures

Under general anesthesia (equithesin, 4.4 ml/kg) and using aseptic techniques, stainless steel guide cannulae were stereotaxically implanted above the NAc, or caudate-putamen (CP), approximately 18 h prior to the microdialysis experiment. The guide cannulae (22-gauge thin wall tubing 10 mm in length) were affixed to the skull with the aid of steel screws and dental acrylic cement. While the animals were still anesthetized, microdialysis probes were inserted through the cannulae into the target brain structures. The microdialysis probes were of a concentric design and were constructed in our laboratory according to the procedure of previous investigators (Robinson and Camp, 1991). Briefly, hollow nitrocellulose dialysis fibers (nominal MW cut-off of 6000 Daltons; Spectra/Por, Spectrum Medical, Los Angeles, CA) were used to produce probes with a dialyzing region 3 mm in length and 250-μm-wide, and less than 500-μm-wide immediately dorsal to the dialysis membrane. In vitro probe recoveries for DA were about 5% when perfusing at a flow rate of 2 μl/min.

Relative to bregma (AP and ML) and skull surface at bregma (DV), and with the incisor bar set at −3.3 mm, the coordinates for the ventral tip of the dialyzing region were as follows: for the nucleus accumbens, AP = +1.0, ML = −1.5, DV = −8.5; and for the dorsolateral caudate-putamen, AP = +1.0, ML = −3.5, DV = −6.0. The dorsal part of the dialyzing region (approx. 0.5 mm) of the NAc probe was in the ventromedial caudate-putamen, a region that receives its DA innervation from ventral tegmental area (A10) dopamine neurons, as does the NAc (Björklund and Lindvall, 1986). The probes were cemented in place, the rats connected to a steel spring tether and the inlet perfusion tubing (PE20). Animals were then placed in the test cage (49.2 cm × 25.4 cm × 29.5 cm = L × W × H) and allowed to recover from anesthesia.

During the experiment artificial cerebrospinal fluid (CSF; 147 mM NaCl, 3 mM KCl, 1.2 mM CaCl2, 1.0 mM $MgCl_2$) was continuously perfused through the probes at 2 μl/min by means of a syringe pump (Harvard Apparatus, South Natick, MA). Dialysis samples were collected at 20-min intervals, followed by the addition of 10 μl 0.1 M perchloric acid to each sample to prevent air oxidation of the neurotransmitters. The outlet tubing (fused glass silica) was placed in a microvial which was secured to the spring tether just above the rat's head. Samples were withdrawn from the microvial with 100 μl Hamilton syringes and were refrigerated for up to 12 h prior to assay, or frozen at −70°C for later assay. At the conclusion of the experiment, rats were sacrificed by overdose with equithesin. The brains were removed and stored in 10% formalin until histological sectioning, which confirmed the accuracy of all probe placements reported in the results below.

Drugs

Fluoxetine HCl was synthesized using a published procedure (Srebnik et al., 1988) and the chemical structure was verified by 1H and 13C NMR spectroscopy. In the acute fluoxetine study, following the collection of baseline microdialysis samples, rats were given a control saline injection (0.1 ml/kg, i.p.) followed 1 h later by the injection of fluoxetine (either 2.5, 5.0, or 10.0 mg/kg, i.p.). Three hours later rats received an injection of cocaine HCl (10 mg/kg, i.p.; Sigma, St. Louis, MO) and samples were collected for two more hours. In addition to examining the possibility that fluoxetine pretreatment would alter DA release evoked by a stimulant drug, the cocaine injection also provided further confirmation of the identity of the DA peak in the chromatogram. In the chronic fluoxetine study, rats were divided into two groups that received 21 daily injections of either fluoxetine (5 mg/kg, i.p.), or saline. On the day of the microdialysis experiment, basal DA levels were compared between the two chronic treatment groups, as were the responses to a final injection of fluoxetine (5 mg/kg, i.p.), followed by the cocaine challenge.

