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# The Role of Central Serotonergic Mechanisms on Head-Twitch and Backward Locomotion Induced by Hallucinogenic Drugs

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YAMAMOTO, T. AND S. UEKI. *The role of central serotonergic mechanisms on head-twitch and backward locomotion induced by hallucinogenic drugs.* PHARMAC. BIOCHEM. BEHAV. 14(1) 89–95, 1981.—Head-twitch induced by lysergic acid diethylamide, mescaline and 2,5-dimethoxy-4-methylamphetamine (DOM) was significantly increased by medial raphe (m-R) lesions, but dorsal raphe (d-R) lesions did not produce any changes. Hallucinogen-induced head-twitch was inhibited by methysergide and tended to be increased by PCPA. These results suggest that 5-HT receptors innervated with the ascending 5-HT pathway originating in the m-R play a vital role in the manifestation of hallucinogen-induced head-twitch. That is, increase of head-twitch is ascribed to supersensitivity of 5-HT receptors. On the other hand, DOM-induced backward locomotion was inhibited by m-R or both dorsal and medial raphe lesions and methysergide, and was reversed to forward locomotion, differently from the hallucinogen-induced head-twitch. A reversion of backward locomotion was not obtained with d-R lesions or PCPA treatment.

Raphe nuclei  Abnormal behavior  Head-twitch  Backward locomotion  Psychotomimetics

ADMINISTRATION of hallucinogens such as mescaline or lysergic acid diethylamide (LSD-25) to the mouse and rat produces an abnormal behavior, including characteristic head-twitch [6,26], scratching [19] and backward locomotion [24,26]. Corne and Pickering [6] indicated that head-twitch in the mouse can serve as an useful parameter for predicting psychotomimetic activity. These abnormal behaviors induced by hallucinogens constitute a promising experimental model of mental disorders. As aids in elucidating the etiology of psychoses, they are expected to play a vital role in the research and screening of psychotherapeutic agents [7,8].

Head-twitch may similarly be induced by the intraventricular injection of serotonin (5-hydroxytryptamine, 5-HT) or 5-methoxytryptamine [21,22], which directly mimicks 5-HT at 5-HT receptors [16]. The intraperitoneal injection [7] of 5-hydroxytryptophan (5-HTP) also induces head-twitch. These results suggest that serotonergic function is of importance in the manifestation of head-twitch following hallucinogen administration. Ascending or descending 5-HT fibers have been demonstrated to originate in the raphe nuclei, including 5-HT containing cell bodies in the midbrain, pons and medulla oblongata [3,10]. The dorsal raphe nuclei ($B_7$; d-R) and medial raphe nuclei ($B_8$; m-R), located in the midbrain, are thought to comprise the main source of 5-HT ascending pathways. However, the ascending pathways arising from the d-R and m-R do not project to similar regions of forebrain [18,20], suggesting functional differences in the midbrain raphe. In fact, it has been reported that the effects of d-R and m-R lesions on locomotor activity [12, 17, 25] and EEG activity [28] differ. It would be interesting to elucidate how the serotonergic function of different regions of the brain participate in manifestation of hallucinogen-induced abnormal behavior. As of yet, studies focussing primarily on this point have not appeared in the literature and explanation of the specific mechanism involved would be difficult based on the results of previous studies.

Therefore we carried out investigations to clarify the relationship between the mechanisms involved in hallucinogen-induced abnormal behavior and brain serotonergic activity. Lesions were selectively made in the midbrain raphe nuclei of the rat to investigate changes in hallucinogen-induced abnormal behavior.

## METHOD

### *Animals*

Female Wistar King A rats aged 8–10 weeks and weighing 160–200 g at the time of surgery, supplied by Kyushu University Institute of Laboratory Animals, were used. They were housed in groups of 4 or 5 in plastic cages (30×35×17 cm) at a controlled temperature of 22 ± 1°C. Illumination was provided from 7:00 a.m. to 7:00 p.m. The animals were given food and water ad lib throughout the experiment.

