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Modification of Behavioral Responses to Methamphetamine Evoked by the Stimulant's Metabolite *p*-Hydroxynorephedrine in Rats

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SHIMOSATO, K. AND S. WATANABE. *Modification of behavioral responses to methamphetamine evoked by the stimulant's metabolite* p-*hydroxynorephedrine in rats*. PHARMACOL BIOCHEM BEHAV 33(2) 423–429, 1989.—The central effect of *p*-hydroxynorephedrine (OH-NE), one of the *p*-hydroxylated metabolites of methamphetamine (MAP) and amphetamine (AMP), was investigated in rats. Locomotion and stereotypy were examined after SC injections of 0.5–5 mg/kg of MAP or 0.02–0.5 mg/kg of apomorphine (APO) in animals treated with either saline or 5–50 mg/kg of OH-NE IP 20 hr before behavioral assessment. The locomotor stimulating effect of both 0.5–2 mg/kg of MAP and 0.2 mg/kg of APO was enhanced by 5 mg/kg of OH-NE. On the other hand, 30 mg/kg of OH-NE severely suppressed the stimulating effect of MAP but had no influence on that induced by 0.2 mg/kg of APO. The stereotypy induced by 5 mg/kg of MAP or 0.5 mg/kg of APO was enhanced and prolonged in the OH-NE-treated rats. Subsequently, examinations were performed to determine whether OH-NE had any effect on the dopaminergic mechanism. Hypomotility induced by 0.02 mg/kg of APO was alleviated by 5 mg/kg of OH-NE, but was aggravated by 30 mg/kg. These results suggest that OH-NE administered prior to SC injections of MAP or APO influences their behavioral effects via the dopaminergic mechanism. The possibility that other neural mechanisms may be involved in this OH-NE-induced behavioral modification is also discussed.

Methamphetamine *p*-Hydroxynorephedrine Apomorphine Locomotion Stereotypy Hypomotility Rats

REPEATED administration of amphetamine (AMP) or methamphetamine (MAP) to animals results in a progressive augmentation of locomotor activity and stereotypy, i.e., compulsive sniffing, chewing, biting, licking, gnawing or head swaying. It has been proposed that this behavioral augmentation is caused by either a conditioned response (14,31) or cerebral accumulations of the metabolites of the stimulants, including *p*-hydroxyamphetamine (OH-AMP) and *p*-hydroxynorephedrine (OH-NE) (8,22). Both mechanisms have been shown to produce neurochemical changes in cerebral catecholaminergic neurons (8,12). Browne and Segal (1), however, have indicated that neither a conditioned response nor metabolic factors account for this augmented behavioral responsiveness. Therefore, the mechanism underlying this phenomenon still remains unclear.

OH-AMP and OH-NE have been reported to have central effects on behavioral responses. After intraventricular administration, OH-AMP has mainly elicited an increase in locomotion, whereas OH-NE has predominantly caused an increase in stereotypy (29). These metabolites accumulate in various tissues, including the brain, after acute and chronic administration of AMP (5,18), although it is supposed that their penetration of the brain is limited by the blood-brain barrier. In the brain, they have inhibited the uptake of noradrenaline into chopped cerebral cortex (33) and of dopamine into rat striatal homogenates (4). Recently, Dougan *et al.* reported that 10 mg/kg of OH-AMP administered IP 24 hr before injection of AMP inhibited the locomotor stimulating effect of 0.5 mg/kg of AMP, but enhanced the stereotypy induced by 4 mg/kg of AMP (8). These results raise again the possibility that the *p*-hydroxylated metabolites of AMP and MAP may play an important role in the enhanced behavioral responsiveness observed after repeated administration of these drugs.

In the present study, we investigated the central effect of OH-NE, which was administered IP 20 hr before the behavioral assessment, on MAP-induced increases in locomotion and stereotypy. We also attempted to determine the role played by the dopaminergic mechanism in the central effects of OH-NE. This was done by investigating the effects of higher doses and a low dose, respectively, of the mixed D-1/D-2 dopamine receptor

