L-Dihydroxyphenylalanine: Effect on S-Adenosylmethionine in Brain

Abstract. *Forty-five minutes after intraperitoneal injection of a single dose (100 milligrams per kilogram) of* L-*dihydroxyphenylalanine, the concentration of* S-*adenosylmethionine in rat brain was lowered by 76 percent. As little as 10 milligrams of* L-*dihydroxyphenylalanine per kilogram decreased content of* S-*adenosylmethionine in the adrenal medulla by 51 percent, whereas 100 milligrams per kilogram did not significantly depress concentration of* S-*adenosylmethionine in the liver in this time interval. Concentration of* S-*adenosylmethionine in the brain varied diurnally;* L-*dihydroxyphenylalanine lowered this concentration whether administered at the daily peak or at the nadir.*

The efficacy of L-dihydoxyphenylalanine (L-dopa) in the treatment of Parkinson's disease has been correlated with the fact that this catechol amino acid is the physiological precursor for brain dopamine. Its administration to experimental animals causes an increase in content of dopamine in the brain (*1*). Moreover, brains of parkinsonian patients often contain subnormal amounts of dopamine (*2*), and the concentration of its chief metabolite, homovanillic acid (HVA), in their cerebrospinal fluid is depressed (*3*). Finally, the administration of L-dopa to human subjects elevates the HVA content of the urine and cerebrospinal fluid (*3, 4*), which indicates that significant quantities of the exogenous amino acid are converted to dopamine, as occurs with endogenous dopa.

After intraperitoneal administration, L-dopa is largely methylated to 3-*O*-methyl-dopa, which is then decarboxylated and converted to HVA. A surprisingly high percentage (more than half) of a dose of L-dopa is *O*-methylated within the first 20 minutes after administration (*5*). Conversion to central catecholamines is actually a very minor metabolic route of exogenous L-dopa. Since *S*-adenosylmethionine (SAMe) is the methyl donor in the *O*-methylation of L-dopa and dopamine (*6*), it seemed likely that large amounts of SAMe must be utilized in the process. We now present evidence that the administration of L-dopa to rats in a single dose equivalent to that generally used in treating Parkinson's disease causes a marked reduction of SAMe content in the brain.

All experiments utilized adult male Sprague-Dawley rats housed in individual cages under alternating 12-hour periods of light (Vita-Lite, 40 to 60 μw/cm^2) and darkness; the animals had free access to Purina chow and to water. The L-dopa (Nutritional Biochemicals) was dissolved in 0.05*M* HCl (10 mg/ml) and administered intraperitoneally; control animals received only the diluent. Concentrations of SAMe in tissue were assayed by the double label, isotope dilution, isotope derivative method of Baldessarini and Kopin (*7*).

The concentrations of norepinephrine and dopamine in several regions of rat brain exhibit significant diurnal fluctuations (*8*). Since these catecholamines are methyl acceptors (*6, 9*), a study was performed to determine whether concentrations of SAMe in the brain also varied diurnally. Such variations, if present, could influence the amount of the cofactor utilized after a given dose of L-dopa. Concentrations of SAMe in the brain were lowest at the middle of the daily light period and rose by 50 percent to a maximum in the middle of the dark period 12 hours later; the concentrations at the ends of both the light and the dark periods were similar, 25 percent above those present at the nadir. The SAMe content in the adrenal medulla also varied diurnally ($P < .01$); however, the amplitude of the daily rise was slightly less than that seen in the brain (31 percent), and the nadir and peak occurred at the ends of the light and dark periods, respectively.

To examine the effects of exogenous L-dopa on concentration of SAMe in the brain, groups of five rats received 0, 10, 30, or 100 mg of the catechol amino acid per kilogram in the middle of the daily dark period and were killed 45 minutes later. Treatment with 30 mg of L-dopa per kilogram was associated with a 36 percent reduction ($P < .001$) of SAMe in the brain (Table 1); treatment with 100 mg/kg caused a 67 percent reduction ($P < .001$). As little as 10 mg of L-dopa per kilogram caused a 51 percent decrease in concentration of SAMe in the adrenal

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Table 1. Relation between dose of L-dopa and extent of depletion of SAMe content in tissue. Groups of five rats received L-dopa intraperitoneally and were killed 45 minutes later. Data are presented as mean concentration of SAMe (micrograms per gram of wet tissue) ± standard error of the mean.