### *Drugs*

The following hallucinogens were used; mescaline sul-

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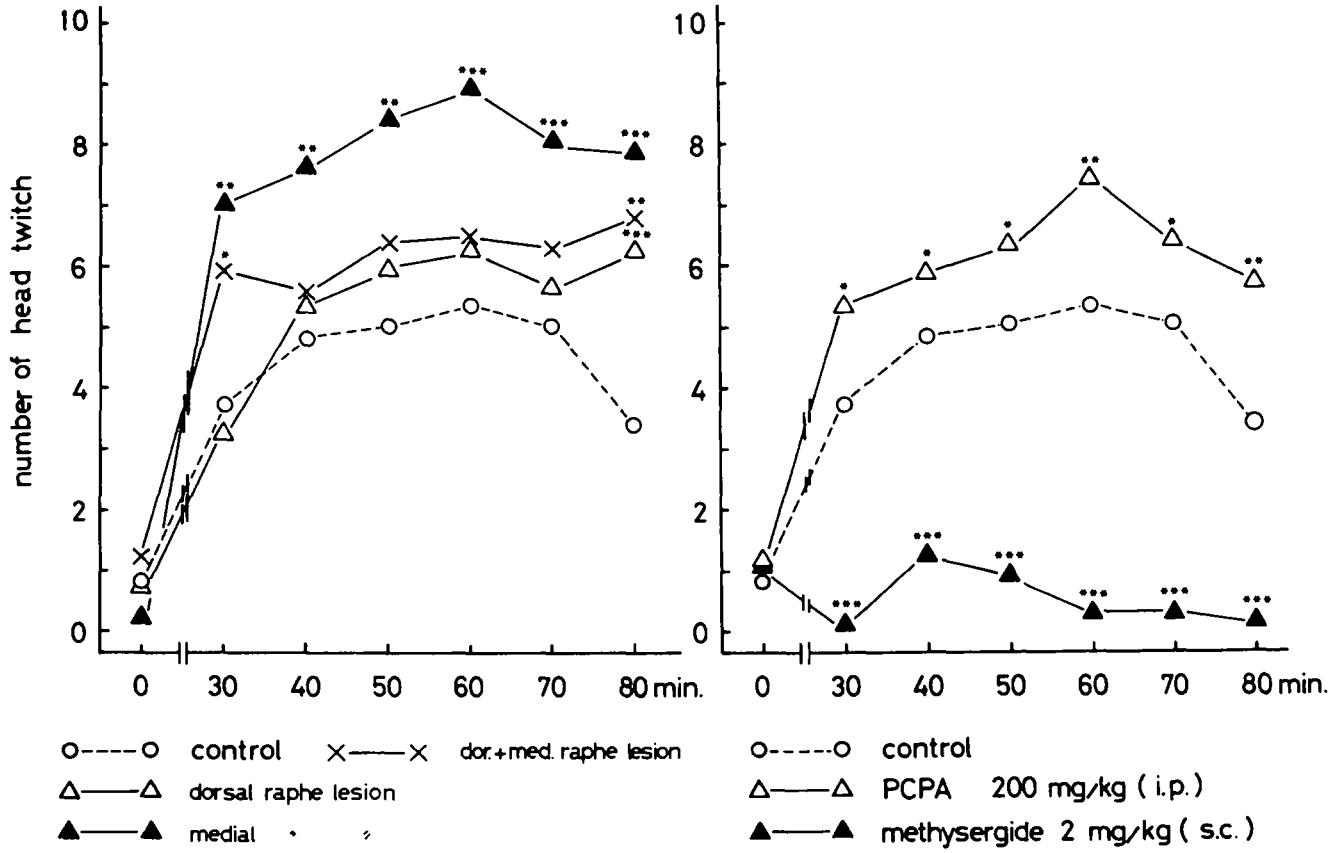


FIG. 1. The time course of head-twitch induced by mescaline in female rats. Ordinate indicates the number of head-twitches counted in a 2 min observation period, and abscissa the time in minutes after IP administration of mescaline. Left panel: effects of midbrain raphe lesions on head-twitches induced by mescaline (50 mg/kg IP). Right panel: effects of p-chlorophenylalanine (PCPA, before 48 hr) and methysergide (simultaneous injection with mescaline) on head-twitches induced by mescaline. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$, for the difference from the control, using Mann-Whitney U test.

