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Effects of L-Threo- and Erythro-3,4-Dihydroxyphenylserine on Learning Performance and Concentrations of Brain Noradrenaline and its Metabolites in Rats

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HARADA, H., T. NOTO, M. TSUJI, C. TAGA, H. HASHIMOTO AND T. NAKAJIMA. *Effects of L-threo- and erythro-3,4-dihydroxyphenylserine on learning performance and concentrations of brain noradrenaline and its metabolites in rats.* PHARMACOL BIOCHEM BEHAV 43(1) 215–221, 1992.—Effects of L-threo and L-erythro-3,4-dihydroxyphenylserine [DOPS, precursor amino acids for noradrenaline (NA)] on the learning performance in a maze paradigm designed to model on the water maze paradigm using a multicomputerized behavioral analysis system were studied. A marked facilitation of learning performance was observed in rats after an intraventricular injection of 5 μg L-threo-DOPS (the *s*-NA precursor), and this effect was inhibited by a simultaneous administration of 1 or 2 μg propranolol (a β-adrenergic antagonist). As concentrations of brain NA, 3-methoxy-4-hydroxyphenylglycol, and normethanephrine were increased by the injection of 5 μg L-threo-DOPS, the effect seemed to be derived from activation of β-adrenoceptors in the CNS by the formed *s*-NA. On the other hand, an intraventricular injection of 5 μg L-erythro-DOPS (the *r*-NA precursor) attenuated the learning performance, and this effect was probably caused by the formed *r*-NA from L-erythro-DOPS.

L-threo-DOPS L-erythro-DOPS Noradrenaline Learning

3,4-DIHYDROXYPHENYLSERINE (DOPS), an unnatural amino acid, is decarboxylated by aromatic L-amino acid decarboxylase to noradrenaline (NA) in mammals, and *s*- and *r*-NA are formed from L-threo- and erythro-DOPS, respectively. In 1973, Pletscher (19) and Sano et al. (21) examined the metabolism of DOPS in view of an agent that specifically changes the content of brain *s*-NA, and L-erythro-DOPS was proved to be decarboxylated about 20 times more rapidly than L-threo-DOPS by the enzyme prepared from hog kidney (4). It was also shown that when L-erythro-DOPS was given to rats the *r*-NA produced in the brain turned out and replaced endogenous *s*-NA (20), inducing a decrease of noradrenergic activity in the CNS. Therefore, L-threo- and erythro-DOPS seem suitable for manipulation of the noradrenergic activity via the produced *s*- and *r*-NA in the CNS, and L-erythro-DOPS was shown to suppress drug-induced locomotor activity in mice (12) and increase slow-wave sleep in rats (11). Furthermore, L-threo-DOPS is now clinically used for the treatment of orthostatic hypotension in familial amyloidosis (22)* and freezing in Parkinsonism (16,17).

The present article reports effects of L-threo- and erythro-DOPS on learning behavior in rats, and data on concentrations of brain NA and its metabolites of rats treated with L-threo- or erythro-DOPS are also presented.

METHOD

Chemicals

L-threo- and erythro-DOPS and propranolol HCl were supplied by Sumitomo Kagaku Kogyo Co. (Osaka, Japan) and ICI Pharma Co. (Osaka, Japan), respectively. Other reagents used in the present experiments were commercially available.

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Administration of Drugs

Male rats (Wistar strain, 200–250 g body weight) were used. A rat was anesthetized with an intraperitoneal injection of sodium pentobarbital (40 mg/kg). A 23-ga stainless steel guide cannula was implanted at the right parasagittal point above the lateral ventricle, and the tip of the cannula was placed at stereotaxic coordinates of AP 5.6, Lat 1.6, and HV 4.6 mm (14). The cannula was fixed to the skull with acrylic dental cement. A stylet was kept within the cannula and a protective cap was screwed onto the pedestal to prevent damages. Operated animals were separately maintained for at least 1 week to recover from the surgery in a controlled stock room (temperature, 24–28°C; lighting, from 6 a.m. - 6 p.m.) with food and water ad lib.