Neurochemical analysis

Microdialysis samples were analyzed by high performance liquid chromatography (HPLC) using a dual potentiostat electrochemical detector (Bioanalytical Systems, W. Lafayette, IN). Samples were injected directly onto the HPLC via a refrigerated autoinjector (CMA/Microdialysis, Stockholm); no internal standard was used. The glassy carbon electrodes were set in parallel at applied potentials of 600 mV and 450 mV relative to an Ag/AgCl reference electrode. The two electrodes set at different potentials allowed for identification and

exclusion of unknown ghost peaks when they occasionally occurred. The mobile phase composition was 50 mM NaH_2 PO_4 monobasic, 0.1 mM EDTA, 1 mM SOS, 9.0% MeOH, pH 4.0. Mobile phase was delivered at a rate of 1.0 ml/min on to a 10 cm × 3.2 mm chromatography column with ODS 3-μm packing (BAS). All measured peaks were well-resolved and had retention times of approximately 2.2, 3.0, 5.5, and 7.5 min, for 3,4-dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindoleacetic acid (5HIAA), and homovanillic acid (HVA), and DA, respectively. Extracellular levels of these compounds per each microdialysis sample were identified in this assay, and converted to picogram amounts by comparing the peak heights of these compounds to that of known amounts of external standards. Serotonin was not measured; in this assay serotonin had a retention time of about 20 min, and was below the level of detection in the samples.

Data analysis

Data presented as the percentage of baseline were calculated by comparison to the average of three baselines collected prior to the first injection (defined as 100%). Data were statistically analyzed first by repeated measures (rm)ANOVA to determine if a significant group × time interaction existed. Following a significant rmANOVA, factorial ANOVAs were run at selected time points and coupled to post hoc means tests (Fisher PLSD) to reveal differences between treatment groups.

RESULTS

Figure 1 shows the effect of single acute injections of fluoxetine (2.5, 5.0, or 10.0 mg/kg) on extracellular DA and metabolite levels in the NAc (left column) and CP (right column). Relative to the saline-treated control group, fluoxetine produced a significant reduction in extracellular levels of the serotonin metabolite 5HIAA (bottom two graphs in Fig. 1) in both the NAc ($F(3,33) = 6.2, P < .0001$), and in the CP ($F(3,33) = 3.6$, $P < .0001$). This effect on 5HIAA is consistent with an increase in extracellular serotonin (not measured in this study), as has previously been shown in serotonin microdialysis studies (Perry and Fuller, 1992; Rutter and Auerbach, 1993; Tanda et al., 1994). In the present study, factorial ANOVA analysis revealed that the fluoxetine-induced suppression of 5HIAA to approximately 70% of baseline was more reliably produced in the NAc than in the CP. Thus, as soon as 20 min after injection of the 10 mg/kg dose of fluoxetine, a significant decrease in NAc 5HIAA was observed relative to control ($P < .05$), and by 2 h postinjection all three doses of fluoxetine had produced a significant reduction in 5HIAA levels in the NAc ($P < .001$). The reduction of 5HIAA in the CP reached a similar magnitude as in the NAc at the later time points, but the response of individual subjects was more variable leading to noticeably higher P values when compared to the control group in the post hoc analysis (typically > .05). A strong dose response relationship is not seen in either structure for the fluoxetine-induced 5HIAA reduction, suggesting that a maximal reduction of 5HIAA occurs in the lower end of the dose range of fluoxetine used (cf., Rutter and Auerbach, 1993).

In contrast to the effect on 5HIAA, no large effects of acute fluoxetine treatment were observed on extracellular DA, or DA metabolites in either the NAc or the CP (Fig. 1). Extracellular DA and metabolites in the CP (Fig. 1, top three right panels) were not altered by treatment with acute fluoxetine. However, the small decrease in extracellular DA in the NAc seen following the highest dose of fluoxetine (10 mg/kg, see upper left panel) was highly significant (rmANOVA, $F(3,33) = 1.89, P < .005$). Subsequent analysis revealed that this effect was due exclusively to the high dose group which was significantly lower than the saline control group by 1 h postinjection (factorial ANOVA/Fisher PLSD, $P < .02$) and remained significantly reduced ($P < .05$) at the 2 h and 3 h time points. In the NAc the highest dose of fluoxetine also somewhat reduced the extracellular levels of DOPAC and HVA (Fig. 1, middle left panels), but this reduction was only significant for HVA in the repeated measures ANOVA ($F(3,33) = 1.63$, $P < .05$), and the post hoc contrasts in subsequent factorial ANOVAs were not significant at $P < .05$ for HVA compared to the saline group.

