Pharmacology Biochemistry & Behavior, Vol. 30, pp. 715–721. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Mechanisms of Effects of *d*-Fenfluramine on Brain Serotonin Metabolism in Rats: Uptake Inhibition Versus Release

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Received 26 October 1987

FULLER, R. W., H. D. SNODDY AND D. W. ROBERTSON. *Mechanisms of effects of d-fenfluramine on brain serotonin metabolism in rats: Uptake inhibition versus release.* PHARMACOL BIOCHEM BEHAV 30(3) 715–721, 1988.—*d*-Fenfluramine is an anorectic drug believed to act by enhancement on serotonergic function in the brain. *d*-Fenfluramine (or the racemate) releases serotonin through a carrier-dependent mechanism, and serotonin release is the mechanism usually thought to produce its serotonergic effects. However, *d*-fenfluramine also inhibits serotonin uptake in vitro, and serotonin uptake inhibition is sometimes suggested to contribute to its mechanism of anorectic activity. Neurochemical experiments were done to examine serotonin release and serotonin uptake inhibition as mechanisms of action of *d*-fenfluramine in rats and to compare *d*-fenfluramine to fluoxetine, a serotonin uptake inhibitor. *d*-Fenfluramine decreased serotonin concentration in rat brain as early as 1 hr; at 1 hr 5-hydroxyindoleacetic acid (5HIAA) concentration was slightly increased, but at later times 5HIAA was also decreased. Fluoxetine, in contrast, did not change serotonin concentration in whole brain but decreased 5HIAA concentration at all time points. At all time intervals studied, the 5HIAA/serotonin ratio was *increased* by *d*-fenfluramine (and by Ro 4-1284, a nonspecific serotonin releaser) but was *decreased* by fluoxetine, a serotonin uptake inhibitor. No decrease in 5HIAA concentration or in the 5HIAA/serotonin ratio was apparent at any time or after any dose of *d*-fenfluramine studied. The possibility that doses of *d*-fenfluramine below those needed for serotonin release might inhibit serotonin uptake was tested by determining whether *d*-fenfluramine could block the acute depletion of brain serotonin by p-chloroamphetamine, or the long-term neurotoxic effect of p-chloroamphetamine on brain serotonin neurons. No protective effect of *d*-fenfluramine was found up to doses that themselves did not cause acute or long-term depletion of brain serotonin. Both *d*-fenfluramine and fluoxetine increased serum corticosterone concentration, but only *d*-fenfluramine increased serum prolactin concentration. These data in conjunction with earlier published data support the interpretation that *d*-fenfluramine initially enhances serotonergic function by carrier-dependent release of serotonin and not by uptake inhibition. At longer times and after higher doses of *d*-fenfluramine, brain serotonin becomes depleted.

Fenfluramine p-Chloroamphetamine Fluoxetine Corticosterone, serum Serotonin, brain
Prolactin, serum 5-Hydroxyindoleacetic acid

d-FENFLURAMINE and *dl*-fenfluramine are used as anorectic drugs in the treatment of human obesity [29,30]. Extensive evidence from animal studies indicates these agents act by enhancing a central serotonergic input that limits food intake or alters food preference [18,45]. Three possible mechanisms for the enhanced serotonergic function have been considered: release of serotonin, inhibition of serotonin uptake, and direct actions on serotonin receptors [28]. Most evidence argues against a direct agonist action of fenfluramine [3,33]. Fenfluramine is generally thought to act by serotonin release, but fenfluramine (especially *d*-fenfluramine) does inhibit serotonin uptake in vitro, and uptake inhibition is sometimes considered as contributing to its mechanism of anorectic action and other pharmacologic effects in vivo [20]. The present in vivo experiments were done to examine further the relative importance of uptake inhibition and release to the actions of *d*-fenfluramine on brain serotonergic neurons in rats.