All drugs were dissolved in an artificial cerebrospinal fluid (ACSF) that contained 127.65 mM Na^+, 2.55 mM K^+, 1.26 mM Ca^{2+}, 0.93 mM Mg^{2+}, and 134.58 mM Cl^- and was adjusted to pH 5.8 with CO_2 gas (15). One microliter of the solution was injected into the lateral ventricle of an operated rat under nonanesthesia through the implanted guide cannula using a 0.3-mm (outer diameter) stainless steel injection cannula, which was connected to a polyethylene tube (PE 10) filled with each drug solution. The tip of the injection needle was inserted into the lateral ventricle, and then a volumetrically calibrated polyethylene tube was vertically lifted to inject 1 μl solution.

Apparatus for Behavioral Analysis

An Osaka University Computerized Electronic Maze (OUCEM-86) was used for analysis of learning performance and locomotor activity of rats (1). The OUCEM, whose experimental box is 62 × 62 × 30 cm with a translucent white Plexiglas top, is a multicomputerized system integrated by the following components: a programmable electronic platform (PEP) equipped with 48 photo beam sensors (OPX-T30); a programming panel (PP), Model BECM-0064, for paradigm stimulation; a shock generator scrambler (SGS) to apply continuous or discontinuous electric current to PEP; a control station (CS), (Model BEC 16-Bio Computer Control Station BCS-1105, Bio-Medica Ltd. Osaka, Japan), which processes inputs/outputs as an interface device to automatically computerized behavioral parameters; and a computer system (NEC PC-9801 VX) with 1 Mb RAM for data processing and experimental setting.

Behavioral analyses of animals were performed under two different paradigms, that is, maze and open-field paradigms.

Learning Performance in a Maze Paradigm

Effects of drugs on learning performance were investigated in a maze paradigm using OUCEM-86 (Fig.1). The maze paradigm was designed to model on the water maze paradigm (13) in which a location of the escape platform was not below water but in a fixed location. A performance session consisted