fate, lysergic acid diethylamide (LSD-25), 2,5-dimethoxy-4-methylamphetamine HCl (DOM) and $\Delta^9$-tetrahydrocannabinol (THC). THC was emulsified in 1% Tween 80 to a concentration of 1% and diluted appropriately with saline. The other hallucinogens were dissolved in saline. All hallucinogens were administered by intraperitoneal (IP) injection. The 5-HT synthesis blocker p-chlorophenylalanine (PCPA) was suspended in 0.5% carboxymethylcellulose and injected IP. L-5-hydroxytryptophan (L-5-HTP) and the 5-HT receptor blocker methylsergide hydrogen maleinate were dissolved in saline and injected subcutaneously (SC).

*Surgical Procedure*

Rats were anesthetized with 40 mg/kg of pentobarbital Na (IP). Lesions of midbrain raphe nuclei were carried out by inserting an insulated, stainless steel wire, monopolar electrode of 0.4 mm in diameter, according to the rat brain atlas of König and Klippel [14], and applying a direct current of 3 mA for 15 sec. All other procedures have been described previously [27]. Three treated groups were formed (1) dorsal raphe lesion [d-R; frontal (F): 0.16, lateral plane (L): 0, horizontal plane (H): −1.0], (2) medial raphe lesion [m-R; F: 0.16, L: 0, H: −2.5] and (3) both dorsal and medial lesions (dm-R). Sham operations were performed with the same surgical procedure except insertion of electrodes. After termination of the experiments, the heads of animals which had undergone brain lesioning were perfused with 10% Formalin. Brain sections of 50 $\mu$ thick were made, stained with cresyl violet and the site of lesions were verified histologically. The rats in which brain lesions were unsuccessful were excluded from the final data.

*Procedures*

The test of abnormal behavior was conducted on postoperative days 5 to 7.

*Determination of head-twitch.* Rats were placed in groups of 3 each in a plastic cage (30×35×75 cm) equipped with a 100 W incandescent lamp set at a height of 80 cm from the center of the floor. After a 10 min period of adaptation, the experiment was started. Head-twitch was continually measured for 2 min at 10 min intervals after hallucinogen or L-5-HTP administration.

*Determination of walking backward.* The backward locomotion was measured for 3 min by means of an open-field apparatus. This apparatus, similar to that used by Hall [11], consisted of a circular floor measuring 60 cm in diame-