METHOD

Male Sprague-Dawley rats weighing 170–200 g were purchased from Charles River Breeding Laboratories (Portage, MI). (±)p-Chloroamphetamine hydrochloride was purchased from Regis Chemical, Morton Grove, IL. *d*-Fenfluramine hydrochloride and fluoxetine hydrochloride was synthesized in the Lilly Research Laboratories. Ro 4-1284 was a gift from Hoffmann-LaRoche, Nutley, NJ. At specified times after the compounds were injected IP, rats were decapitated, and whole brains were removed quickly,

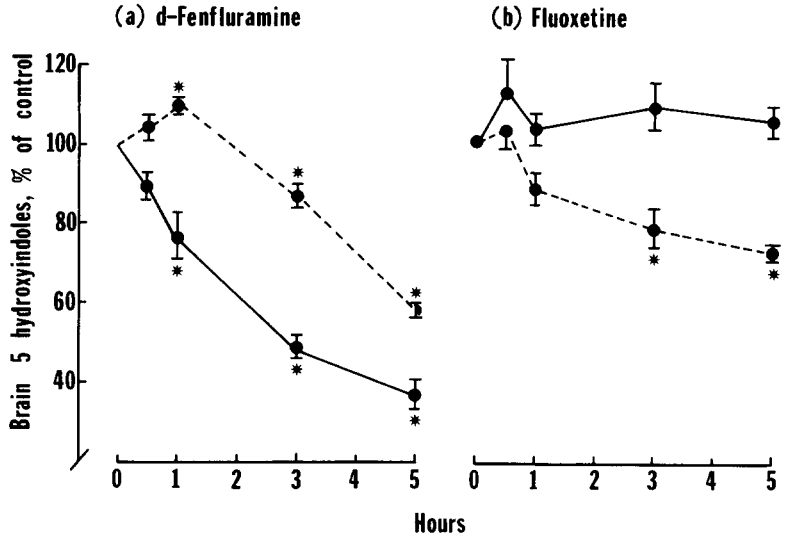

FIG. 1. Time course of changes in serotonin (solid lines) and 5HIAA (broken lines) concentrations in rat brain after injection of (a) *d*-fenfluramine (15 mg/kg IP) or (b) fluoxetine (10 mg/kg IP). Mean values ±standard errors for 5 rats per group are shown. Asterisks indicate groups that differed significantly from the respective control groups ($p<0.05$). Control group values were 2.05±0.08 nmoles/g for serotonin and 1.55±0.05 nmoles/g for 5HIAA in the *d*-fenfluramine experiment and 2.60±0.10 nmoles/g for serotonin and 2.57±0.11 nmoles/g for 5HIAA in the fluoxetine experiment.

TABLE 1

5-HYDROXYINDOLE CONCENTRATIONS IN WHOLE BRAIN AFTER INJECTION OF FLUOXETINE, d-FENFLURAMINE OR Ro 4-1284 IN RATS

Dose (mg/kg)	Brain 5-Hydroxyindoles (nmoles/g) Fluoxetine	d-Fenfluramine	Ro 4-1284
	Serotonin		
0	2.54 ± 0.17	2.64 ± 0.09	2.54 ± 0.17
1.25	2.63 ± 0.12	2.38 ± 0.07	1.11 ± 0.14*
2.5	2.60 ± 0.09	2.57 ± 0.08	0.80 ± 0.06*
5	2.47 ± 0.11	2.31 ± 0.18	0.45 ± 0.05*
10	2.76 ± 0.11	1.99 ± 0.09*	0.46 ± 0.05*
20	3.03 ± 0.07*	1.69 ± 0.17*	0.31 ± 0.03*
	5-Hydroxyindoleacetic Acid		
0	2.33 ± 0.09	2.11 ± 0.05	2.33 ± 0.09
1.25	2.29 ± 0.09	2.19 ± 0.04	4.21 ± 0.17*
2.5	2.08 ± 0.06*	2.24 ± 0.06	4.99 ± 0.16*
5	1.87 ± 0.03*	2.38 ± 0.16	4.80 ± 0.10*
10	1.95 ± 0.06*	2.18 ± 0.08	5.19 ± 0.04*
20	1.89 ± 0.04*	2.27 ± 0.05	4.54 ± 0.18*

*Significant difference from control ($p<0.05$).

Fluoxetine hydrochloride, d-fenfluramine hydrochloride or Ro 4-1284 was injected 1 hr before rats were killed.

Mean values ± standard errors for 5 rats per group are shown.

frozen on dry ice, and stored at −15°C prior to analysis. Serotonin and 5HIAA in brain were measured by liquid chromatography with electrochemical detection [15]. Trunk blood taken after decapitation was allowed to clot; serum collected after centrifugation was stored at −15°C prior to analysis. Corticosterone in serum was determined spectrofluorometrically by the method of Solem and Brinck-Johnsen [37]. Prolactin in serum was measured by radioimmunoassay using the National Institute of Arthritis, Metabolism and Digestive Diseases kit with rat prolactin RP-1.