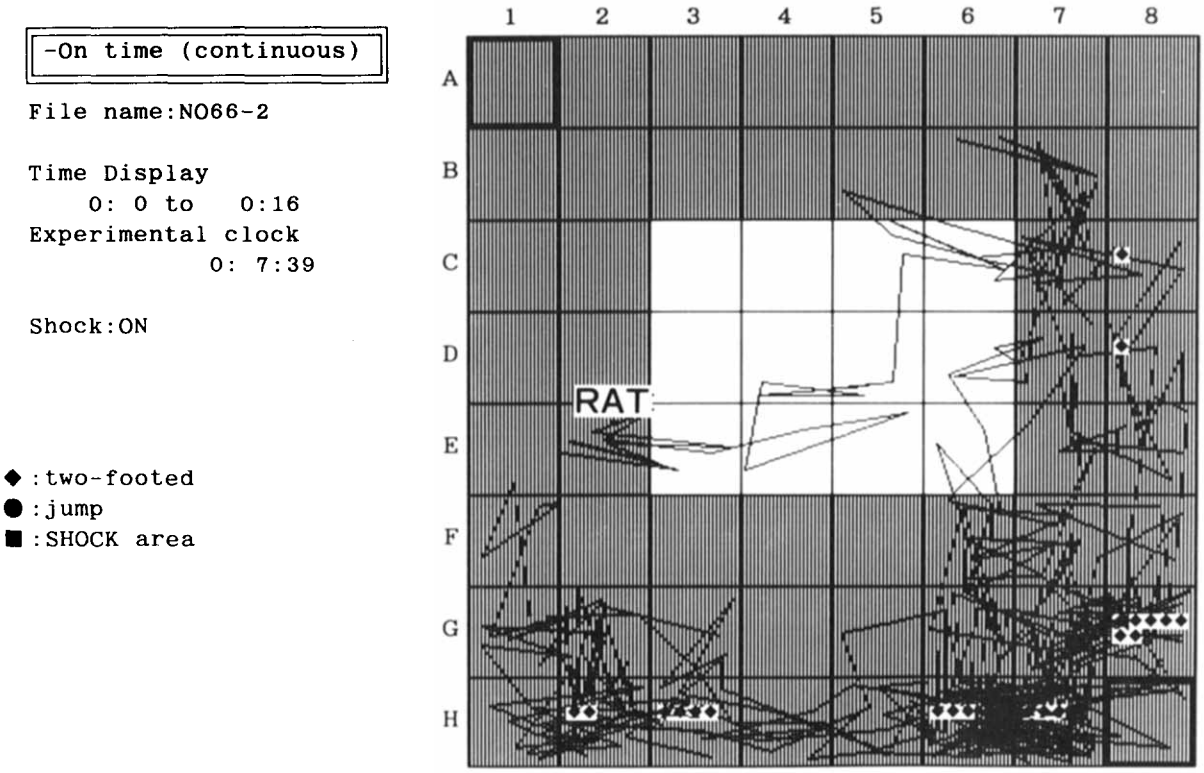

FIG. 1. Direct tracing of rat behavior on the programmable electronic platform of the OUCEM-86. In a maze paradigm, a rat must learn to escape from the shock area (white rectangle) to avoid a continuous 1.5-mA foot-shock delivered from the shock generator scrambler.

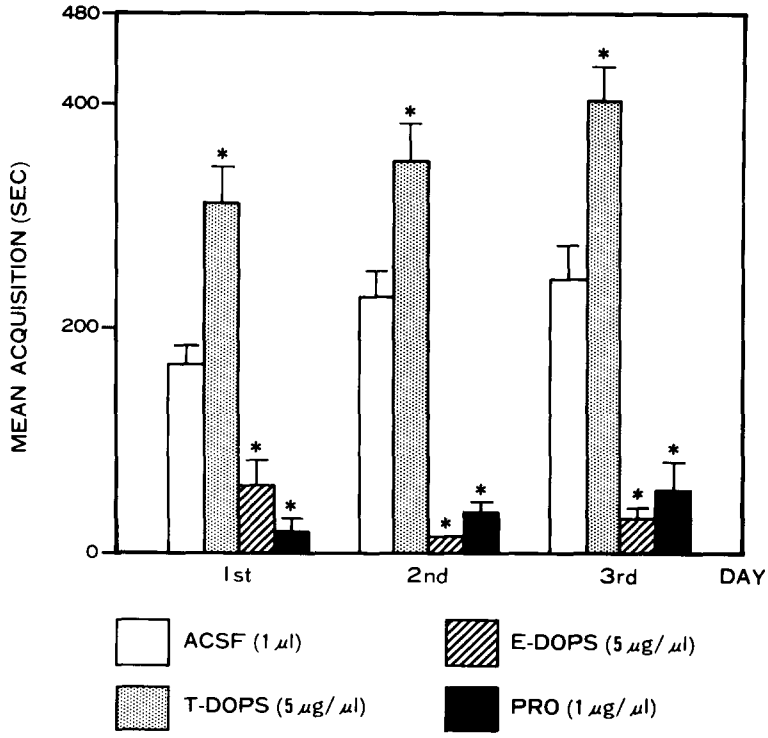

FIG. 2. Effects of intraventricular injection of 5 μg L-threo- or erythro-DOPS or 1 μg propranolol on learning performance of rats. A rat was placed on the programmable electronic platform 30 min after injection of each drug. The learning performance conditioning was analyzed by the OUCEM-86 in a maze paradigm and represented as the total time (seconds) the rat stayed in the nonshock area during the foot-shock periods in a 3-day experiment. An animal injected with 1 μl ACSF served as the control. Values represent mean ± SEM (seconds) of eight animals. p values for the difference in learning performance between the control and drug-treated groups were obtained by application of two-tailed Wilcoxon's test. *$p < 0.05$.

of a nonshock period for 120 s and a shock period for the following 120 s, and four sessions were successively repeated in 1 day. The one set of the performance sessions was carried out for 3 days. During the nonshock period, a well-lit white light was on, and then the light was dimmed during the shock period. The light was settled in a fixed location above the experimental box to serve as a spatial cue to experimental rats, and SGS was set to deliver a continuous foot-shock of 1.5 mA during the dim light period. In this maze paradigm, a rat must learn to escape from the shock area to the nonshock area of the PEP, which was settled at the center of the PEP (the white area in Fig.1).

