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Effect of DL-Erythro-Dihydroxyphenylserine on the Locomotor Activity of the Mouse

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MORI, T., T. NAKAJIMA, H. HASHIMOTO, T. NOTO AND N. KATO. *Effect of DL-erythro-dihydroxyphenylserine on the locomotor activity of the mouse.* PHARMACOL BIOCHEM BEHAV 22(6) 979–983, 1985.—Effect of dihydroxyphenylserine (DOPS) on the locomotor activity of mice pretreated with β-phenylisopropylhydrazine was studied using an Animex activity meter. An intraperitoneal injection of DL-erythro-DOPS (200 mg/kg) suppressed significantly the locomotor stimulation by the MAO inhibitor, while DL-threo-DOPS (200 mg/kg) had no effect. Only slight suppression was observed after the administration of 100 mg/kg of DL-erythro-DOPS. Effect of DOPS on the concentrations of brain catecholamines and serotonin of mice pretreated with the MAO inhibitor was also analysed. The administration of DL-erythro-DOPS significantly increased the concentration of noradrenaline, while DL-threo-DOPS did not affect the contents of brain amines in the experimental condition. The suppressive effect of DL-erythro-DOPS on the locomotor stimulation by the MAO inhibitor was confirmed by a simultaneous administration of the amino acid and d-phenylisopropylmethylamine to mice. Based on these findings, the neural mechanisms of the locomotor activity and a clinical application of DL-erythro-DOPS to the manic syndrome were discussed.

Locomotor activity DL-erythro-DOPS DL-threo-DOPS Noradrenaline Dopamine Serotonin

RESERPINE, an alkaloid of Rauwolfia serpentina, is known to produce a syndrome in animals that includes sedation and motor retardation, and to deplete serotonin (5-HT), noradrenaline (NA) and dopamine (DA) from the central nervous system (CNS). On the other hand, monoamine oxidase inhibitors (MAOI) produce euphoria and overactive behavior, and increase brain concentrations of DA, NA and 5-HT by inhibiting monoamine oxidase (MAO). Since these findings were reported, attention of investigators not only in the neuropsychiatric field but also in the basic neuroscience has been focused on the relationship between brain monoamines and brain function, i.e., motor activity, sensation, cognition, affection, etc. Based on the basic and clinical research, precursor amino acids of brain monoamines have been tried in the treatment of pathological conditions and L-dopa therapy was established to Parkinsonism. L-5-Hydroxytryptophan (L-5-HTP), the direct precursor of 5-HT, has also been tried in the treatment of depressive states [12,18] and L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS) for treatment of orthostatic hypotension in familial amyloid neuropathy [21] and freezing phenomenon in Parkinsonism [13].

DOPS was thought to be the precursor amino acid for NA in animals on the analogy of its structure, and its occurrence and metabolism in animals were intensively studied. Although DOPS was proven to be decarboxylated by mammalian aromatic L-amino acid decarboxylase to NA in both in vitro [2] and in vivo [20] experiments, its occurrence in animals was denied and DA was shown to be the direct precursor of NA, resulting in a fading interest in this amino acid. In 1973, Pletscher [15] and Sano *et al.* [19] re-examined the metabolism of DOPS in view of an agent which specifically elevates the content of brain 1-NA. There are 4 isomers of the amino acid, and L-erythro-DOPS was decarboxylated about 20 times more rapidly than L-threo-DOPS by the enzyme prepared from hog kidney [7]. L-erythro-DOPS is the most effective precursor amino acid for the specific increase of the concentration of brain NA, and the produced NA from this amino acid is d-NA, which is an unnatural form and a biologically inactive one. It was also shown that when L-erythro-DOPS was administered to animals the produced d-NA in brain took the place of endogenous 1-NA [16]. Therefore, DOPS was thought unsuitable for elevation of the content of brain 1-NA. However, turning to the view of an agent which specifically lowers the content of brain 1-NA to reduce noradrenergic activity in CNS, L-erythro-DOPS is one of the most suitable drugs, and its effects on brain function was interesting to us.