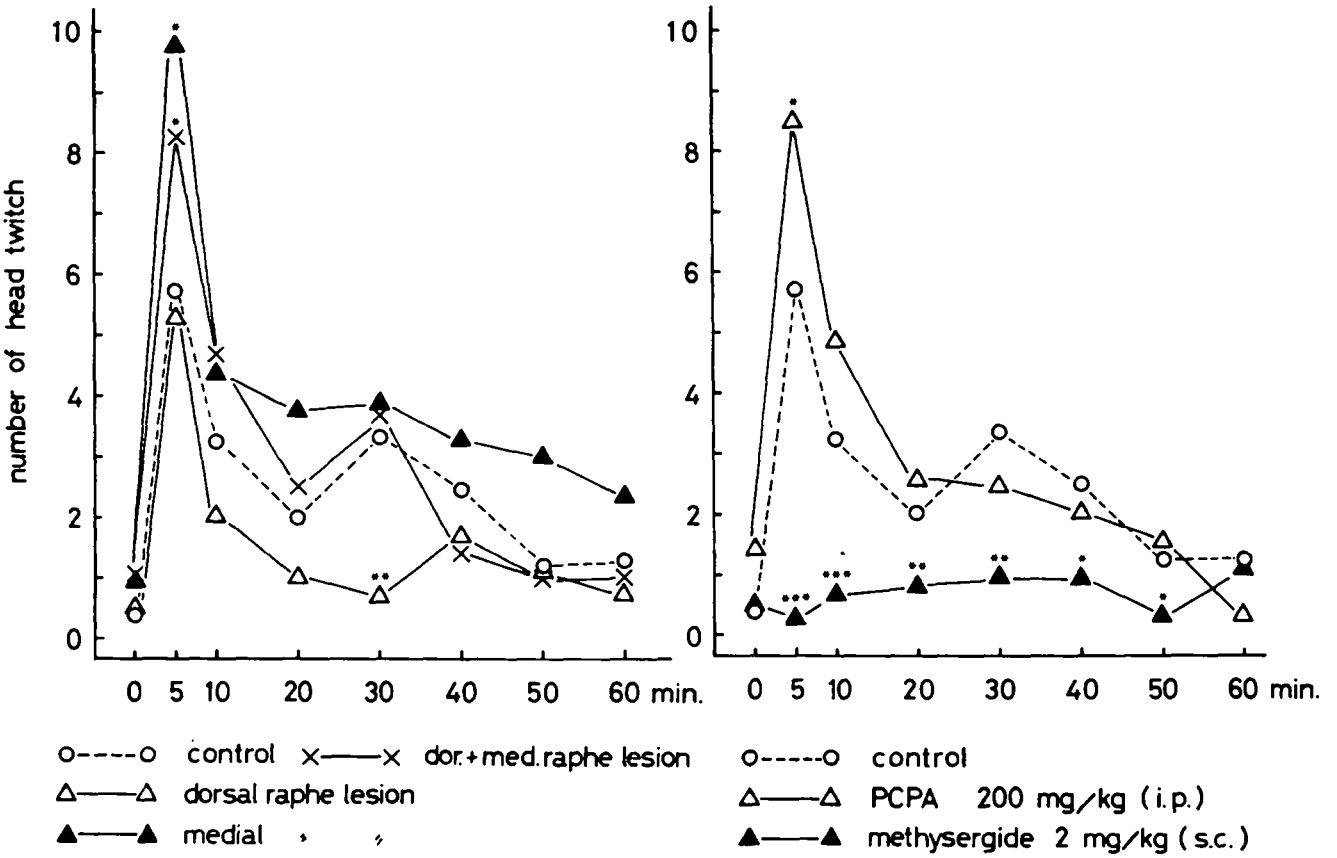


FIG. 2. The time course of head-twitch induced by LSD-25 in female rats. Ordinate indicates the number of head-twitches counted in a 2 min observation period, and abscissa the time in minutes after IP administration of LSD-25. Left panel: effects of midbrain raphe lesions on head-twitches induced by LSD-25 (0.2 mg/kg IP). Right panel: effects of p-chlorophenylalanine (PCPA, before 48 hr) and methysergide (before 30 min) on head-twitches induced by LSD-25. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$, for the difference from the control, using Mann-Whitney U test.

ter bounded by a 50 cm high wall. The inside of the apparatus was painted grey, and the floor was divided into 19 blocks of approximately equal width with painted lines. A 100 W lamp was placed 80 cm above the center of the apparatus in order to keep constant illumination. Thirty minutes after IP administration of DOM (20 mg/kg) the rat was placed in the center of the open-field and observed during a 3 min period. Ambulation (the number of blocks traversed by the rat) was recorded in terms of forward locomotion and backward locomotion. The results were statistically analyzed by the method of a one-tailed Mann Whitney U test.

## RESULTS

### *Head-twitch*

*Mescaline.* The peak time of head-twitch was 60 min after IP injection of 50 mg/kg of mescaline. The average number of head-twitches at this time was 5.3 ± 1.6/2 min (average ± SD, N=9).

In the m-R lesioned rats (N=9), the number of head-twitches induced by mescaline significantly increased to approximately twice that in the sham operated rats at any time during the experimental period (Fig. 1). In contrast, head-twitch in the d-R lesioned rats (N=9) did not significantly differ from that in the sham operated rats, except for 80 min after administration. Head-twitch in the dm-R lesioned rats (N=8) significantly increased at 30 min ($p<0.05$) and 80 min ($p<0.001$) after drug administration, but the number was distinctly less than that in the m-R lesioned rats.

In rats pretreated with 200 mg/kg of PCPA IP, 48 hr before mescaline administration (N=9), head-twitch significantly increased at all determination times (Fig. 1). Conversely, rats concomitantly receiving mescaline with SC injection of methysergide (N=9) exhibited a significant reduction in head-twitch at all determinations (Fig. 1).

