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Elevation of 3,4-dihydroxyphenylacetic acid concentration by L-5-hydroxytryptophan in control and fluoxetine-pretreated rats

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5-Hydroxytryptophan (5-HTP), the immediate precursor to 5-hydroxytryptamine (5-HT), has been reported to increase acutely the concentration of dopamine metabolites in brain (Awazi & Guldberg 1978; Everett 1979). This effect may occur via conversion of 5-HTP to 5-HT within the dopamine neuron and displacement of vesicular dopamine by the 5-HT (Ng et al 1972; Butcher et al 1972), but a possible alternative explanation is that 5-HTP elevates the concentration of 5-HT at a 5-HT synapse influencing dopamine turnover. Consistent with the latter possibility are reports that 5-HT uptake inhibitors increase dopamine metabolite concentrations in haloperidol-treated rats (Waldmeier & Delini-Stula 1979) and that (+)-fenfluramine, a 5-HT releaser, elevates dopamine metabolites in rat striatum in control rats but not in rats pretreated with *p*-chlorophenylalanine or with a 5-HT uptake inhbitor to prevent the 5-HT activating effect of (+)-fenfluramine (Crunelli et al 1980).

Different effects of pretreatment with a 5-HT uptake inhibitor would be predicted depending on which of the above mechanisms were involved. 5-HT uptake inhibition would not be expected to alter the decarboxylation of 5-HTP within dopamine neurons and should not influence the 5-HTP effect on dopamine neurons if the first of the above mechanisms were correct. On the other hand, uptake inhibition should enhance the action of 5-HT on receptors at 5-HT synapses by preventing its inactivation by neuronal uptake. Several actions of 5-HTP thought to be mediated by 5-HT synapses are enhanced by uptake inhibition. For instance, pretreatment of rats with fluoxetine, a 5-HT uptake inhibitor, potentiates the suppression of food intake in rats (Goudie et al 1976), the elevation of serum corticosterone (Fuller et al 1975a) and prolactin (Krulich 1975) in rats, the suppression of REM sleep in cats and rats (Slater et al 1978), and the lowering of blood pressure in hypertensive rats (Fuller et al 1979) by 5-HTP.

The experiment described in this communication was done to see if fluoxetine pretreatment would alter the ability of 5-HTP to increase the concentration of the dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), in rat brain. Male Wistar rats (130–150 g) from Harlan Industries, Cumberland, Indiana, were

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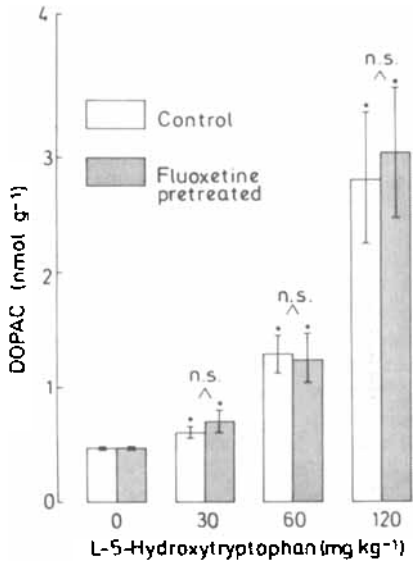

FIG. 1. L-5-HTP-induced elevation of brain DOPAC in control and fluoxetine-pretreated rats. L-5-HTP was injected i.p. at the doses indicated 1 h before rats were killed and 16 h after fluoxetine hydrochloride (10 mg kg^{-1} i.p.). Mean values ± standard errors for 5 rats per group are shown. Asterisks indicate significant ($P < 0.05$) elevation of DOPAC compared with the corresponding group not receiving L-5-HTP. The designation 'n.s.' means the difference between control and fluoxetine-treated groups were not statistically significant ($P = 0.05$).

given i.p. injections of L-5-HTP (Sigma) at doses of 30, 60 or 120 mg kg^{-1}, 1 h before they were killed. Some rats were pretreated with fluoxetine hydrochloride (LY110140) (10 mg kg^{-1} i.p.) 16 h before the injection of L-5-HTP. DOPAC concentration in whole brain was measured by high performance liquid chromatography with electrochemical detection (Perry & Fuller 1979). The results were evaluated using Student's *t*-test.

The results in Fig. 1 show that L-5-HTP at doses of 30, 60 and 120 mg kg^{-1} produced a dose-dependent increase in brain DOPAC concentration. Fluoxetine pretreatment did not affect DOPAC concentration nor did it influence the elevation of DOPAC by 5-HTP. Pretreatment with fluoxetine at this exact dose and time has been shown to inhibit 5-HT uptake in rats (Fuller et al 1975b) and to enhance the 5-HTP-induced elevation of serum corticosterone in rats (Fuller & Snoddy 1980).

These results show that not all actions of 5-HTP are potentiated by fluoxetine pretreatment and are consistent with the idea that only those actions mediated by 5-HT synapses are potentiated by inhibition of the membrane uptake pump on 5-HT neurons. The results then favour the interpretation that the elevation of brain DOPAC by 5-HTP, reported by Awazi & Guldberg (1978) and by Everett (1980), is due to displacement of vesicular dopamine by 5-HT formed within the dopaminergic neuron from the injected 5-HTP rather than to influences on dopamine turnover and release mediated by 5-HT synapses.

The administration of precursor amino acids is a commonly used means of enhancing monoaminergic neuron function. Various workers have properly cautioned against the unqualified interpretation of results obtained in this way, pointing out that certain amino acid precursors like 5-HTP and dihydroxyphenylalanine can be converted to 5-HT and to catecholamines in cells that do not normally form these particular monoamines. For example, 5-HTP may alter catecholaminergic neuron function by displacing vesicular catecholamines at the same time as it increases 5-HT neuron function (Ng et al 1972; Butcher et al 1972). As a means of discerning which of these actions is involved in a functional change produced by 5-HTP, a 5-HT uptake inhibitor such as fluoxetine is useful. The present results show that fluoxetine does not alter the effects of 5-HTP on catecholamine neurons. Thus various actions of 5-HTP that have been shown to be potentiated by fluoxetine are likely to involve 5-HT synapses.

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