RESULTS

Figure 1 shows the time course of changes in brain serotonin and 5HIAA concentrations at early times after injection of *d*-fenfluramine or fluoxetine. After *d*-fenfluramine administration, brain serotonin concentration was slightly but not significantly decreased within 30 min. At 1 hr, 3 hr and 5 hr, brain serotonin concentration was significantly decreased. At 1 hr there was a significant increase in 5HIAA concentration, but at 3 and 5 hr there were significant decreases in 5HIAA concentration. Fluoxetine caused a rapid and persistent decrease in 5HIAA concentration but did not change serotonin concentration significantly, although mean values were slightly higher than control values at early times. The 5HIAA/serotonin ratio was increased by *d*-fenfluramine and decreased by fluoxetine at all of the time intervals studied.

Table 1 shows 5-hydroxyindole concentrations measured at 1 hr after injection of *d*-fenfluramine, fluoxetine or Ro

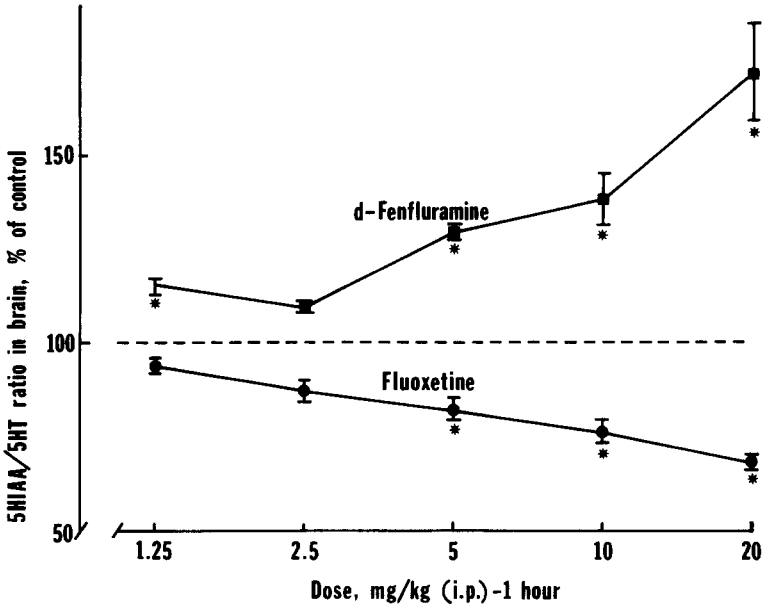

FIG. 2. Dose-dependent changes in the 5HIAA/serotonin ratio 1 hr after injection of *d*-fenfluramine or fluoxetine. Data are derived from Table 1. Asterisks indicate ratios that differed significantly ($p<0.05$) from the corresponding control ratio.

4-1284, a serotonin-releasing drug that is nonspecific in that it releases other monoamines also [9,59]. Fluoxetine did not change serotonin concentration except for a small significant increase at the highest dose, but decreased 5HIAA concentration at all doses except the lowest dose. In contrast, Ro 4-1284 markedly decreased serotonin concentration and increased 5HIAA concentration at all doses tested. The direction of changes after *d*-fenfluramine was like that after Ro 4-1284, namely a decrease in serotonin and an increase in 5HIAA, but the magnitude of changes was smaller than after Ro 4-1284, and in this experiment none of the changes in 5HIAA concentration reached statistical significance. Figure 2 shows the mean and standard errors for the 5HIAA/serotonin concentration ratios calculated for each rat. *d*-Fenfluramine caused an increase in this ratio throughout the dose range studied, whereas fluoxetine caused a decrease in the ratio.

Figure 3 shows the influence of *d*-fenfluramine on brain serotonin concentration in control rats and in rats treated with p-chloroamphetamine (PCA), a serotonin-releasing drug. PCA depletes brain serotonin through a carrier-dependent mechanism, and antagonism of PCA depletion of brain serotonin is a test for serotonin uptake inhibitors [11,27]. The values in the control column show that *d*-fenfluramine caused significant depletion of brain serotonin at 2.5 and 5 mg/kg doses but no significant effects at the two lower doses. The values in the column labeled "PCA-treated" show that no significant antagonism of the PCA-induced depletion of brain serotonin was found with any dose of *d*-fenfluramine.