*Lysergic acid diethylamide (LSD-25).* Head-twitch appeared promptly after LSD-25 0.2 mg/kg administration, attaining peak levels in 5 min. Ten minutes after treatment, there was a remarkable decrease in head-twitch and the effect of LSD-25 was no longer evident. The number of head-twitches at the time of peak effect was 5.7 ± 1.6/2 min.

Head-twitch in the dm-R lesioned rats increased significantly 5 min after LSD-25 administration (Fig. 2). However, from 10 min after administration, there was no difference from the control group; head-twitch did not persist any longer. In d-R lesioned rats there were no signs of such an augmentation of head-twitch and, conversely, 30 min after administration head-twitch was significantly inhibited.

On the other hand, LSD-induced head-twitch was significantly inhibited by concomitant administration of methysergide (N=9) at any of the determination times (Fig. 2). Conversely, pretreatment with PCPA (N=8) produced a signifi-

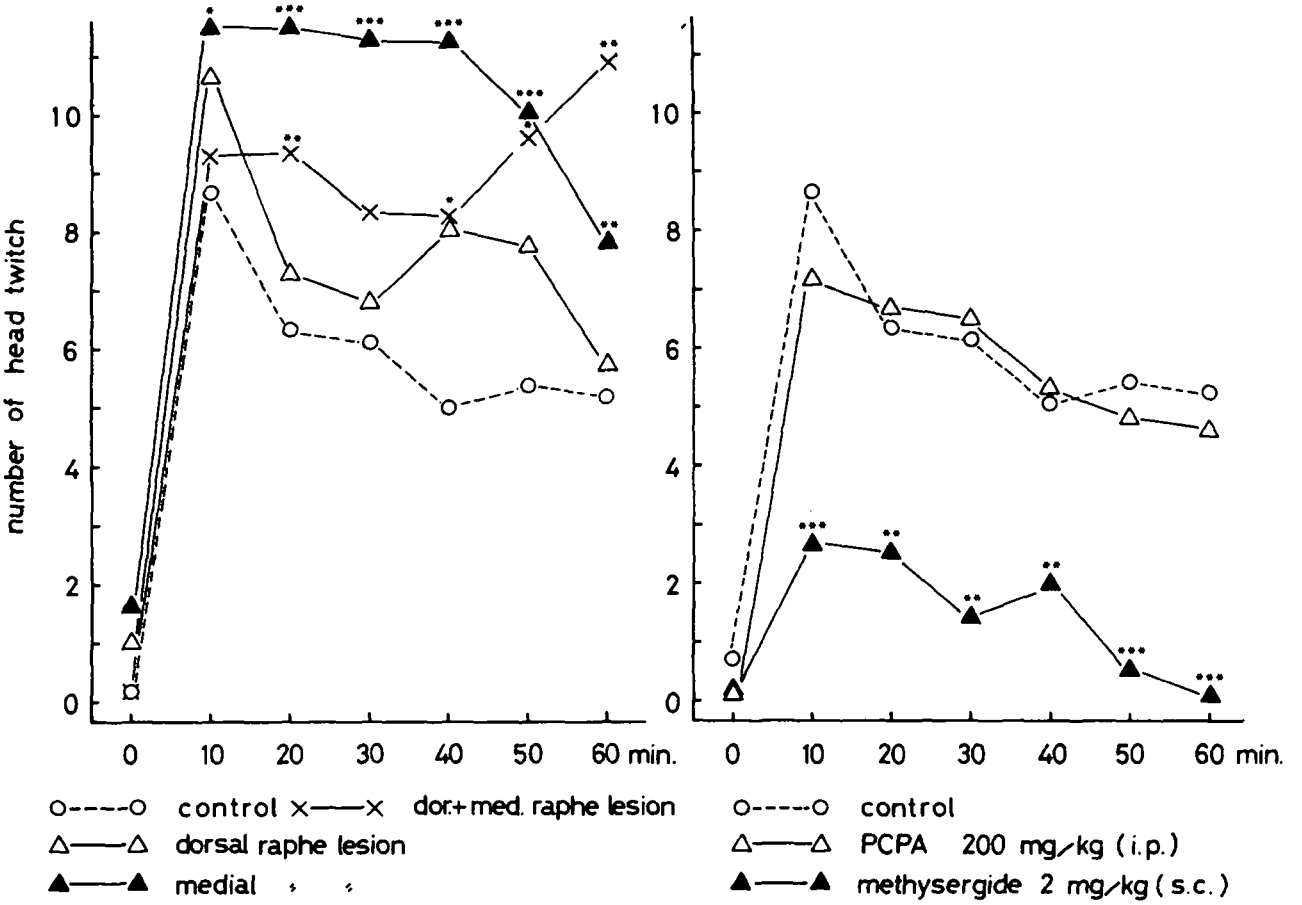


FIG. 3. The time course of head-twitch induced by DOM in female rats. Ordinate indicates the number of head-twitches counted in a 2 min observation period, and abscissa the time in minutes after IP administration of DOM. Left panel: effects of midbrain raphe lesions on head-twitches induced by DOM (0.5 mg/kg IP). Right panel: effects of p-chlorophenylalanine (PCPA, before 48 hr) and methysergide (before 15 min) on head-twitches induced by DOM. *=$p<0.05$, **=$p<0.01$, ***=$p<0.001$, for the difference from the control, using Mann-Whitney U test.

cant increase in head-twitch at the time of peak effect 5 min after administration of LSD-25, but there was no difference from controls after 10 min.

*2,5-Dimethoxy-4-methylamphetamine (DOM).* The peak time of DOM (0.5 mg/kg, IP)-induced head-twitch was 10 min after treatment. The number of head-twitches at this time was 8.7 ± 3.1/2 min (N=9).

DOM-induced head-twitch was not influenced by d-R lesion (N=6; Fig. 3). In contrast, head-twitch significantly increased in the m-R lesioned rats 10 min after DOM administration. This increase was observed at all determinations up to 60 min after treatment (N=6). In dm-R lesioned rats, head-twitch showed a significant increase, but the degree was less than that in m-R lesioned rats (N=5).

