EFFECT OF L-DOPA ON EMOTIONAL RESPONSES AND SEROTONIN METABOLISM IN THE RAT BRAIN

L. Kh. Allikmet-s and A. M. Zharkovskii

UDC 612.82.018:547.756

Experiments on male Wistar rats showed that injection of L-dopa in doses of 100-200 mg/kg causes a parallel increase in the dopamine and homovanillic acid concentrations in the brain, elevation of the 5-hydroxyindoleacetic acid level, and a decrease in the serotonin concentration. Increased emotional reactivity and aggressiveness of the animals was observed at the same time. L-dopa (100 mg/kg) reduced the binding of serotonin formed from tryptophan (100 mg/kg) and accelerated its catabolism in the brain. At the same time, L-dopa abolished the depressant effect of tryptophan on emotional reactivity and aggressiveness. It is suggested that inhibition of the serotoninergic system in the brain is an essential component of the mechanism of strengthening of emotional responses under the influence of L-dopa.

KEY WORDS: L-dopa; emotional responses; serotonin metabolism; rat brain.

The role of monoamines of the brain such as noradrenalin, dopamine, and serotonin in emotional reactions is now firmly established [1, 2, 6, 8, 17]. The dopamine precursor L-dihydroxyphenylalanine (L-dopa) and dopaminomimetic substances (amphetamine, apomorphine, etc.) strengthen emotional reactivity and aggressiveness of experimental animals [5, 7, 8, 13, 18], whereas serotonin precursors (L-tryptophan and 5-hydroxytryptophan) inhibit emotional responses [2, 5, 6, 10, 13, 18]. However, the mechanism of these effects is not yet fully understood.

Interaction between catecholaminergic and indoleaminergic systems of the brain has virtually not been studied and there are likewise no convincing data on the mutual effects of the monoaminergic systems of the brain, on the one hand, and the cholinergic system on the other [5, 8, 11, 18]. According to recently published observations, dopamine, noradrenalin, and serotonin can not only act on their own specific receptors but can also affect the activity of other mediator systems. Large doses of L-dopa can cause exhaustion of the brain serotinin and tryptophan reserves; i.e., they can affect not only the catecholaminergic, but also the serotoninergic systems [3, 4, 11, 14].

The objects of this investigation were: 1) to study the effect of L-dopa simultaneously on emotional reactions and metabolism of endogenous serotinin and dopamine in the rat brain and also the effect of L-dopa on metabolism of exogenous L-tryptophan via the serotonin pathway; and 2) to study the relationship between changes in emotional behavior evoked by L-dopa, L-tryptophan, and changes in dopamine and serotonin metabolism.

EXPERIMENTAL METHOD

Male Wistar rats were used. L-dopa was made up as a 2.5% solution, pH 6.0-6.5, and L-tryptophan as a 2.5% solution, pH. 7.0-7.5. Animals of the control group received injections of distilled water with the same pH as the solutions of these amino acids. The substances were injected intraperitoneally. Behavioral tests were carried out 0.5-1 and 1.5 h after injection of the substances.

The level of emotional response was judged from the threshold of the alternating current (in volts) evoking a squeak and aggressiveness in a pair of rats when applied through metal netting on the floor of the

Department of Pharmacology, Tartu University. (Presented by Academician of the Academy of Medical Sciences of the USSR S. V. Anichkov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 81, No. 2, pp. 134-137, February, 1976. Original article submitted May 20, 1975.

TABLE 1. Effect of L-dopa (100 mg/kg) on Content of Dopamine (DA), Noradrenalin (NA), and Homovanillic Acid (HVA) in Brains of Albino Rats (in μg/g brain tissue)

Substance, dose	Time after injection (in h)	Forebrain			Diencephalon	
		DA	NA	HVA	DA	NA
Distilled water (control)	0.5-1	1,50±0,20	0,44±0,06	0,16±0,06	0,19±0,05	0,78±0,14
L-dopa:						
100 mg/kg	0.5	2,60±0,25	0,19±0,10	1,90±0,10	2,40±0,12	0,57±0,19
100 mg/kg	1	4,42±0,15	0,45±0,09	4,46±0,14	3,39±0,16	0,83±0,15

Legend. Arithmetic mean values and their confidence limits for $P \leq 0.05$ are shown.