Figure 4 shows an analogous experiment to investigate possible antagonism of PCA effects by *d*-fenfluramine, but the effect measured was not the acute depletion of serotonin as in Fig. 3 but instead the long-term neurotoxic depletion of serotonin at 1 week after PCA administration. Again, *d*-fenfluramine failed to antagonize serotonin depletion by PCA and at higher doses began to mimic the effect of PCA.

Figure 5 shows the effects of *d*-fenfluramine and of fluoxetine on two serum hormones, corticosterone and prolactin. *d*-Fenfluramine caused a dose-related increase in both hormones. Fluoxetine increased corticosterone but had no effect on prolactin.

DISCUSSION

The depletion of serotonin and the increase in the 5HIAA/serotonin ratio produced by *d*-fenfluramine distinguish it from fluoxetine and indicate that *d*-fenfluramine acts primarily by serotonin release rather than by serotonin uptake inhibition. However, *d*-fenfluramine is not simply a serotonin-releasing drug like Ro 4-1284, since the latter compound increases 5HIAA concentration, whereas *d*-fenfluramine decreases 5HIAA except for a transient and small increase immediately after drug administration. Fenfluramine previously has been shown to decrease brain serotonin turnover [10,22], whereas Ro 4-1284 increases brain serotonin turnover [35]. Fenfluramine causes a rapid and long-lasting decrease in tryptophan hydroxylase [13,34].

d-Fenfluramine is structurally and pharmacologically related to PCA, another serotonin-releasing drug. Both drugs deplete brain serotonin by a carrier-dependent mechanism; their depletion of serotonin is prevented by prior treatment with an uptake inhibitor [13, 17, 19, 21, 27]. Both *d*-fenfluramine and PCA inhibit serotonin uptake by brain synaptosomes in vitro [17, 28, 43]; this inhibition may represent competition between substrates for the uptake carrier. Accumulation of *d*-fenfluramine or PCA by the membrane carrier in vivo may precede and be necessary for their deple-

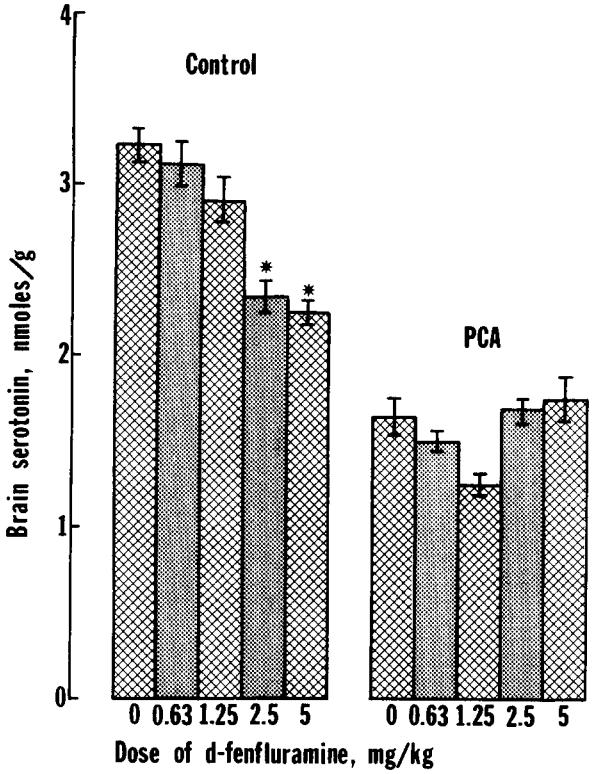

FIG. 3. Inability of *d*-fenfluramine to antagonize the acute depletion of brain serotonin by p-chloroamphetamine. Bars at left show brain serotonin concentration in rats treated with *d*-fenfluramine 2 hr and 15 min before they were killed. Bars at right show brain serotonin concentration in rats treated with the same doses of *d*-fenfluramine in addition to p-chloroamphetamine hydrochloride (10 mg/kg IP) 2 hr before they were killed. Mean value ±standard errors for 5 rats per group are shown. Asterisks indicate significant effects due to *d*-fenfluramine ($p<0.05$).