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TABLE 1

EFFECTS OF OH-NE 5 AND 30 mg/kg ON 0.02 mg/kg OF APO-INDUCED HYPOMOTILITY IN RATS

Treatment	Injection	Time After Injection 10	20	30	40	50	60
Saline	Saline	24.7(2.5)	14.8(1.3)	9.1(3.0)	3.6(1.2)	5.1(1.2)	4.9(2.5)
	APO	5.2(1.1)‡	4.9(1.7)‡	1.6(0.7)*	6.1(1.5)	9.7(2.6)	3.1(1.4)
OH-NE 5	Saline	25.9(2.9)	15.4(2.5)	8.4(2.4)	7.0(2.0)	8.8(2.7)	2.3(0.8)
	APO	14.9(2.4)†§	3.3(1.2)‡	4.4(1.8)	17.8(2.7)†§	21.8(8.2)	1.9(1.0)
OH-NE 30	Saline	18.0(3.5)	8.1(3.0)	7.7(2.6)	5.4(1.5)	8.1(1.2)	7.8(2.5)
	APO	6.3(0.8)†	4.9(1.3)	1.2(0.5)*	1.4(0.7)*§	4.6(1.6)	4.1(2.7)

*, † and ‡ denote the significance of difference ($p<0.05$, 0.01 and 0.001, respectively) between the APO and saline-injected rats receiving the same treatment, and § denotes the significance of difference ($p<0.01$) between the APO-injected rats receiving saline treatment and those receiving 5 or 30 mg/kg of OH-NE.

agonist, apomorphine (APO), on behavioral stimulation and sedation.

METHOD

Subjects

Male Sprague-Dawley rats (Clea Japan, Japan), weighing 180–230 g at the time of the behavioral assessment, were used once. The animals were housed in groups of five or six in a temperature-controlled room (24°C) under a constant 14-hr light (7:00 a.m. to 9:00 p.m.) and 10-hr dark cycle for at least 7 days before the experiments. Food and water were freely available except during the behavioral assessment.

dl-OH-NE·HCl (Aldrich, USA) and MAP·HCl (Dainippon Pharmac, Japan) were dissolved in saline, and administered to the rats in doses of 5, 10, 20, 30 or 50 mg/kg and 0.5, 1, 2 or 5 mg/kg, respectively, in a volume of 1 ml/400 g body weight. APO·HCl (Sigma, USA) was dissolved in saline containing 0.1% ascorbic acid (Nacalai Tesque, Japan) by rapid heating and administered in doses of 0.02, 0.2 or 0.5 mg/kg in a volume of 1 ml/kg. All doses were expressed as hydrochloric salts with the exception of ascorbic acid.

Behavioral Assessment

Locomotor activity was measured by a pair of sensitivity-matched activity meters MK-Animex® (DSE, Muromachi Kikai, Japan) in a quiet room. The sensitivity of these meters was adjusted to predominantly monitor MAP-induced locomotor behavior and to exclude stereotypy. The rats, seven to ten in each group, received either saline or OH-NE IP 20 hr prior to the behavioral measurements. Before SC administration of MAP or APO, a pair of the rats were placed singly in two transparent observation cages (30 × 40 × 30 cm) set on the activity meters for 30 min to acclimate them to their surroundings, during which time spontaneous locomotion was monitored. After acclimation, MAP or APO was gently administered SC to the animals between 10:30 and 11:00 a.m., and locomotor activity was measured during 10-min intervals for 180 or 90 min, respectively.

The intensity of stereotypy was assessed using the scoring system of Naylor and Costall (21), which is as follows: 0, same behavior as saline-injected rats; 1, discontinuous sniffing, constant exploratory activity; 2, continuous sniffing and small head swaying, periodic exploratory activity; 3, continuous sniffing and small head swaying, very brief periods of locomotor activity; 4, continuous licking, gnawing or biting, no exploratory activity. During the last minute of each interval MAP- or APO-induced stereotypic episodes were observed visually and the predominant episode was scored according to the system described above.

To investigate the effect of OH-NE on a low dose of APO-induced sedation or hypomotility, unacclimated rats, which had been treated with either saline or OH-NE as described above, received either 0.02 mg/kg of APO or saline SC. Five minutes later a pair of rats were placed in the two observation cages and their locomotion was measured during 10-min intervals. Immediately after the first interval, the rats were transferred from one cage to the other by gentle handling and their activity was measured again. With transference of the rats from one cage to the other in this manner, locomotion was monitored during 10-min intervals up to 60 min.

