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PRELIMINARY COMMUNICATION

ANTAGONISM BY L-DOPA OF THE ELEVATION OF HYPOTHALAMIC EPINEPHRINE BY MONOAMINE OXIDASE INHIBITION IN RATS

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3,4-Dihydroxy-L-phenylalanine (L-dopa), formed by hydroxylation of L-tyrosine, is the physiological precursor to the catecholamines. Administration of exogenous L-dopa increases dopamine concentration in brain, an effect that is the basis of the therapeutic use of L-dopa in Parkinson's disease. Many investigators have noted that L-dopa administration produces little or no increase in norepinephrine concentration in brain [1-3]. We reported that epinephrine concentration in rat hypothalamus was slightly decreased after a 200 mg/kg i.p. dose of L-dopa [4]. Recently Edwards and Rizk [5] emphasized that norepinephrine formation is increased more by L-dopa injection than is norepinephrine concentration. To evaluate whether L-dopa might increase epinephrine formation, we determined if L-dopa injection would enhance the increase in hypothalamic epinephrine concentration produced by monoamine oxidase (MAO, EC 1.4.3.4) inhibition. Instead L-dopa injection totally prevented the increase in epinephrine while enhancing the increase in norepinephrine and dopamine.

Male Wistar rats weighing 130-150 g were obtained from Harlan Industries, Cumberland, Indiana. L-Dopa (Monsanto, St. Louis, MO) was injected i.p. in acacia suspension at a dose of 200 mg/kg. LY51641, N-[2-(o-chlorophenoxy)ethyl]cyclopropylamine HCl (Lilly Research Laboratories) was injected i.p. in aqueous solution at a dose of 30 mg/kg to inhibit MAO. Rats were decapitated 6 hrs after drug injection, and hypothalami were dissected, frozen on dry ice, and stored at -15°C. Catecholamines were measured by liquid chromatography with electrochemical detection [6].

Table 1 shows that LY51641 increased the concentration of all three catecholamines in rat hypothalamus. The percentage increase was greater for epinephrine than for norepinephrine or dopamine, as observed in other studies [7]. Administration of L-dopa increased dopamine significantly and caused an apparent slight but not significant increase in norepinephrine and decrease in epinephrine. Injection of L-dopa with LY51641 prevented the increase in epinephrine but enhanced the increase in norepinephrine slightly and the increase in dopamine dramatically.

Additional study will be needed to elucidate the mechanism(s) by which L-dopa antagonizes the MAO inhibitor-induced elevation of epinephrine in hypothalamus. A plausible explanation might be that extensive O-methylation of L-dopa by catechol O-methyltransferase (EC 2.1.1.6) elevates the tissue concentration of S-adenosyl-L-homocysteine (SAH), the product of methyl transfer reactions, which inhibits various methyltransferases including norepinephrine N-methyltransferase (the epinephrine-forming enzyme, EC 2.1.1.28) [8]. The increase in SAH and a concomitant decrease in the concentration of S-adenosyl-L-methionine [9], the methyl donor, could then impair N-methylation of norepinephrine, accounting for the slight decrease in epinephrine concentration by L-dopa alone and complete prevention of the

Table 1. Effect of L-dopa on the elevation of hypothalamic catecholamines by an MAO inhibitor, LY51641*

Treatment Group	Amine concentration in hypothalamus, pmoles/g		
	Epinephrine	Norepinephrine	Dopamine
Control	75 ± 7	6804 ± 176	1366 ± 39
LY51641	118 ± 8 (+57%)	9412 ± 220 (+38%)	1619 ± 49 (+20%)
L-Dopa	61 ± 16	8032 ± 1352	1603 ± 99 (+19%)
LY51641 + L-Dopa	59 ± 16	12059 ± 747 (+77%)	5038 ± 56 (+273%)

*Mean values ± standard errors for 5 rats per group are shown. Percentage changes are shown for all groups that differed significantly from control ($P<.05$).

increase in epinephrine concentration by MAO inhibition. Consistent with this explanation is the decreased O-methylation of norepinephrine in brain following L-dopa administration to rats observed by some [9,10], though not by all workers [5]. Another possibility is that inhibition of norepinephrine N-methyltransferase by excess norepinephrine [11] produced by L-dopa plus MAO inhibition results in decreased epinephrine formation. The study of lower doses of L-dopa and other treatment intervals may help in evaluating these and other possible mechanisms.

Whatever the mechanism, these findings suggest a useful application in drug studies aimed at identifying physiologic functions of catecholamine neurons. An effect of MAO inhibitors mediated by dopamine should be enhanced by L-dopa. The same should be true for norepinephrine, though less enhancement would be expected. In contrast, an effect of MAO inhibition mediated by epinephrine should be antagonized by L-dopa. In this experiment, we observed aggressiveness and stereotypy in rats treated with the combination of L-dopa and LY51641, effects that are probably mediated by dopamine.

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