Each drug was administered intraventricularly to a rat 30 min before starting an experiment. The learning performance conditioning of the experimental rat was evaluated using the total time of four sessions when the rat stayed on the nonshock area during the foot-shock period. Therefore the complete learning performance conditioning was represented as 480 s (120 × 4 s).

Locomotor Activity in a Novelty Condition

Effects of drugs on locomotor activities of rats in a novelty condition were examined in an OUCEM-86 open-field paradigm. Thirty minutes after intraventricular injection of each drug, the rat was placed on the PEP. Its locomotor activity was automatically recorded for 16 and 60 min and represented as total movements (cm^2) in four-foot position.

Determination of Brain NA and its Metabolites

Concentrations of brain NA and its metabolites of a rat were measured by a modified method of Furukawa et al. (3), that is, by using a reverse-phase analytical column [Cosmosil 5C18-P (4.6 i.d. × 250 mm), Nacalai Tesque, Inc., Kyoto, Japan] in a 31°C water bath and a high-performance liquid chromatography (LC-6A, Shimadzu Ltd., Kyoto, Japan) with an electrochemical detector (CB-100, EICOM, Kyoto, Japan) at a potential gradient of +0.8 V vs. Ag/AgCl reference electrode. Five hundredths molar citrate buffer, pH 4.3, containing 0.04 mM disodium ethylenediaminetetraacetate, 0.018% sodium 1-octanesulfonate, and 7.5% acetonitrile was used as the mobile phase at a flow rate of 1.1 ml/min and vanillic acid was used as the internal standard. After an intraventricular injection of 5 μg L-threo- or erythro-DOPS, the rat was killed by decapitation at an indicated interval. The whole brain was quickly removed, homogenized in 5 vol acetone:*N*-formic acid (15:85 by vol), and centrifuged at 15,000 × g for 20 min. Two hundred microliters of the supernatant was mixed well

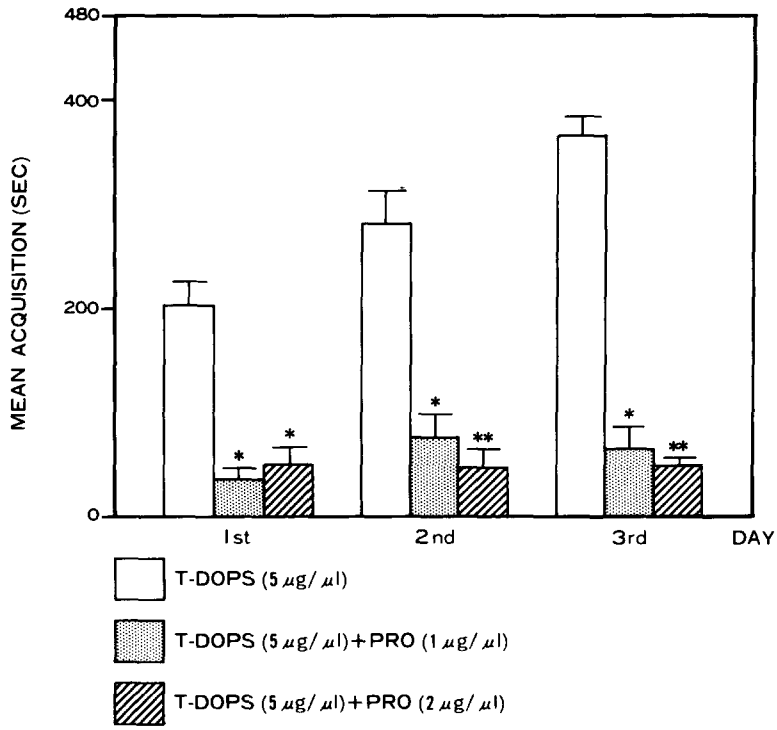

FIG. 3. Effects of simultaneous injection of 5 μg L-threo-DOPS with 1 or 2 μg propranolol on learning performance of rats. A rat was placed on the programmable electronic platform 30 min after injection of drugs. The learning performance conditioning was analyzed by the OUCEM-86 in a maze paradigm and represented as the total time (seconds) the rat stayed in the nonshock area during the foot-shock periods in a 3-day experiment. An animal injected with 5 μg L-threo-DOPS served as the control. Values represent mean ± SEM (seconds) of eight animals. p values for the difference in learning performance between the control and propranolol-treated groups were obtained by application of two-tailed Wilcoxon's test. * $p < 0.05$; ** $p < 0.01$.