Chronic (21 day) treatment with 5.0 mg/kg fluoxetine had no effect on basal extracellular levels of DA, DA metabolites, or 5HIAA in the NAc compared to controls chronically injected with saline (Fig. 2; rmANOVA for DA, main effect, $F(1,12) = 1.2$, $P = 0.3$), The chronic treatment with fluoxetine also did not alter the response of these neurochemicals to the final injection of 5.0 mg/kg fluoxetine. In Figure 2 the data are plotted as pg/sample, rather than as percent baseline, in order to illustrate that the chronic treatment produced no quantitative change in basal levels for any of the neurochemicals measured. An inspection of the chronic data plotted as percent baseline (not shown) revealed no discrepancies compared to the pg data shown (Fig. 2). As expected, based on the results of the acute study, extracellular 5HIAA decreased significantly in response to the final injection of 5.0 mg/kg fluoxetine for the group treated chronically with saline ($F(1,15) = 4.80, P < .0001$). The group treated chronically with fluoxetine showed a very similar decrease in 5HIAA in response to this final injection of fluoxetine, indicating the neither tolerance nor sensitization was produced by the chronic fluoxetine treatment (no G × T interaction in the rmANOVA, $P = 0.4$). A saline injection given to all rats (e.g., first arrow in Fig. 2) did not alter extracellular levels of the neurochemicals measured.

Although pretreatment with fluoxetine slightly enhanced the cocaine-induced increase in extracellular