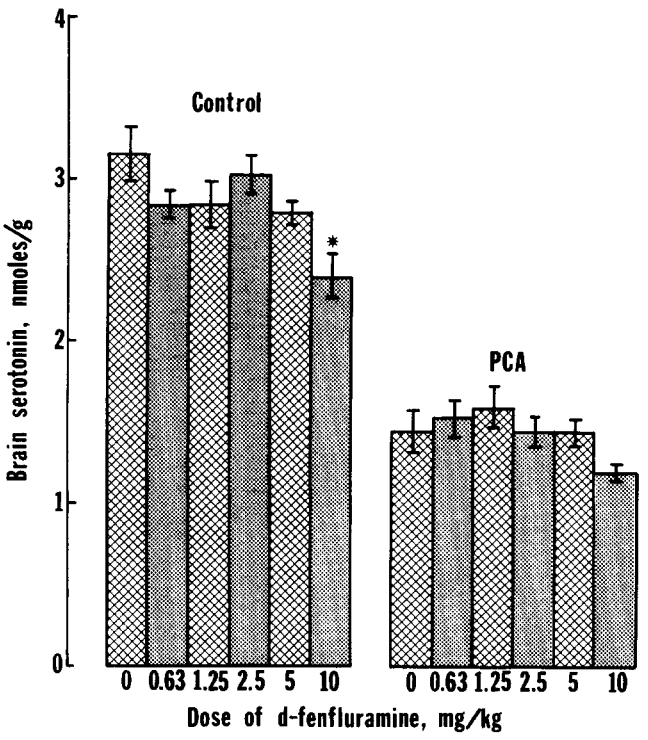

FIG. 4. Inability of *d*-fenfluramine to antagonize the neurotoxic long-term depletion of brain serotonin by p-chloroamphetamine at one week. Bars at left show brain serotonin concentration in rats treated with *d*-fenfluramine alone one week before they were killed. Bars at right show brain serotonin concentration in rats treated with the same doses of *d*-fenfluramine 15 min before injection of p-chloroamphetamine hydrochloride (10 mg/kg IP) one week before they were killed. Mean value ±standard errors for 5 rats per group are shown. Asterisk indicates significant effect due to *d*-fenfluramine ($p<0.05$).

tion of serotonin, a phenomenon that would explain the block of serotonin depletion by uptake inhibitors [7].

The possibility that *d*-fenfluramine might inhibit serotonin uptake at doses below those that depleted serotonin was considered and was investigated by determining if *d*-fenfluramine would antagonize brain serotonin depletion by PCA. Antagonism of PCA-induced depletion of brain serotonin has been widely used as a test for inhibition of uptake into brain serotonin neurons [11, 27, 40]. Neither the acute depletion of brain serotonin 2 hr after PCA nor the neurotoxic depletion of brain serotonin one week after PCA was antagonized by *d*-fenfluramine. A higher doses, *d*-fenfluramine mimicked both of these effects of PCA.

Our data provide no evidence that inhibition of serotonin uptake contributes to the in vivo pharmacologic actions of *d*-fenfluramine. The affinity of *d*-fenfluramine for the serotonin uptake carrier is apparently vital to its effects on serotonin neurons, not because it leads to inhibition of serotonin uptake but because it allows accumulation of *d*-fenfluramine which is necessary for serotonin release.

Functional effects of both fluoxetine and fenfluramine, such as a reduction in food intake [1,44], presumably relate to increased concentrations of serotonin in the synaptic cleft and subsequent stimulation of postsynaptic receptors for serotonin. The increased concentrations of serotonin in the synaptic cleft apparently arise by inhibition of serotonin reuptake in the case of fluoxetine and release of serotonin in the case of *d*-fenfluramine. A consequence of increased concentrations of serotonin in the synaptic cleft is a reduced rate of synthesis and release of serotonin and a reduced rate of firing of serotonin neurons [2, 6, 16, 36]. Because of these rapid adaptive responses, there is a ceiling in the concentration of serotonin that can be reached in the synaptic cleft following injection of fluoxetine and other uptake inhibitors. With releasing drugs such as *d*-fenfluramine and PCA, the firing rate of serotonin neurons is not of consequence, and the concentration of serotonin in the synaptic cleft can be increased independent of physiologically controlled serotonin release. Marsden *et al.* [26] measured extraneuronal concentrations of serotonin by in vivo voltammetry in rat brain and found a small but persistent increase after fluoxetine injection. After injection of PCA, a much larger initial increase in the signal was obtained, but after a few hours the signal fell to below baseline. The large initial increase in signal was prevented by pretreatment with fluoxetine.