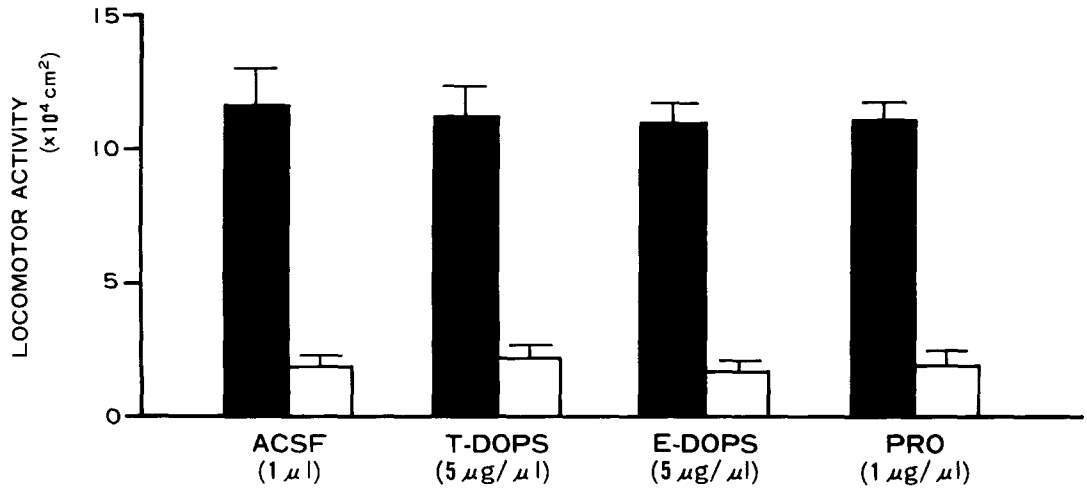

FIG. 4. Effects of intraventricular administration of 5 μg L-threo- or erythro-DOPS or 1 μg propranolol on the locomotor activity of rats in a novelty condition. Each drug was injected 30 min before the rat was placed on the programmable electronic platform for the measurement of locomotor activity by the OUCEM-86 in an open-field paradigm. The locomotor activity of the rat was recorded for 16 and 60 min and represented as total movements (cm^2) in four-foot position. An animal injected with 1 μl ACSF served as the control. Values represent mean ± SEM (cm^2) of six animals. No significant differences in locomotor activities were obtained between the control and drug-treated groups by Student's t-test. Open column, locomotor activity for 16 min; solid column, locomotor activity for 60 min.

TABLE 1

CHANGES IN CONCENTRATIONS OF FREE FORMS OF NA AND ITS METABOLITES IN BRAINS OF RATS FOLLOWING ADMINISTRATION OF L-DOPS

	Time After Injection (min)				
	0	30	60	120	180
L-Threo-DOPS					
NE	324.1 ± 22.8	386.8 ± 50.0*	374.8 ± 44.6*	392.8 ± 31.0†	381.9 ± 60.5
MHPG	31.0 ± 8.0	47.1 ± 13.7*	52.9 ± 9.4†	33.0 ± 5.0	39.5 ± 12.9
NM	15.8 ± 4.1	13.8 ± 2.8	14.6 ± 3.4	14.6 ± 1.5	9.4 ± 1.3
L-Erythro-DOPS					
NE	324.1 ± 22.8	439.8† ± 46.8†	398.9 ± 60.2*	381.2 ± 57.1	324.4 ± 20.7
MHPG	31.0 ± 8.0	50.1 ± 6.3*	37.7 ± 14.2	38.5 ± 14.3	28.4 ± 6.5
NM	15.8 ± 4.1	36.0 ± 5.1†	20.7 ± 5.4	22.4 ± 3.3*	11.5 ± 1.4

A rat was injected intraventricularly with 5 μg L-threo- or erythro-DOPS and free forms of NA and its metabolites of the brain were determined at the indicated intervals by the method described in the Method section. Values represent mean ± SD (ng/g wet weight) of six to eight animals. p values for the difference in concentrations between the control (0 min) and experimental groups were obtained by application of Student's t-test.