This paper reports the effect of DL-erythro-DOPS on the locomotor activity of mice pretreated with β-phenylisopropylhydrazine (pheniprazine) and on the activity of mice treated with d-phenylisopropylmethylamine (methamphetamine). Data on the concentrations of brain catecholamines and 5-HT of mice treated with the amino

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acid and the drug are also presented, and a possible clinical application of L-erythro-DOPS is discussed.

METHOD

Chemicals

DL-erythro-DOPS, pheniprazine and methamphetamine were supplied by Sumitomo Kagaku Kogyo, Co., Chugai Seiyaku, Co. and Dainippon Seiyaku, Co., Japan, respectively. The other reagents used in the experiment were commercially available.

Determination of the Locomotor Activity of Mice

Male mice (ddy, 30–40 g body weight) were used. The animals were maintained in a controlled stock room (temperature, 24–27°C; lighting from 6 a.m. to 6 p.m.), and stock diet and water supplied ad lib. The locomotor activity of mice was determined using an Animex activity meter, type SE, LKB-Farad, which was connected to an Animex printing counter, type 1-X-O. The printing time of the counter was set on 5 min. At 10 a.m. 3 mice were put into a transparent plastic cage (25×40×15 cm) on the Animex activity meter, the sensitivity of which was set on 35 μA, and their locomotor activity was counted at intervals of 5 min for the indicated periods. Five groups of 3 mice were used for evaluation of the effect of a drug and mean values±SD of counts for 5 min/mouse were presented in the figures.

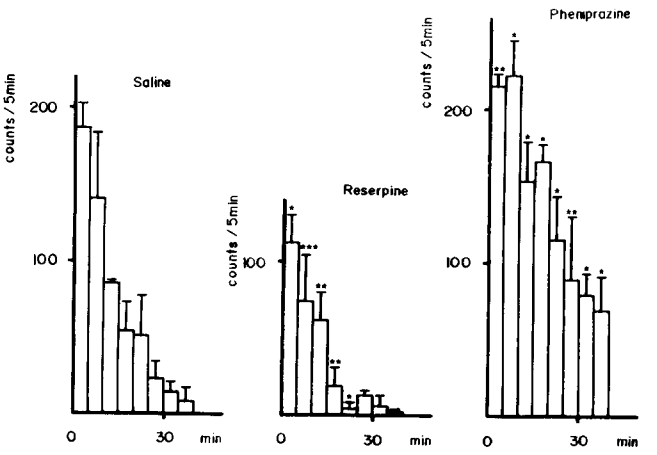

FIG. 1. Effects of reserpine and pheniprazine on the locomotor activity of the mouse. Reserpine (1 mg/kg) or pheniprazine (50 mg/kg) was intraperitoneally injected into a mouse 17 hr before the determination of the locomotor activity using an Animex activity meter. An animal injected with 0.2 ml of 0.9% NaCl served as the control. Left, the control; middle, reserpine and right, pheniprazine. p Values for the difference in locomotor activities for the corresponding periods of 5 min between the control and the drug-treated one were obtained by application of "t" test. *, $p<0.01$; **, $p<0.02$; ***, $p<0.05$.

Administration of Drugs

Reserpine (1 mg/kg), pheniprazine (50 mg/kg), methamphetamine (1.4 mg/kg) and DL-erythro-DOPS (200 or 100 mg/kg) were dissolved in 0.2 ml of 0.9% NaCl, respectively, and injected intraperitoneally into a mouse. DL-threo-DOPS (200 mg/kg) was dissolved in 0.2 ml of 0.2 N HCl and, after adjusting pH of the solution to 7 with sodium bicarbonate, the solution was immediately injected into a mouse.