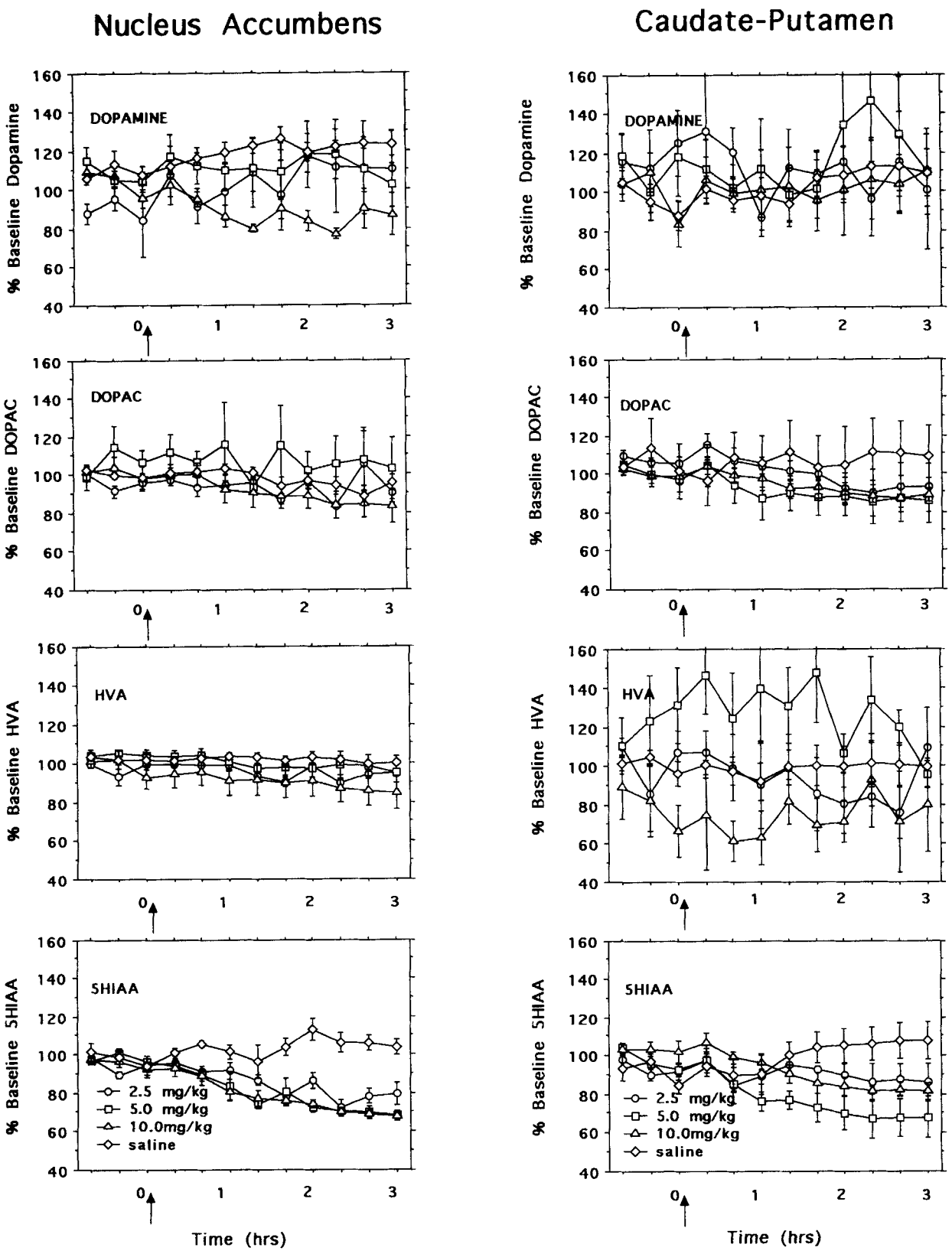

Fig. 1. The graphs depict the effect of acute fluoxetine administration on extracellular DA, DOPAC, HVA, and 5HIAA levels in the NAc (**left** column) and CP (**right** column). In both structures 5HIAA levels were significantly reduced by fluoxetine, relative to the saline-treated control group (**bottom** two graphs, $P < .0001$). The acute doses of fluoxetine had no effect on extracellular DA, or DA metabolite levels in the CP or NAc, with the exception of the high dose causing a small but significant decrease in DA level in the NAc (**upper left** panel, $P < .005$). Group sizes were as follows: saline (NAc, 7; CP, 5); 2.5 mg/kg (NAc, 5; CP, 3); 5.0 mg/kg (NAc, 6; CP, 5); 10.0 mg/kg (NAc, 7; CP, 4). Asterisks indicating significance were omitted for clarity. The arrow indicates the time point of the fluoxetine or saline injection.