The ceiling on serotonin concentration in the synaptic

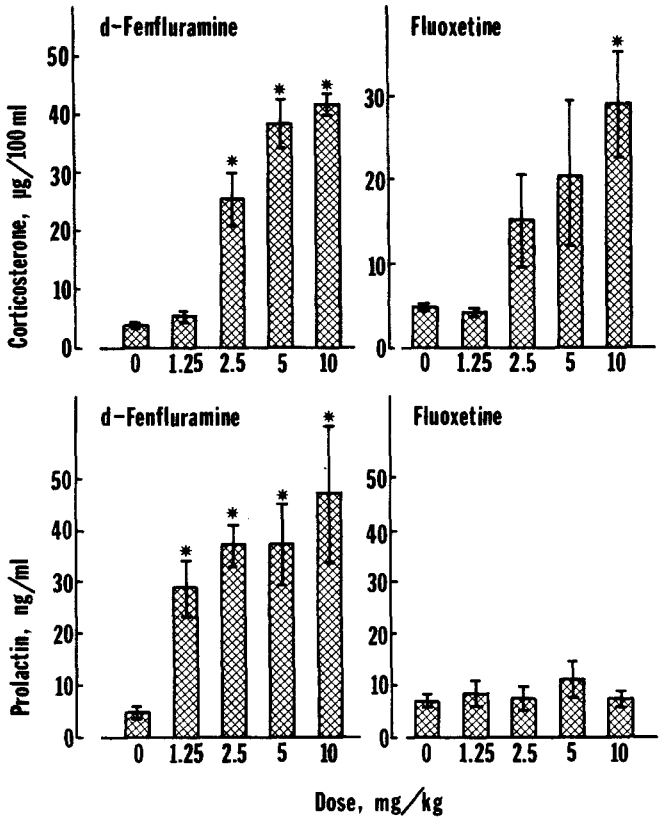

FIG. 5. Effect of *d*-fenfluramine and fluoxetine on serum corticosterone (top graphs) and on serum prolactin (bottom graphs) concentrations in rats. Mean values ±standard errors for 5 rats per group are shown. Asterisks indicate significant differences from control group ($p<0.05$).

cleft that can be reached by uptake inhibition may account for some differences in functional effects between uptake inhibitors and serotonin-releasing drugs. Figure 5 shows that whereas both drugs increase serum corticosterone concentration, *d*-fenfluramine but not fluoxetine increases serum prolactin concentration. These findings are consistent with previous literature. Increased concentrations of serum corticosterone have been reported to occur with fluoxetine and other serotonin uptake inhibitors [8,14] as well as with fenfluramine and PCA [12]. *d*-Fenfluramine has previously been reported to increase serum prolactin, and evidence has been presented that the mechanism involves carrier-dependent release of serotonin [32,42]. Fluoxetine has previously been reported not to increase serum prolactin concentration unless combined with the serotonin precursor, 5-hydroxytryptophan, to "push" more serotonin into the synaptic cleft [2,23].

The different mechanisms for functional effects produced by fluoxetine and by fenfluramine are also indicated by other published data. Several functional effects of fenfluramine are antagonized by pretreatment with fluoxetine, supporting the interpretation that the effects of fenfluramine result from carrier-dependent release of serotonin. Such effects would then be antagonized by inhibition of the carrier. For instance, fluoxetine has been reported to antagonize all of the following functional effects of fenfluramine: discriminative stimulus properties in rats [24], hyperthermia in rats housed at 27–28°C [39], elevation of serum corticosterone concentration [25], elevation of serum prolactin concentration [42], the initial elevation of plasma renin activity in rats [41] and the increase in striatal acetylcholine concentration in rats [5]. Fluoxetine also antagonizes the acute [4] and long-term [21,38] depletion of brain serotonin by fenfluramine.

In conclusion, the current data and previous literature cited support the interpretation that *d*-fenfluramine acts through a carrier-dependent mechanism to release serotonin. This action is like that of PCA and distinguishes the two drugs from serotonin uptake inhibitors. These serotonin-releasing drugs, like serotonin uptake inhibitors, increase serotonin concentrations in the synaptic cleft and cause functional changes secondary to enhanced serotonergic neurotransmission. Because of the different mechanisms, these serotonin-releasing drugs produce some effects not caused by serotonin uptake inhibitors and, in addition, their effects (serotonin depletion as well as functional effects resulting from increased activation of postsynaptic serotonin receptors) are blocked by serotonin uptake inhibitors.

ACKNOWLEDGEMENTS

We thank Mr. E. E. Beedle for his assistance in the preparation of *d*-fenfluramine and Dr. J. A. Clemens for the prolactin assays.

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