*$p < 0.05$.

†$p < 0.01$.

with 0.1% disodium ethylenediaminetetraacetate and 10 μl 0.01 N acetic acid containing the internal standard. The mixed solution was evaporated to dryness under N_2 gas. The dried residue was dissolved in 170 μl 0.05 M acetate buffer, pH 5.0, containing 0.01% disodium ethylenediaminetetraacetate and 0.1 μM pargyline. The buffer was divided into halves. One half of the buffer was mixed well with 5 μl concentrated perchloric acid and 10 μl 4.3 N KOH and then centrifuged at 4,000× g for 10 min. The supernatant was used for determination of free forms of NA and its metabolites. The other half of the buffer was incubated with 40 U sulfatase (Type H-1, Sigma Chemical Co., St. Louis, MO) at 37°C for over 3 h. The enzyme reaction was terminated by adding 5 μl concentrated perchloric acid and 10 μl 4.3 N KOH. The buffer was centrifuged at 4,000× g for 10 min and the supernatant was used for measurement of free and conjugated forms of NA and its metabolites.

Statistical Analysis

Significant differences in evaluation scores of passive avoidance conditioning among control and drug-treated groups were calculated by two-tailed Wilcoxon's test. Student's t-test was applied to evaluate differences in locomotor activities and concentrations of NA and its metabolites among the groups.

TABLE 2

CHANGES IN CONCENTRATIONS OF FREE AND CONJUGATED FORMS OF NA AND ITS METABOLITES IN BRAINS OF RATS FOLLOWING ADMINISTRATION OF L-DOPS

	Time After Injection (min)				
	0	30	60	120	180
L-Threo-DOPS					
NE	320.6 ± 47.6	379.6 ± 44.2*	373.7 ± 32.9*	380.2 ± 41.8*	375.9 ± 68.4
MHPG	48.5 ± 4.7	62.4 ± 13.3†	58.2 ± 6.3*	45.8 ± 4.1	47.2 ± 14.7
NM	13.9 ± 2.2	17.6 ± 4.5	18.3 ± 2.2*	16.3 ± 3.5	13.1 ± 1.7
L-Erythro-DOPS					
NE	320.7 ± 27.6	447.2 ± 51.9†	370.6 ± 49.4*	380.7 ± 50.5*	335.3 ± 48.2
MHPG	48.5 ± 4.7	84.5 ± 4.9†	73.8 ± 18.1†	76.9 ± 6.1†	53.4 ± 6.6
NM	13.9 ± 2.2	38.6 ± 5.8†	22.2 ± 8.7	17.9 ± 3.6*	13.4 ± 3.4

A rat was injected intraventricularly with 5 μg L-threo- or erythro-DOPS and free and conjugated forms of NA and its metabolites of the brain were determined at the indicated intervals by the method described in the Method section. Values represent mean ± SD (ng/g wet weight) of six to eight animals. p values for the difference in concentrations between the control (0 min) and experimental groups were obtained by application of Student's t-test.

*$p < 0.05$.

†$p < 0.01$.

RESULTS

Effects of L-*Threo- or Erythro-DOPS or Propranolol on Learning Performance of Rats*

As shown in Fig.2, intraventricular injection of 5 μg L-erythro-DOPS or 1 μg propranolol (PRO) to a rat lowered significantly the total time of the learning performance conditioning compared to treatment with ACSF. On the other hand, injection of 5 μg L-threo-DOPS significantly increased the total time, and this effect was blocked by simultaneous administration of 1 or 2 μg PRO (Fig. 3).

Effects of L-*Threo- or Erythro-DOPS or PRO on Locomotor Activity*

An intraventricular administration of 5 μg L-threo- or erythro-DOPS or 1 μg PRO to a rat did not affect significantly locomotor activities compared with ACSF for 16 or 60 min in the novelty condition (Fig.4).