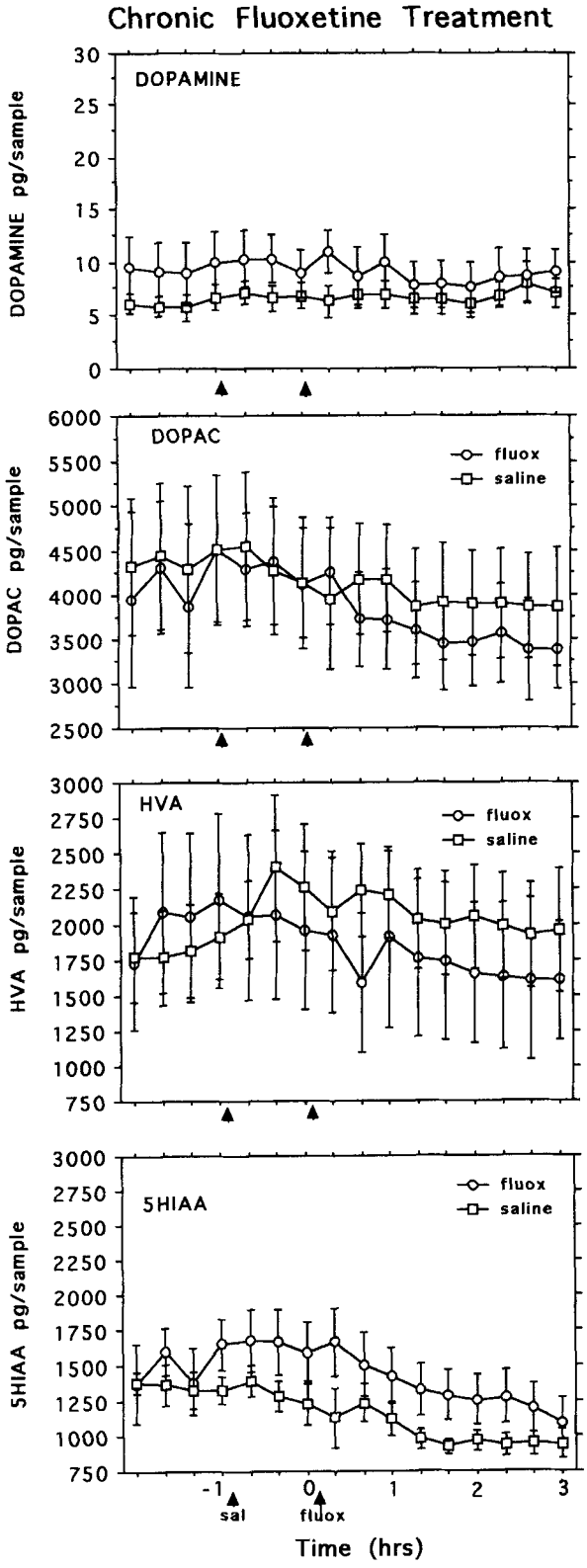

Fig. 2. Chronic (21 day) treatment with 5.0 mg/kg fluoxetine (circles, N = 7) had no effect on basal extracellular levels of DA, DA metabolites, or 5HIAA in the NAc, compared to the saline-treated control group (squares, n = 6). Picograms per sample are plotted on the Y axis because a quantitative comparison of basal levels between the two groups is important in this experiment. A saline injection was given at the first arrow, followed by a final fluoxetine injection at the second arrow.

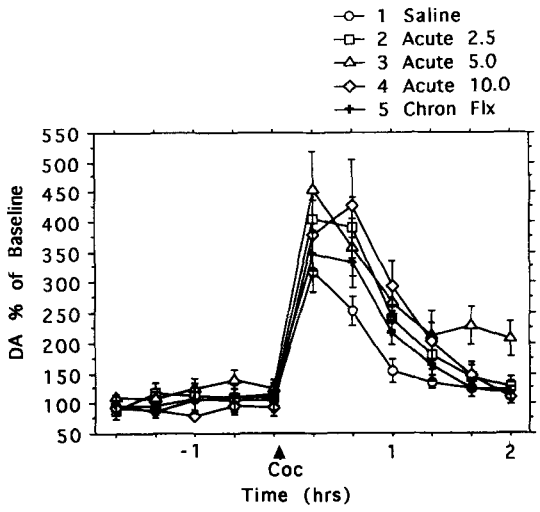

Fig. 3. The cocaine-induced (coc; 10 mg/kg, i.p.) increase in NAc extracellular DA was slightly enhanced by pretreatment with fluoxetine, as shown above. This drug interaction was not quite significant ($P < .06$), and, as illustrated, there was no apparent dose response relationship.

DA in the NAc (Fig. 3), this effect was not quite significant (rmANOVA for the first 80 min postcocaine: $F(4,25)$ main effect = 2.64, $P < .06$). Pretreatment with fluoxetine caused no obvious change in the response of the measured metabolites to cocaine (data not shown).