Statistical Analysis

Analysis of locomotor activity data for statistical significance was done by the two-tailed Student's *t*-test. As for stereotypy, data were analyzed first by the Mann-Whitney U-test and then by the Fisher exact probability test using the frequencies of rats scoring 4 for more than 30 min and those of the other rats. The duration times during which the rats were engaged in stereotypy were statistically examined by the chi-square test and then by the Fisher exact probability test using the frequencies of the rats scoring 0 and those of the rest of the rats in each corresponding interval.

RESULTS

Appetite and Spontaneous Locomotion

No significant difference in gains in weights was observed between the saline control rats and those treated with 5 or 10 mg/kg of OH-NE during 20 hr of treatment, but weight gains in those treated with 20, 30 and 50 mg/kg, respectively, were reduced to 43, 37 and 3% of those of the control rats. There were no differences in spontaneous locomotion between the saline control rats and the rats treated with 5–30 mg/kg of OH-NE during the 30-min acclimation period before MAP injections. Spontaneous locomotion in the rats treated with 50 mg/kg of OH-NE, however, was 53% of that of the control rats (data not shown, see also Table 1).

MAP-Induced Locomotion

Time-lapse changes in the locomotor activity produced by

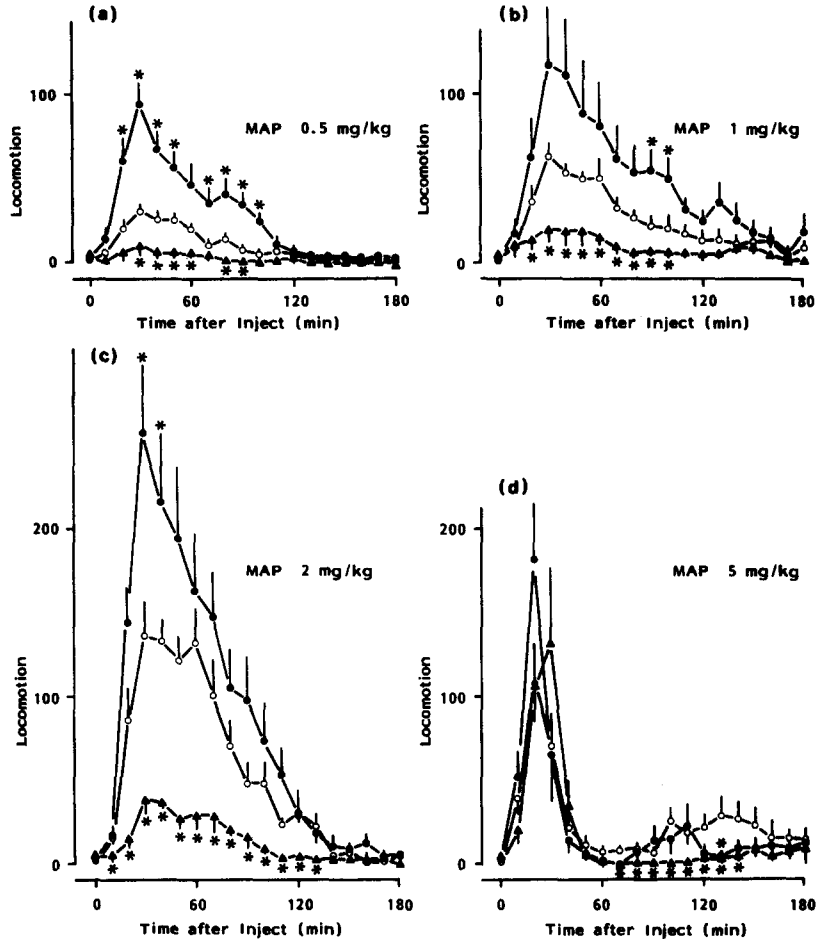

FIG. 1. Modification of locomotor response to various doses of MAP by 5 (●) and 30 (▲) mg/kg of OH-NE in rats. Open circles (○) indicate locomotor activity in the saline control rats. Each bar represents the standard error of the mean (S.E.M.) and each asterisk denotes the significance of difference ($p<0.05$) versus the control rats.