Determination of Brain Catecholamines and 5-HT

Brain NA, dopamine (DA) and 5-HT were determined by a modification of the method of Ogasahara *et al.* [14]. A mouse was sacrificed by bleeding. The brain was immediately removed and homogenized in 10 ml of 3% perchloric acid containing 0.2% disodium ethylenediaminetetraacetate and 0.2% ascorbic acid at 0–4°C for 30 sec with Hiscotoron (Tokyo Seiki, C., Japan). The homogenate was centrifuged at 3,000 rpm for 15 min. The supernatant solution was pooled, and its pH was adjusted to 5.8–6.2 by adding dropwise 4.0 and 0.1 N KOH at 0–4°C. This was centrifuged at 4°C for 20 min to remove potassium perchlorate. The supernatant solution was passed through a 0.6×4.3 cm column of Amberlite CG 50 (200–300 mesh), which was previously equilibrated with 0.1 M sodium phosphate buffer, pH 6.0. After washing the column with 10 ml of water and 3.5 ml of 0.01 M sodium phosphate buffer, pH 6.0, containing 1.5% boric acid, NA was eluted with 3.5 ml of the same buffer, and then DA with 3.5 ml of 0.1 M sodium phosphate buffer, pH 6.0, containing 4% boric acid. The column was then washed with 4 ml of 0.1 N HCl, and 5-HT was eluted with 2 ml of 1 N HCl.

NA and DA were determined fluorometrically by the ethylenediamine condensation reaction [24]. 0.25 ml of 1 N ethylenediamine dihydrochloride and 0.5 ml of 50% ethylenediamine solution were successively added to the fraction containing NA or DA. The mixture solution was heated at 60°C for 20 min and kept in a dark place at room temperature for over 2 hr. One g of solid NaCl was added to the cooled solution and the produced fluorophores were extracted into 4 ml of isobutanol. The fluorescence of the organic phase was measured at an excitation wavelength of 420 nm and emission wavelengths of 480 and 520 nm for NA and DA, respectively.

5-HT was determined fluorometrically by the acidic o-phthalaldehyde reaction [10]. Ten μl of thioglycolic acid, 0.1 ml of 0.04% o-phthalaldehyde in ethanol and 1 ml of conc. sulphuric acid were added to the fraction containing 5-HT. The mixture solution was heated in boiling water for 15 min and then cooled in tap water for 30 min. The fluorescence in the solution was measured at an excitation wavelength of 368 nm and an emission wavelength of 480 nm.

In the above procedure, recoveries of NA, DA and 5-HT (50–1,000 μg) added to the acidic extract of mouse brain were 91±2, 96±2 and 102±3% (mean±S.E.M., n=5), respectively.

RESULTS

Effects of Reserpine and Pheniprazine on the Locomotor Activity and Concentrations of Brain Monoamines of Mice

When mice are transferred from a stock cage into another one, the animals become nervous, move around in the cage for a while, and then become calm and squat down. Effects of reserpine and pheniprazine on the above habit were examined using an Animex activity meter. The locomotor activity was decreased by treatment with reserpine, and significantly increased by treatment with pheniprazine (Fig. 1).

Effects of reserpine and pheniprazine on concentrations of DA, NA and 5-HT in brains of mice were also analysed. The contents of these amines were significantly decreased by

TABLE 1

CONCENTRATIONS OF CATECHOLAMINES AND SEROTONIN IN THE BRAINS OF MICE ADMINISTERED WITH RESERPINE OR PHENIPRAZINE

Treatment	Noradrenaline	Dopamine	Serotonin
Control (5)	365 ± 25	791 ± 57	399 ± 47
Reserpine (5)	184 ± 35*	258 ± 68*	130 ± 38*
Pheniprazine (5)	1085 ± 79*	1026 ± 122†	1260 ± 39*

Reserpine (1 mg/kg) or pheniprazine (50 mg/kg) was intraperitoneally injected into a mouse. An animal injected with 0.2 ml of 0.9% NaCl served as the control. The animals were sacrificed 17 hr after the injection, and the brain amines were determined by the method described in the Method section. Values represent Mean ± SD (ng/g wet weight). The number of experiments is given in parenthesis. p Values for the difference in the concentrations of brain amines between the control and the drug-treated one were calculated by application of "t" test. *, $p<0.01$; †, $p<0.05$.

the treatment with reserpine and markedly increased by the treatment with pheniprazine (Table 1).

Effects of DOPS on the Locomotor Activity and Concentrations of Brain Monoamines of Mice Treated With Pheniprazine

Because the concentration of brain d-NA reaches the maximal level 30–60 min after an intraperitoneal injection of L-erythro-DOPS [7], the locomotor activity was measured from 30 min after the administration of DOPS with an Animex activity meter (Fig. 2). As compared with pheniprazine-treated mice, an intraperitoneal injection of 200 mg/kg of DL-erythro-DOPS into mice treated with pheniprazine reduced significantly the locomotor activity and a slight decrease in the activity was demonstrated by an administration of 100 mg/kg of the amino acid. However, DL-threo-DOPS did not affect the behavior.