DISCUSSION

As has been shown in previous microdialysis studies in the striatum (Perry and Fuller, 1992; Rutter and Auerbach, 1993), and diencephalon (Rutter and Auerbach, 1993), all doses of fluoxetine consistently produced a 20% to 30% decrease in striatal and accumbens 5HIAA. This effect on extracellular 5HIAA, the major metabolite of serotonin, provided indirect confirmation that fluoxetine was effective in inhibiting serotonin reuptake in the present study. Rutter and Auerbach (1993) found that three doses of fluoxetine (2, 5, 10 mg/kg, i.p.) produced a clear dose-related increase in 5-HT levels in the diencephalon and striatum (maximal increase of threefold), whereas the suppressive effect of these doses on 5HIAA was less clearly dose-dependent, reaching a maximum of about 25% reduction for all doses, except the lowest dose in the striatum which produced a 10% reduction. In the present study, the accumbens 5HIAA response to fluoxetine (Fig. 1) closely resembles the diencephalic 5HIAA response, whereas the striatal 5HIAA response is very similar in both papers (cf., Rutter and Auerbach, 1993). Chronic (21 day) treatment with 5.0 mg/kg fluoxetine did not alter the response of NAc 5HIAA to a final injection of fluoxetine (Fig. 3), suggesting that the chronic treatment did not produce either tolerance nor sensitization to the fluoxetine effect on 5HIAA.

The present results on the effect of fluoxetine on extracellular DA and DA metabolites is generally consistent with the existing microdialysis literature (Perry and Fuller, 1992; Tanda et al., 1994), whereas studies measuring tissue or CSF levels of DA and metabolites have themselves been inconsistent (for review see Baldessarini et al., 1992). In the present study, acute or chronic injections of fluoxetine had no effect on extracellular DA and DA metabolite levels in the NAc and CP, with the exception that the 10 mg/kg dose produced a significant 20% reduction of extracellular DA in the NAc (Figs. 1 and 2). Combined with the observation that fluoxetine produced a greater reduction in 5HIAA in the NAc compared to the CP, the high dose-induced decrease of NAc DA suggests that fluoxetine may act more potently in the NAc than in the CP. Measurement of fluoxetine's effect on 5-HT release in these different structures would address this possibility.

Serotonergic neurons of the dorsal raphe nucleus project to both the NAc and the CP, as well as to the DA cells in the ventral tegmental area and substantia nigra where the DA innervation of these forebrain structures originates (Herve et al., 1987; Van der Kooy and Hattori, 1980). However, the effect of 5-HT on extracellular DA could vary between structures due to the different distributions of 5-HT receptor subtypes. For example, the 5-HT3 receptor is most dense in the NAc, amygdala, hippocampus and frontal cortex (Kilpatrick et al., 1987), whereas the 5-HT2 receptor is most abundant in the caudate and cerebral cortex (Schott et al., 1984). Although the present study did not use 5-HT receptor subtype-selective drugs, the increase in extracellular 5-HT produced by fluoxetine can be expected to have different effects in regions that differ in 5-HT receptor subtype distributions. For example, Tanda et al. (1995) recently found that acute fluoxetine treatment produced an increase in extracellular DA in the prefrontal cortex that was mediated by the 5-HT3 receptor subtype.