0.5–5 mg/kg of MAP in the rats treated with 5 and 30 mg/kg of OH-NE and the saline control rats are shown in Fig. 1. The locomotor stimulating effect produced by the lower and moderate doses of MAP (0.5–2 mg/kg) in the control rats reached a maximum at 30 min, and decreased gradually in the following 120 min to the levels in the last interval of the acclimation period. Five mg/kg of OH-NE drastically enhanced the locomotor stimulating effect produced by 0.5, 1 and 2 mg/kg doses of MAP. Activity counts in the rats treated with 5 mg/kg of OH-NE were two or three times higher than those in the control rats at the peak levels. Thirty mg/kg of OH-NE, however, severely suppressed locomotion produced by 0.5–2 mg/kg of MAP. Behavior in the rats treated with 30 mg/kg of OH-NE, such as sniffing and small head movements, was similar to that in the control rats. The treatment, therefore, seemed to only inhibit the locomotor activity produced by MAP. As for OH-NE's influence on the locomotor stimulating effect produced by the highest dose of MAP (5 mg/kg), surprisingly, neither 5 nor 30 mg/kg of OH-NE had any effect on locomotion evoked in the prestereotypic phase. However, the locomotor stimulating effect of MAP was suppressed at between 70–150 min in the rats treated with 30 mg/kg of OH-NE.

Because no substantial difference was noted in the patterns of the time-lapse changes in locomotion, we compared the cumulative activity counts of the above-mentioned three groups and rats receiving 10, 20 or 50 mg/kg of OH-NE during the first 120 min after the MAP doses (unpublished data). In the 10 mg/kg OH-NE-treated rats, the locomotor stimulating effect produced by 1 and 2 mg/kg doses of MAP was enhanced by 10 mg/kg of OH-NE, but that produced by 0.5 mg/kg of MAP was greatly suppressed. Treatment with 20 mg/kg of OH-NE enhanced the effect produced by 1 mg/kg of MAP, but suppressed the effect produced by 0.5 and 2 mg/kg of MAP. However, all MAP-induced locomotor activity was severely reduced in the rats treated with 50 mg/kg of OH-NE.

MAP-Induced Stereotypy

In the control rats, stereotypy began 20 min after administration of 5 mg/kg of MAP and reached the maximal level at 40 min, at which it continued up to 100 min, and then faded gradually into the poststereotypic phase (Fig. 2). At the maximal level, the stereotype behavior score was 2 in one of the ten control rats, 3 in seven, and 4 in two. In the rats treated with 30 mg/kg of OH-NE, the stereotypy was intensified to licking behavior and its duration was prolonged. Stereotypy began 10 min after administration of the MAP dose and the maximal level continued for 140 min. At

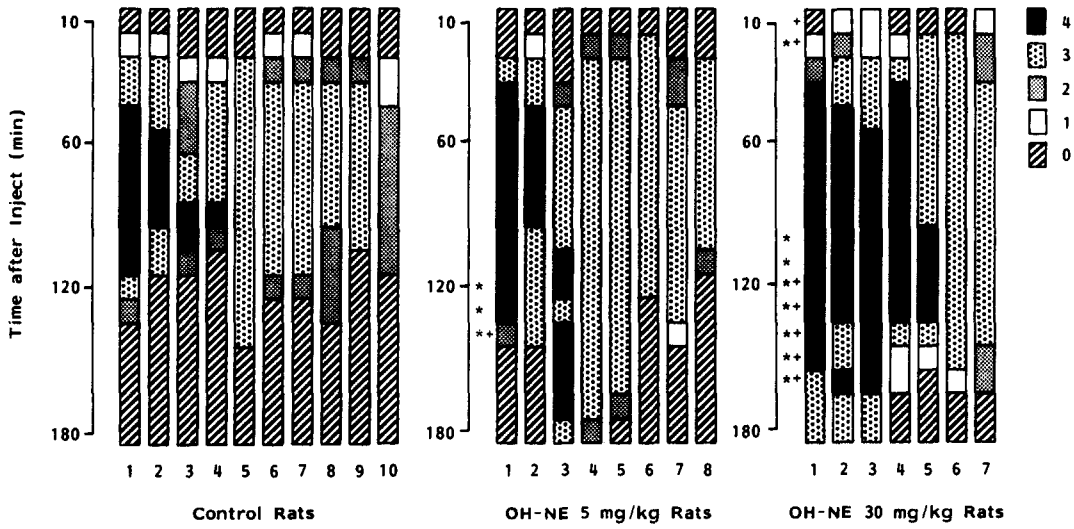

FIG. 2. Modification of stereotype response to 5 mg/kg of MAP by 5 (middle) and 30 (right) mg/kg of OH-NE in rats. Each stripe indicates the time-lapse changes in stereotype behavior, the scores of which are represented by the various designs used above. The asterisks and crosses denote the significance of difference ($p<0.05$) versus the control rats after analyses of the Mann-Whitney U-test and the Fisher exact probability test, respectively.

the maximal level, two of these seven rats scored 3 and five scored 4 ($p<0.05$ vs. the control rats by the Fisher exact probability test). In the rats treated with 5 mg/kg of OH-NE, the pattern of time-lapse changes in the stereotypy score fell between those of the control rats and the rats treated with 30 mg/kg of OH-NE.