The sedative effect of DL-erythro-DOPS was also examined using mice untreated with pheniprazine (Fig. 3). The locomotor activity was inclined to decrease by an intraperitoneal injection of 200 mg/kg of DL-erythro-DOPS.

In order to examine the levels of brain NA, DA and 5-HT in the above behavioral experiments, DOPS was intraperitoneally injected into mice pretreated with pheniprazine and the amine level was determined 30 min after the injection. Table 2 shows that DL-erythro-DOPS raised the level of brain NA, while DL-threo-DOPS did not affect the levels of the brain amines in the experimental condition.

The effect of DL-erythro-DOPS on the concentrations of brain NA, DA and 5-HT was also analysed using mice untreated with pheniprazine (Table 2). The level of brain NA was elevated by an intraperitoneal injection of the amino acid (200 mg/kg), and there was no significant change in levels of brain DA and 5-HT.

Influence of DL-Erythro-DOPS on the Methamphetamine-Induced Locomotor Activity

In order to confirm the sedative effect of DL-erythro-DOPS, the influence of the amino acid on the

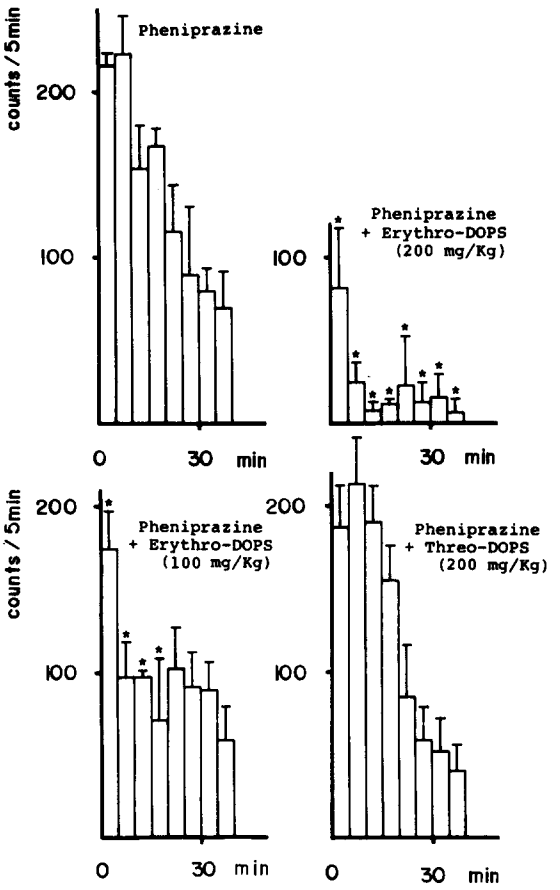

FIG. 2. Effect of DOPS on the locomotor activity of the mouse pretreated with pheniprazine. Pheniprazine (200 mg/kg) was administered to a mouse 17 hr before an injection of DOPS. DL-threo-DOPS (200 mg/kg) or DL-erythro-DOPS (100 or 200 mg/kg) was intraperitoneally injected into the animal, and 30 min after the injection of DOPS the locomotor activity was counted at intervals of 5 min for 40 min using an Animex activity meter. p Values for the difference in counts for the corresponding periods between pheniprazine and pheniprazine + DOPS were estimated by application of "t" test. *, $p<0.01$.

methamphetamine-induced locomotor activity of the mouse was examined by a simultaneous administration of the stimulant and the amino acid (Fig. 4). After an intraperitoneal injection of 1.4 mg/kg of methamphetamine, the locomotor activity was enhanced rapidly, reached a maximum about 5 min after the injection, kept a plateau for about 35 min, and decreased gradually. On the other hand, a marked inhibition of the enhancement effect was observed when methamphetamine (1.4 mg/kg) and DL-erythro-DOPS (200 mg/kg) were simultaneously injected into mice.