Tissue	L-Dopa dose (mg/kg)			
	0	10	30	100
Brain	16.8 ± 0.6	16.0 ± 1.1	10.7 ± 0.3*	5.5 ± 0.4*
Adrenal	39.4 ± 1.8	19.4 ± 3.9†	15.1 ± 4.9†	14.1 ± 3.6*
Liver	56.8 ± 3.5	65.9 ± 2.0	71.2 ± 5.3	61.4 ± 5.4

* $P < .001$ differs from control group. † $P < .01$ differs from control group.

medulla ($P < .01$); in contrast, the content of SAMe in the liver was not significantly altered 45 minutes after the injection of as much as 100 mg of L-dopa per kilogram. In another experiment, we observed that the decrease in SAMe concentration in brains of rats receiving 100 mg of L-dopa per kilogram was at least as pronounced in the middle of the daily light period (that is, when these contents were normally lowest) as at their daily peak in the middle of the dark period. The decrease in concentration of SAMe in the brain after administration of L-dopa was observed in four separate experiments.

The time course of the effect of L-dopa on SAMe in the brain was next examined among groups of four rats that received 100 mg of L-dopa per kilogram and were killed at various intervals thereafter. Untreated rats were also killed with each experimental group to control for changes due to the daily rhythm in SAMe concentration in the brain. Forty-five minutes after administration of L-dopa, there was a 76 percent reduction in concentration of SAMe in the brain (Table 2). By the 6th hour after treatment with L-dopa, SAMe concentration was no longer depressed in the brain.

Doses of L-dopa proportional on the basis of milligrams per kilogram of body weight to those administered to parkinsonian patients (*10*) produce a marked and rapid decline in SAMe concentration in the brain. The decrease after a single dose is of relatively short duration. Moreover, no significant decrease is observed in the liver, an organ that contains large amounts of the methionine-activating enzyme and can synthesize SAMe rapidly (*7*). Thus, it seems most likely that this effect of L-dopa reflects the transient inability of SAMe synthesis to keep pace with the amounts of the compound needed for *O*-methylation after administration of L-dopa. There are now a considerable number of patients who have been receiving as much as 40 to 50 mmole (8 to 10 g) of L-dopa per day for many months (*10*). Inasmuch as dietary methionine, the main source of methyl groups available to humans, is generally consumed in much smaller daily quantities [approximately 10 to 15 mmole (*11*)], it seems possible that long-term administration of L-dopa might cause a relative depletion of methionine in the body. Unless this depletion were corrected (for example, by increasing the consumption of the methyl donor choline or of proteins rich in methionine, or by decreasing the fraction of ingested L-dopa that is metabolized by *O*-methylation), a variety of metabolic consequences might follow. One such consequence might be decreased concentration of SAMe in tissues and decreased availability of this methyl donor for transmethylation reactions.

Table 2. Time course of effect of L-dopa on concentration of SAMe in the brain. Groups of four rats received L-dopa (100 mg/kg) intraperitoneally. Data are presented as mean ± standard error of the mean.

Time after injection	Control (μg/g brain)	L-Dopa (μg/g brain)
45 minutes	17.5 ± 1.7	4.2 ± 0.3*
6 hours	18.2 ± 1.1	21.9 ± 1.5
24 hours	18.4 ± 1.7	24.6 ± 4.4

* $P < .01$ differs from control group.

A significant fraction of endogenously synthesized dopamine and norepinephrine in the brain is normally metabolized by *O*-methylation (*9*). If the reduction in concentration of SAMe in the brain that follows administration of L-dopa is sufficient to limit the rate of *O*-methylation of catecholamines, it seems possible that one additional mechanism by which L-dopa might produce its neurological effects would be to potentiate the actions of endogenous dopamine and norepinephrine, that is, by slowing the rate at which they are metabolized. This mechanism would allow administered L-dopa to influence central noradrenergic transmission in spite of the fact that very little of the amino acid is converted to norepinephrine (*5*). It is also possible that 3-*O*-methyldopamine, formed by the decarboxylation of 3-*O*-methyl-dopa, may play a role in the actions of L-dopa. For example, *O*-methylated metabolites including 3-*O*-methyl-dopamine, enhance the uptake of norepinephrine into adrenergic nerve endings (*12*).

Methods of potentiating the effect of a dose of L-dopa have been under consideration for some time. Thus, inhibitors of the peripheral decarboxylation of L-dopa enhance the conversion of the precursor to catecholamines in the brain (*13*). Methyl-group acceptors or inhibitors of methyl transfer might similarly be of use in potentiating the clinical efficacy of L-dopa.

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