APO-Induced Locomotion and Stereotypy

In the control rats, higher doses (0.2 and 0.5 mg/kg) of APO caused an increase in locomotor activity, which reached a maximum at 20 min and then faded sharply into a sedative phase (Fig. 3). Although 5 mg/kg of OH-NE, as observed in the experiment on MAP-induced locomotion, enhanced the locomotor stimulating effect produced by 0.2 mg/kg of APO, 30 mg/kg of OH-NE had no effect. This latter result was in striking contrast to that obtained in the experiment on MAP-induced locomotion. On the other hand, 0.5 mg/kg of APO produced locomotor responses which elicited double-peaked changes in locomotion in both the 5 and 30 mg/kg of OH-NE-treated rats. In these rats, the activity counts became lower than those in the control rats at 20–40 min.

When 0.5 mg/kg of APO was administered to the rats, it caused stereotypy which reached a maximal level at 30 min and thereafter declined promptly in all the treated rats (Fig. 4). Both OH-NE treatments elevated the mean stereotypy score from 2 to 3 in the OH-NE-treated rats. At the maximal level, of the nine rats receiving each treatment (saline, and 5 and 30 mg/kg of OH-NE) one, two and four rats, respectively, scored 4.

APO-Induced Hypomotility

The effect of OH-NE on the presynaptic dopamine receptors was investigated in an experiment in which hypomotility was induced by 0.02 mg/kg of APO (Table 1). After injection of saline, the control rats exhibited exploratory locomotion, especially in the first and second intervals of the acclimation period. During later intervals they acclimated themselves to the experimental environment and calmed down. APO suppressed exploratory locomotion during the first, second and third intervals of the acclimation period and elicited sedation, which was followed by a slight exploration. Neither of the OH-NE treatments had any effect on exploratory locomotion after the saline injection, although the locomotor activity in the first and second intervals was slightly attenuated in the rats treated with 30 mg/kg of OH-NE. Low dose APO-induced hypomotility was markedly, but incompletely, alleviated by 5 mg/kg of OH-NE during the first interval, and during the fourth and fifth intervals it conspicuously elicited exploratory locomotion. On the other hand, in the rats treated with 30 mg/kg of OH-NE, the action of the low dose of APO was strengthened and prolonged. In these rats, even in the fourth and fifth intervals, the activity counts were lower than those in the control rats after injection of APO.

DISCUSSION

The present investigation revealed that OH-NE, which was administered IP 20 hr before the behavioral assessment, produced bimodal effects on behavioral responses to MAP in rats. Our results agree well with those of Dougan *et al.* (8), who administered 10 mg/kg of OH-AMP IP 24 hr before AMP injection, and then observed a reduction in the locomotion induced by 0.5 mg/kg of AMP and enhancement of the stereotypy caused by 4 mg/kg of AMP. We also found that 10 mg/kg of OH-NE suppressed the locomotor stimulating effect of 0.5 mg/kg of MAP and that it enhanced the stereotypy induced by 5 mg/kg of MAP (unpublished data). However, after 1 and 2 mg/kg doses of MAP locomotion was remarkably enhanced in the rats treated with 10 mg/kg of OH-NE. The mechanism of OH-NE's effect on the behavioral responses is complicated and its effectiveness seems to depend on the doses of both OH-NE and MAP.