The concentrations of brain NA, DA and 5-HT were determined 30 min after an intraperitoneal injection of methamphetamine or methamphetamine together with 200 mg/kg of DL-erythro-DOPS (Table 3). Slightly lower levels of brain NA and DA were observed after an injection of the stimulant, which releases brain catecholamines and accelerates the turnover of their metabolism at an administration of its low dosage [11]. When the stimulant and the amino acid were simultaneously injected, there was no significant

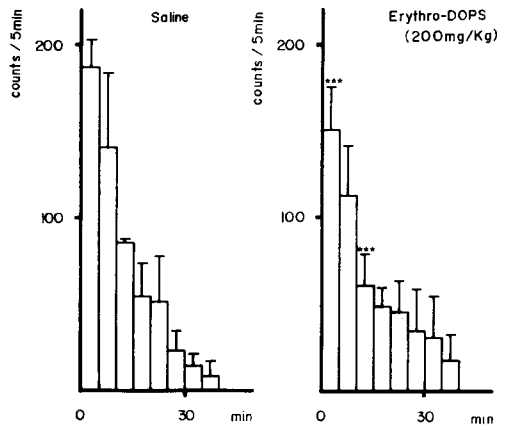

FIG. 3. Effect of DL-erythro-DOPS on the locomotor activity of the mouse. DL-erythro-DOPS (200 mg/kg) was intraperitoneally injected into a mouse, and 30 min after the injection of the amino acid the locomotor activity was counted at intervals of 5 min for 40 min. An animal injected with 0.2 ml of 0.9% NaCl (Fig. 1) served as the control. *p* Values for the difference in counts for the corresponding periods between the control and the animal injected with the amino acid were obtained by application of "*t*" test. *, $p<0.05$.

TABLE 2

CONCENTRATIONS OF BRAIN MONOAMINES OF MICE INJECTED WITH DOPS

Treatment	Noradrenaline	Dopamine	Serotonin
Pheniprazine + saline (5)	832 ± 88	941 ± 56	942 ± 133
Pheniprazine + DL-threo-DOPS (5)	704 ± 64	895 ± 12	984 ± 106
Pheniprazine + DL-erythro-DOPS (5)	1,476 ± 105*	895 ± 52	821 ± 92
Saline (6)	400 ± 45	652 ± 38	344 ± 70
DL-erythro-DOPS (5)	742 ± 94*	641 ± 54	341 ± 30

Pheniprazine (50 mg/kg) was intraperitoneally injected into a mouse 17 hr before administration of DOPS. The animal was sacrificed 30 min after an intraperitoneal injection of DL-threo- or DL-erythro-DOPS (200 mg/kg), and the brain amines were determined by the method described in the Method section. Values represent Mean ± SD (ng/g wet weight) and the number of experiments is given in parenthesis. *p* Values for the difference in the concentrations of brain amines between pheniprazine + saline and phiniprazine + DOPS or saline and DL-erythro-DOPS were calculated by application of "*t*" test. *, $p<0.01$.

change in the concentrations of brain catecholamines, while a slight increase was observed in that of brain 5-HT.

DISCUSSION

From the effects of altering dopaminergic neurotransmission by synthesis inhibitors or receptor antagonists and by destroying dopamine neurons with 6-hydroxydopamine, the locomotor stimulation produced by amphetamine, cocaine and some other drugs appears generally to depend on the