Nonetheless, the reduction in extracellular DA in the NAc following the high dose of fluoxetine did not fit our prediction which was based on recent findings that 5-HT (Guan and McBride, 1988; Parsons and Justice, 1993) and 5-HT3 agonists (Blandina et al., 1989; Chen et al., 1991; Jiang et al., 1990) produce a facilitation of DA release in the NAc. For example, Parsons and Justice (1993) recently found that the addition of 0.1, 0.2 and 0.4 μM of serotonin to the microdialysate perfusate produced concentration-dependent increases in extracellular DA in the NAc. Concentrations lower than 0.1 μM had no effect. Their further experiments with antagonists to specific 5-HT receptor subtypes determined that the 5-HT2 and 5-HT3 receptors are involved in the serotonin-induced DA increase in the NAc, whereas the role of the 5-HT1 receptor subtype remained unclear (Parsons and Justice, 1993). In the present study, the fluoxetine-induced increase in extracellular 5-HT may not have exceeded the threshold extracellular level of 5-HT required to produce an increase in DA (0.1 μM of 5-HT in the perfusate (Parsons and Justice, 1993). Thus, levels of basal extracellular 5-HT in the NAc are estimated to be approximately 2 nM (Parsons and Justice, 1993). If fluoxetine produced a four-fold increase in extracellular 5-HT (to 8 nM), this would still be far short of the 40 nM extracellular concentration of 5-HT that Parsons and Justice estimate was produced adjacent to the microdialysis probe by perfusion with 0.1 μM 5-HT. Nonetheless, as indicated by the literature, the dose of 10 mg/kg fluoxetine is quite high and sufficient to produce significant effects in other paradigms. Hence, the 5-HT-induced facilitation of DA neurotransmission in the NAc described by Parsons and Justice (1993) and others may not be relevant to the therapeutic effect of fluoxetine. On the other hand, the decrease in DA in the NAc produced by 10 mg/kg fluoxetine offers some support for the idea that the extrapyramidal motor side effects of fluoxetine therapy may be due to an inhibition of DA release (Baldessarini et al., 1992).

It is uncertain whether the present results with fluoxetine generalize to other SSRIs, or, further, to different classes of antidepressants. In a pilot microdialysis experiment, we found that the SSRI paroxetine (10 mg/kg) also had no clear effect on DA levels in the CP or NAc (data not shown). On the other hand, using PET technology, we have found interesting differences between SSRIs. For example, citalopram (5 mg/kg) produces an increase in striatal D2 binding (implying a decrease in extracellular DA), whereas fluoxetine caused no change in D2 binding as measured by PET radioligand binding (Dewey et al., 1995). Finally, in the present study, pretreatment of rats with fluoxetine enhanced the increase in extracellular NAc DA produced by an injection of 10 mg/kg of cocaine, an effect that was not quite significant ($P < 0.06$). The magnitude of this drug interaction was not great (see Fig. 3), and by itself does not seem to warrant concern for the possible interaction of these two drugs in patients.

ACKNOWLEDGMENTS

The authors acknowledge Nancy Rini and Barbara Hair for their excellent technical assistance, and Chuen Chen for his help in selected experiments. This work was supported in part by a DOE grant (DE-AC02-76CH00016) to C.R.A. and NIDA grant (DA-07456) to R.E.S.

NOTE ADDED IN PROOF

After the acceptance of this article, the following paper was published that supports the present observation that the 10 mg/kg dose of fluoxetine produces a decrease in extracellular levels of DA in the accumbens: Ichikawa, J., and Meltzer, H.Y. (1995) Effect of antide-

pressants on striatal and accumbens extracellular dopamine levels. Eur. J. Pharmacol., 281:255–261.

REFERENCES

Baldessarini, R.J., Marsh, E.R., and Kula, N.S. (1992) Interactions of fluoxetine with metabolisim of dopamine and serotonin in rat brain regions. Brain Res., 579:152–156.

Björklund, A., and Lindvall, O. (1986) Catecholaminergic brain stem regulatory systems. In: Handbook of Physiology: The Nervous System Vol. 4, Intrinsic Regulatory Systems in the Brain. F.E. Bloom, Ed. American Physiological Society, Bethesda, MD, pp. 155–235.

Blandina, P., Goldfarb, J., Craddock-Royal, B., and Green, J.P. (1989) Release of endogenous dopamine by stimulation of 5-hydroxytryptamine 3 receptors in rat striatum. J. Pharmacol. Exp. Ther., 251:803–809.

Chen, J., van Praag, H.M., and Gardner, E.L. (1991) Activation of 5-HT_3 receptor by 1-phenylbiguanide increases dopamine release in the rat nucleus accumbens. Brain Res., 543:354–357.

Dewey, S.L., Smith, G.S., Logan, J.S., Alexoff, D., Ding, Y.S., King, P.T., Pappas, N., Brodie, J.D., and Ashby, C.R. (1995) Serotonergic modulation of striatal dopamine measured with positron emission tomography (PET) and in vivo microdialysis. J. Neurosci., 15:821–829.