Treatment with 5 mg/kg of OH-NE markedly enhanced the locomotor stimulating effect of 0.5–2 mg/kg of MAP and 0.2 mg/kg of APO. It also produced double-peaked changes in locomotion after injection of 0.5 mg/kg of APO owing to enhancement of stereotype behavior. Since higher doses of APO have been shown to produce behavioral responses by directly stimulating the postsynaptic dopamine receptors (2,9), it seems

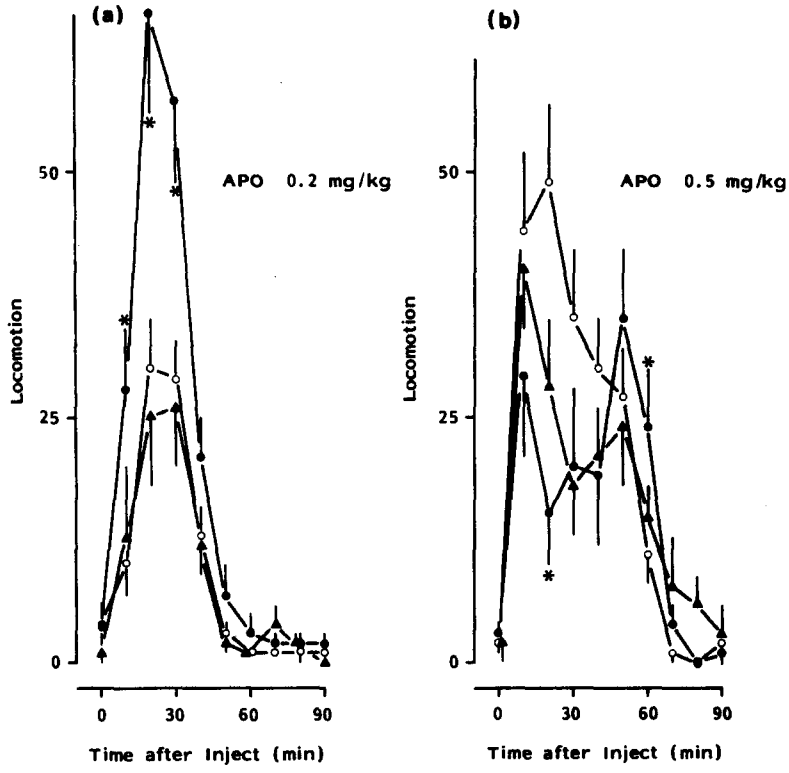

FIG. 3. The locomotor stimulating effect of higher doses of APO in rats treated with either saline (○), OH-HE 5 (●) or 30 (▲) mg/kg. Each bar represents the S.E.M. The asterisks denote the significance of difference ($p<0.05$) versus the control rats.

conceivable that this augmentation of the locomotor stimulating effect of MAP and APO may, at least in part, be due to enhanced activity of the postsynaptic dopamine receptors induced by the treatment with 5 mg/kg of OH-NE. In the present study, it was also found that 5 mg/kg of OH-NE alleviated 0.02 mg/kg APO-induced hypomotility. Since it is generally accepted that low doses of APO produce hypomotility or sedation due to stimulation of the presynaptic dopamine receptors and a resultant decrease in dopamine release (2,9), this result indicates that OH-NE probably blocked stimulation of the presynaptic dopamine receptors by the low dose of APO. These findings are in line with reports that 1) various dopamine D-2 antagonists enhanced the behavioral stimulation induced by AMP doses and 0.5 mg/kg of APO (15,27) and 2) they reversed low dose APO-induced hypomotility (6,26). From the behavioral responses produced by 5 mg/kg of OH-NE, it can be deduced that this dose causes an alteration in the function of the pre- and postsynaptic dopamine D-2 receptors, although the mechanism of this effect is unclear.

Treatment with 30 mg/kg of OH-NE, in contrast, severely suppressed the locomotor stimulating effect of 0.5–2 mg/kg of MAP. The same treatment, however, had no effect on locomotion after administration of 0.2 mg/kg of APO, although double-peaked changes in locomotor activity occurred after injection of 0.5 mg/kg of APO because of enhancement of stereotypy. These results indicate that the postsynaptic dopamine receptors were not impaired in regions which control locomotion, such as the nucleus accumbens (17). In hypomotility induced by 0.02 mg/kg of APO, this treatment aggravated the hypomotility. Based on these results, it can be concluded that treatment with 30 mg/kg of OH-NE affects the presynaptic dopaminergic mechanism and thereby blocks