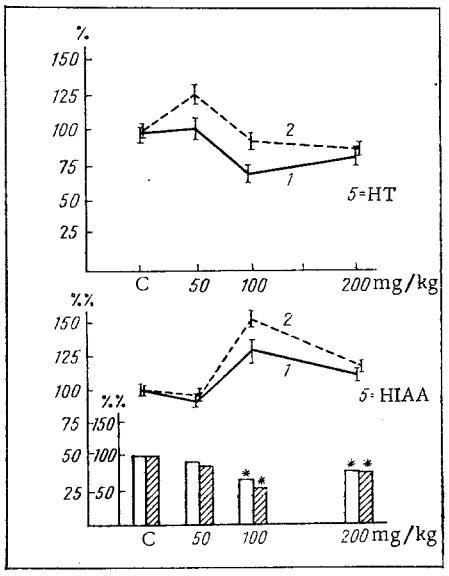

Fig. 1. Effect of L-dopa in doses of 50-200 mg/kg 1 h after intraperitoneal injection on content of serotonin (5-HT, top graph) and 5-HIAA (bottom graph) in forebrain (1) and diencephalon (2) of rats, and also on thresholds of squeaking (unshaded columns) and aggressiveness (shaded columns), expressed as percentages of the control (C). Asterisk indicates significant ($P \leq 0.05$) change in thresholds of squeaking and aggressiveness compared with control (C).

chamber. Emotional responses also were assessed when the animal was gripped by the hand in points as follows: 0) the rat did not respond, 1) it squeaked feebly, 2) squeaked and tried to get away, 3) squeaked and tried to bite the hand. In parallel tests, the orienting reaction was assessed from the number of times the animal stood up and the number of impulses recorded during 2 min in an actometer.

Immediately after the behavioral tests each animal was killed and the brain was quickly cooled and divided into two parts: 1) the forebrain: cerebral cortex, hippocampus, striatum; 2) the diencephalon: thalamus, hypothalamus, septum, preoptic region, corporal quadrigemina. Serotonin and 5-hydroxyindoleacetic acid (5-HIAA) were determined by the method of Curzon and Green [9] with the MPF-2A (Hitachi) fluorescence spectrophotometer. The content of dopamine and homovanillic acid was determined in parallel tests by the methods of Shellenberger and Gordon [15] and Spano and Neff [16].

EXPERIMENTAL RESULTS

L-dopa in a dose of 100-200 mg/kg, 0.5-1 h after its injection, depressed the orienting reaction and strengthened the emotional responses, i.e., lowered the thresholds of squeaking and of aggressiveness. The content of dopamine and homovanillic acid increased in these animals in all parts of the brain; the noradrenalin concentration showed no significant change (in the brain stem) or was reduced (in the forebrain and diencephalon) (Table 1). Parallel with the increase in the dopamine and homovanillic acid content substantial changes were observed in serotonin metabolism. The serotonin level in the forebrain and diencephalon fell considerably 1 h after injection of L-dopa (100-200 mg/kg) whereas the 5-HIAA level rose (Fig. 1). The highest 5-HIAA concentration was found after administration of L-dopa in a dose of 100 mg/kg. Emotional responses were strengthened under these circumstances and the thresholds of squeaking and aggressiveness were clearly lowered (Fig. 1).

To study the dynamics of the changes in the serotonin and 5-HIAA concentrations and emotional behavior under the influence of L-dopa in a dose of 100 mg/kg, serotonin and its metabolite were estimated at various times (0.5-1 and 2 h) after injection of L-dopa. The maximal decrease in the serotonin level and increase in the 5-HIAA level were observed 1 h after injection of L-dopa. The highest level of emotional response and aggressiveness was observed at the same time. The endogenous serotonin level was a little higher 2 h after injection of L-dopa than in the control, but the 5-HIAA concentration remained constantly high, 30% above its initial value. The thresholds of emotional response and aggressiveness were back to their original levels 2 h after injection of L-dopa.

A separate series of experiments was carried out to study the effect of L-dopa on the behavior of the rats after administration of L-tryptophan and on the metabolism of L-tryptophan via the serotonin path-

TABLE 2. Effect of L-dopa (100 mg/kg) on Metabolism of L-tryptophan (L-TP, 100 mg/kg) via the Serotonin Pathway and on Parallel Changes in Orienting and Emotional Responses

Substance	Time after injection (in h)	Forebrain		Diencephalon		Orienting reaction	Emotional responses	
		5-HT	5-HIAA	5-HT	5-HIAA		Squeak	Aggressiveness
Distilled water (control)	0,5-1	0,30±0,04	0,34±0,03	0,52±0,04	0,62±0,07	0	0	0
L-TP	1	0,44±0,06	0,45±0,04	0,78±0,08	0,87±0,05	↑	↓	↓
L-dopa	1	0,23±0,02	0,44±0,05	0,51±0,02	0,89±0,10	↓	↑	↑
L-dopa+L-TP	1	0,41±0,05	0,67±0,08	0,76±0,09	1,50±0,12	0	0	↑
L-TP	0,5	0,42±0,02	0,49±0,08	0,76±0,10	1,00±0,06	↑	↓	↓
L-dopa	0,5	0,32±0,06	0,35±0,09	0,55±0,06	0,78±0,10	↓	↑	↑
L-dopa+L-TP	0,5	0,35±0,10	0,72±0,12	0,63±0,09	1,50±0,15	0	0	0
L-dopa+L-TP	1 and 0,5	0,34±0,06	0,57±0,09	0,68±0,12	1,10±0,11	0	↑	↑

Note. Mean content of serotonin (5-HT) and 5-HIAA (in μg/g brain tissue) and confidence limits for $P \leq 0.05$ are shown.