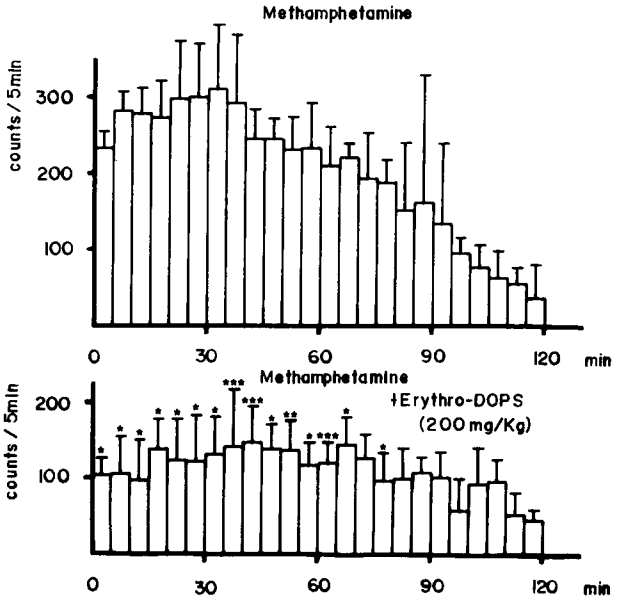

FIG. 4. Effect of DL-erythro-DOPS on the locomotor activity of the mouse administered with methamphetamine. Methamphetamine (1.4 mg/kg) or methamphetamine together with DL-erythro-DOPS was intraperitoneally injected into a mouse and the locomotor activity was measured at intervals of 5 min for 120 min using an Animex activity meter. *p* Values for the difference in counts for the corresponding periods of 5 min between methamphetamine and methamphetamine + DL-erythro-DOPS were estimated by application of "*t*" test. *, $p<0.01$; **, $p<0.02$; ***, $p<0.05$.

TABLE 3

CONCENTRATIONS OF BRAIN AMINES OF MICE AFTER ADMINISTRATION OF METHAMPHETAMINE OR METHAMPHETAMINE TOGETHER WITH DL-ERYTHRO-DOPS

Treatment	Noradrenaline	Dopamine	Serotonin
Control (3)	450 ± 28	886 ± 24	404 ± 46
Methamphetamine (3)	377 ± 27*	790 ± 58†	386 ± 16
Methamphetamine + DL-erythro-DOPS (3)	437 ± 16	856 ± 84	493 ± 31*

Methamphetamine (1.4 mg/kg) or methamphetamine together with DL-erythro-DOPS (200 mg/kg) was intraperitoneally injected into a mouse. The animal was sacrificed 30 min after the injection, and the brain amines were determined by the method described in the Method section. Values represent Mean ± SD (ng/g wet weight) and the number of experiments is given in parenthesis. *p* Values for the difference in the concentrations of brain amines between the control and the drug-treated one were calculated by application of "*t*" test. *, $p<0.05$; †, $p<0.01$.

release of DA from nerve terminals in brain. The mesolimbic DA system likewise is strongly implicated in the locomotor-stimulant effects of psychostimulants, which appear to be antagonized by serotonergic systems, by

γ-aminobutyric acid and by the muscarinic actions of acetylcholine [9]. Indeed, the present finding demonstrates that methamphetamine decreases the concentration of brain DA, although that of brain NA is also decreased. This suggests that there is an increased activity of dopaminergic mechanisms. Noradrenergic mechanisms seem to play no role in amphetamine-induced locomotor activity on the basis of experiments with synthesis inhibitors [4,8], receptor agonists and 6-hydroxydopamine [3,22]. There is, however, some evidence that NA-receptor activation plays a role in the reversal of reserpine-induced suppression of locomotor activity [1], and intraventricular infusion of NA stimulates locomotor activity more strongly than DA [5,6]. In our present experiment methamphetamine reduced not only the concentration of brain DA but that of brain NA, indicating that the noradrenergic system probably acts with the dopaminergic one in the locomotor activity. Furthermore, the finding that suppression of noradrenergic mechanisms by DL-erythro-DOPS causes the decrease in the decrease in the locomotor activity suggests strongly the role and participation of the noradrenergic system in the locomotion.

Locomotor activity has generally been interpreted in terms of intervening variables such as "emotionality" and "exploration." Therefore, the effect of DL-erythro-DOPS on the locomotor stimulation produced by pheniprazine and methamphetamine is clinically interesting to psychiatrists. The principal relevant data obtained by studies on cerebrospinal fluid of patients with affective disorders, postmortem examinations of the brains and studies of the psychological effects produced by drugs indicate the possibility that depression can be associated with a decreased turnover of brain 5-HT and catecholamines, and the manic syndrome with a decreased 5-HT turnover with hyperactivity of catecholamine production, especially of NA production [17,23]. The mechanism of supressive effect of DL-erythro-DOPS on the locomotor stimulation is thought to suppress noradrenergic mechanisms in brain by substitution of endogenous l-NA with d-NA produced from the administered precursor amino acid. Therefore, there is a strong suggestion that DL-erythro-DOPS can be used as a therapeutic strategy to the manic syndrome.

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