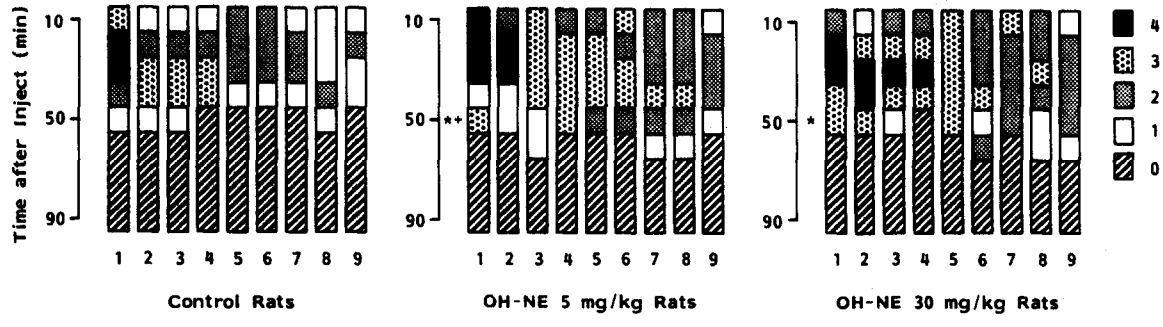

FIG. 4. Effect of 5 (middle) and 30 (right) mg/kg of OH-NE on stereotype behavior induced by 0.5 mg/kg of APO in rats. Other details are described in the legend of Fig. 2.

dopamine release in the nucleus accumbens. On the other hand, stereotypy induced by 5 mg/kg of MAP and 0.5 mg/kg of APO was remarkably intensified and prolonged in the rats treated with 30 mg/kg of OH-NE. The above-mentioned results are consistent with observations that AMP-induced stereotypy was augmented by 50 mg/kg of sulpiride preinjected 20 min before AMP administration and that the locomotor stimulating effect of AMP was completely inhibited by it (23). Although the mechanism of the differential effects of treatment with 30 mg/kg of OH-NE has not been demonstrated, it seems conceivable that the treatment may exert an antagonistic effect on the dopaminergic mechanism.

Another possible explanation for the behavioral modification caused by 30 mg/kg of OH-NE is the noradrenergic mechanism. It has been demonstrated that OH-NE accumulates selectively in areas containing noradrenergic neurons, such as the cerebellum and hypothalamus, after administration of AMP (3, 7, 10). In the present study, however, the regional accumulation of OH-NE was not investigated. The fact that the locomotor stimulating effect of AMP has been attenuated by both locus coeruleus and dorsal noradrenergic bundle lesions indicates some involvement of the central noradrenergic neurons in the behavioral responses to AMP in rats (19). Clonidine, a α_2-adrenergic agonist, has been shown to produce the same behavioral modifications in AMP-induced locomotion (20,25), augmentation of oral stereotypy (20,30), and aggravation of low dose APO-induced hypomotility (28). Therefore, it also seems conceivable that the behavioral modifications produced by 30 mg/kg of OH-NE are elicited via the noradrenergic mechanism, which in turn presumably controls the presynaptic dopamine mechanism (32). Which of these two mechanisms is more predominantly involved in the present phenomena must be further investigated.

Some authors have ruled out any involvement of OH-NE in behavioral augmentation. This conclusion appears to be based on the observation that OH-NE has almost never been found to accumulate in the brain regions after administration of the *l*-isomer of AMP (7,11), even though *l*-AMP has produced behavioral augmentation in rats (1). Furthermore, morphine and cocaine have been reported to produce the same phenomenon in mice (13,16). However, OH-NE and OH-AMP, when administered intraventricularly, have predominantly elicited stereotypy and increased locomotion, respectively, in rats (29). Moreover, Dougan *et al.* (8) recently observed that 10 mg/kg of OH-AMP enhanced the stereotypy induced by 4 mg/kg of AMP. These results seem to indicate that these metabolites may have some effect on the neural mechanism associated with behavioral augmentation. In addition, the present results suggest that OH-NE accumulated in the brain may be responsible for the behavioral augmentation after repeated administration of AMP and MAP. To date it remains unclear whether treatment with both OH-NE and repeated administration of drugs such as *l*-AMP, morphine and cocaine, which never form OH-NE, would produce the same alterations in the neural mechanism. However, in the present investigation we have concluded that at least in species in which aromatic hydroxylation is a major pathway of the metabolism, and this includes man (24), the neural effect of OH-NE must be considered in connection with the phenomenon that follows administration of *dl*- or *d*-AMP and MAP.

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