Guan, X.-M., and McBride, W.J. (1988) Serotonin microfusion into the ventral tegmental area increases accumbens dopamine release. Brain Res. Bull., 23:541–547.

Herve, R.M., Pickel, V.M., Joh, T.H., and Beaudet, A. (1987) Serotonin axon terminals in the ventral tegmental area of the rat: Fine structure and synaptic input to dopaminergic neurons. Brain Res., 435:71–83.

Jiang, L.H., and Asby, C.R., Kasser, R.J., and Wang, R.Y. (1990) The effect of intraventricular administration of the 5-HT_3 receptor agonist 2-methylserotonin on the release of dopamine in the nucleus accumbens: An in vivo chronocoulometric study. Brain Res., 513:156–160.

Kapur, S., and Mann, J.J. (1992) Role of the dopaminergic system in depression. Biol. Psychiatry, 32:1–17.

Kilpatrick, G.J., Jones, B.J., and Tyers, M.B. (1987) Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. Nature, 330:746–748.

Lipinski, J.F., Mallya, G., Zimmerman, P., and Pope, H.G. (1989) Fluoxetine-induced akathisia: Clinical and theoretical implications. J. Clin. Psychiatry, 50:339–342.

Meltzer, H.Y., Young, M., Metz, J., Fang, V.S., Schyve, P.M., and Arora, R.C. (1979) Extrapyramidal side effects and increased serum prolactin following fluoxetine, a new antidepressant. J. Neural Trans. 45:165–175.

Parsons, L.H., and Justice, J.B. Jr. (1993) Perfusate serotonin increases extracellular dopamine in the nucleus accumbens as measured by in vivo microdialysis. Brain Res., 606:195–199.

Perry, K.W., and Fuller, R.W. (1992) Effect of fluoxetine on serotonin and dopamine concentration in microdialysis fluid from rat striatum. Life Sci., 50:1683–1690.

Robinson, T.E., and Camp, D.M. (1991) The feasibility of repeated microdialysis for within-subjects design experiments: studies on the mesostriatal dopamine system. In: Microdialysis in the Neurosciences. T.E. Robinson and J.B. Justice, eds. Amsterdam, Elsevier, pp. 189–234.

Rutter, J.J., and Auerbach, S.B. (1993) Acute uptake inhibition increases extracellular serotonin in the rat forebrain. J. Pharmacol. Exp. Ther., 265:1319–1324.

Schott, A., Maloteaux, J.M., and Laduron, P.M. (1984) Solubilization of serotonin S2-receptors from human brain. Eur. J. Pharmacol., 100:329–333.

Srebnik, M., Ramachandran, P.V., and Brown, H.C. (1988) Chiral synthesis via organoboranes. 18. Selective Reductions. 43. Diisopinocampheylchloroborane as an excellent chiral reducing reagent for the synthesis of halo alcohols of high enantiomeric purity. A high enantioselective synthesis of both optical isomers of tomoxetine, fluoxetine, and nisoxetine. J. Org. Chem., 53:2916–2920.

Tanda, G., Carboni, E., Frau, R., and Di Chiara, G. (1994) Increase of extracellular dopamine in the prefrontal cortex: A trait of drugs with antidepressant potential? Psychopharmacology, 115:285–288.

Tanda, G., Frau, R., and Di Chiara, G. (1995) Local 5HT3 receptors mediate fluoxetine but not desipramine-induced increase of extracellular dopamine in the prefrontal cortex. Psychopharmacology, 119:15–19.

Van der Kooy, D., and Hattori, T. (1980) Dorsal raphe cells with collateral projections to the caudate-putamen and substantia nigra: A fluorescent retrograde double labeling study in the rat. Brain Res., 186:1–7.

Wong, D.T., Bymaster, F.P., and Engleman, E.A. (1995) Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: Twenty years since its first publication. Life Sci., 57:411–441.