Effects of L-*Threo- or Erythro-DOPS on Concentrations of Brain NA and its Metabolites*

Table 1 shows changes in concentrations of free forms of NA, 3-methoxy-4-hydroxyphenylglycol (MHPG), and normethanephrine (NM) in brains of rats following an intraventricular injection of 5 μg L-threo- or erythro-DOPS. The concentration of NA increased significantly from 30–120 min and MHPG from 30–60 min after injection of L-threo-DOPS. The injection did not affect the concentration of NM during the experimental period. The concentration of NA reached a maximum 30 min after injection of 5 μg L-erythro-DOPS and declined gradually. The injection also resulted in a significant increase in the concentration of MHPG after 30 min and of NM after 30 and 120 min, respectively.

Changes in the concentrations of free and conjugated forms of brain NA, MHPG, and NM after an intraventricular injection of 5 μg L-threo- or erythro-DOPS are shown in Table 2. After injection of L-threo-Dops, the concentration of NA remained significantly high from 30–120 min. The injection also raised the concentration of MHPG after 30–60 min and of NM after 60 min. Following intraventricular injection of L-erythro-DOPS, the concentration of NA reached a peak 30 min after the injection and then declined gradually. The injection increased significantly the concentration of MHPG from 30–120 min and of NM after 30 and 120 min, respectively.

DISCUSSION

Since Kety (6) suggested a participation of catecholamines in learning and memory mechanism in 1970, interest of basic and clinical neuroscientists has focused on a role of brain catecholamines, especially NA, in neural mechanisms of learning and memory behavior. Early experiments using agonists or antagonists of catecholamines, inhibitors of catecholamine synthesis, or brain lesions have yielded contradictory evidences with regard to brain NA and learning although a clear role of the peripheral NA system in learning had been indicated (2,5,10,18). In short time, the experiments using amygdaloid lesions and stimulation on learning and memory mechanisms suggested the amygdala may be involved in the mechanisms through modulating influences on other brain systems (5,8,9). The findings of recent animal experiments using intraamygdaloid injection of NA or propranolol (a β-adrenoceptor blocker) revealed that activation of β-adrenergic receptors in the amygdala is possibly involved in the acquisition of learning and memory processing and may play a role in the memory-modulating effect of peripheral epinephrine (7).

The finding from the present experiment was that the learning performance conditioning in the maze paradigm was facilitated by L-threo-DOPS (the *s*-NA precursor) and attenuated by its enantioisomer, L-erythro-DOPS (the *r*-NA precursor) in rats. These effects were unlikely to be derived from nonselective excitation or depression of the CNS by L-threo- or L-erythro-DOPS because the intraventricular administration of 5 μg of these precursor amino acids did not affect the locomotor activities of rats in the experimental conditions. The facilitating effect of L-threo-DOPS was blocked by the simultaneous administration of PRO, and marked elevation of brain NA and its metabolites was observed after intraventricular injection of L-threo-DOPS, suggesting that the effect of L-threo-DOPS on learning performance may be derived from activation of β-adrenoceptors by the formed *s*-NA in the rats' brain, although the site of activation of the formed *s*-NA was not yet identified. However, the facilitating effect of L-threo-DOPS on learning performance increased during the sets of experiments of 3 days, indicating strongly involvement of β-adrenergic systems of the CNS, possibly β-adrenoceptors in the amygdala.

The effect of L-threo-DOPS on learning and memory processing is clinically interesting and usefully in affective illness. It is well known that a kind of demented state (pseudodementia) is frequently observed in the depressive state that is pathogenetically thought to be derived from a decreased activity of brain monoamines, especially serotonin and NA. Therefore, L-threo-DOPS may by useful for the treatment of pseudodementic states observed in the depressive state, although some tricyclic antidepressants, for example, imipramine, are known to inhibit reuptake of serotonin as well as NA.

Furthermore, the effect of L-erythro-DOPS on learning and memory might be useful for the treatment of the anxious state. The central mechanism of anxiety caused by aversive stimuli is substantially interpreted as the activation of a serotonin system and an NA system in the CNS, and the former produces behavioral inhibition and the latter an excess of arousal and attention, resulting in anxiety and impairment of the learning performance. In this viewpoint, L-erythro-DOPS might be clinically useful for the treatment of an anxious state in which agitation and irritability show a bold front.

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