Legend: 0) no change; ↑) significant increase; ↓) significant decrease in intensity of emotional responses compared with control.

way. In a dose of 100 mg/kg, L-tryptophan potentiated the orienting reactions and had a tranquilizing effect on emotional responses and aggressiveness (Table 2). In a dose of 200 mg/kg it depressed the orienting reaction very slightly. These changes in behavior under the influence of L-tryptophan were accompanied by accumulation of serotonin and 5-HIAA in the forebrain and diencephalon. If administered together with L-tryptophan, L-dopa abolished the inhibitory action of the latter on emotional responses and aggressiveness. At the same time the accumulation of serotonin was reduced whereas 5-HIAA formation was considerably increased compared with the situation after L-tryptophan administration alone (Table 2).

L-dopa thus strengthens emotional responses and causes a parallel accumulation of dopamine and its metabolite, homovanillic acid, in the brain. Meanwhile, under the influence of L-dopa the serotonin concentrationwas reduced and the 5-HIAA concentration considerably increased, evidence of increased catabolism of serotonin. L-dopa also blocked the inhibitory action of L-tryptophan on emotional behavior and prevented the accumulation of serotonin observed after administration of L-tryptophan alone. This suggests that the strengthening of emotional responses by L-dopa is connected with its inhibitory effect on the serotoninergic system. As the experiments of Lucke and co-workers [12] showed, administration of L-dopa together with p-chlorophenylalanine, which blocks serotonin synthesis, caused even greater strengthening of aggressiveness in mice than administration of L-dopa alone. The hypothesis that the strengthening effect of L-dopa on emotional responses is mediated partly through inhibition of serotoninergic processes is confirmed by the fact that haloperidol, which blocks dopaminergic receptors, does not completely block emotional responses [1, 5, 17].

Potentiation of dopaminergic processes following administration of L-dopa leads to a decrease in the serotonin concentration and an increase in the 5-HIAA concentration in the rat brain. Other workers [4, 11] also found that under the influence of L-dopa the brain serotonin level falls, although the mechanism of this effect is by no means clear. As shown by the experiments of Ng and co-workers [14], L-dopa causes liberation of labeled serotonin in rat brain homogenates and also blocks the accumulation of tryptophan in the synaptosomes of the brain [11]. Possibly L-dopa is decarboxylated in the brain into dopamine, which acts in serotoninergic synapses as a false mediator, blocking postsynaptic serotoninergic receptors. This may also be connected with the effect of L-dopa on the liberation and metabolism of serotonin in serotoninergic neurons.

LITERATURE CITED

1. L. Kh. Allikmet-s Zh. Vyssh. Nerv. Deyat., No. 3, 597 (1972).
2. L. Kh. Allikmet-s, Zh. Vyssh. Nerv. Deyat., No. 2, 164 (1975).
3. L. Kh. Allikmet-s and A. M. Zharkovskii, in: Problems in Pharmacology of Neurotropic Drugs [in Russian], Riga (1974), pp. 3-7.
4. S. Algeri and C. Cerletti, Europ. J. Pharmacol., 27, 191 (1974).
5. L. Kh. Allikmet-s (L. H. Allikmets), Med. Biol., 52, 19 (1974).
6. O. Benkert, H. Gluba, and N. Matussek, Neuropharmacology, 12, 177 (1973).

7. L. L. Butcher and A. P. Dietrich, Naunyn-Schmiedebergs Arch. Pharmak., 277, 61 (1973).
8. B. Eichelmann, in: Chemical Approaches to Brain Function (ed. by S. Ehrenpreis and I. Kopkin), New York (1973), p. 109.
9. G. Curzon and A. R. Green, Brit. J. Pharmacol., 39, 653 (1970).
10. J. A. Harvey and L. M. Yunger, in: Serotonin and Behavior (ed. by J. Barchas and E. Usdin), New York (1973), p. 179.
11. M. Karobath, J. L. Diaz, and M. Huttunen, Biochem. Pharmacol., 21, 1243 (1972).
12. E. Lucke, K. Modigh, and B. -E. Roos, Experientia, 25, 951 (1969).
13. W. C. McLain and B. T. Cole, Pharmacol. Biochem. Behav., 2, 123 (1974).
14. L. Ng, R. W. Colburn, and I. J. Kopin, J. Pharmacol. Exp. Ther., 183, 316 (1972).
15. M. K. Shellenberger and J. H. Gordon, Analyt. Biochem., 39, 356 (1971).
16. P. F. Spano and N. H. Neff, Analyt. Biochem., 42, 113 (1971).
17. L. Valzelli, Advances Pharmacol., 5, 79 (1967).
18. A. Weissman and C. A. Harbert, Ann. Rep. Med. Chem., 7, 47 (1972).