DOM-induced head-twitch was remarkably inhibited after methysergide administration at all determinations (N=9; Fig. 3). However, PCPA treatment did not cause any significant changes.

*$\Delta^9$-Tetrahydrocannabinol ($\Delta^9$-THC).* $\Delta^9$-THC, 2 mg/kg IP (N=6), did not produce any remarkable signs of head-twitch at any of the determination times. Administration of 5 mg/kg of $\Delta^9$-THC (N=6) produced generally comparable results.

*L-5-Hydroxytryptophan (L-5-HTP).* Thirty, 60 and 90 min after injection of L-5-HTP 100 mg/kg IP, the number of head-twitch for a 2 min period was 3.0 ± 1.6, 6.2 ± 3.0 and 2.7 ± 1.4, respectively (Table 1). At the peak time of 60 min, L-5-HTP-induced head-twitch in the d-R, m-R and dm-R lesioned rats was significantly suppressed. Furthermore, L-5-HTP-induced head-twitch was not appreciably affected by pretreatment with 200 mg/kg of PCPA. However, administration of 2 mg/kg of methysergide produced significant inhibition (Table 1).

*Backward Locomotion*

Administration of DOM at doses over 5 mg/kg made the rat spread its hindlimbs apart, put its forelimbs together and walk backwards raising its hip slightly [26]. This phenomenon is more or less commonly seen with most hallucinogens. DOM, however, is associated with a much higher degree of backward locomotion than LSD or mescaline. In fact, all locomotor activity is comprised of backward locomotion after DOM administration.

After treatment with 20 mg/kg of DOM IP in the rats, the majority of locomotor activity consisted of backward locomotion, having a value of 42.9 ± 17.5 (N=8; Fig. 4). At the same time, rearing, having a value of 15.0 ± 3.9 in a non-drug state, was completely suppressed. Preening, grooming, defecation and urination also completely disappeared. DOM-induced backward locomotion was not significantly affected by d-R lesion (N=17; Fig. 4). However, m-R

TABLE 1

EFFECTS OF MIDBRAIN RAPHE LESIONS, PCPA AND METHYSERGIDE ON L-5-HTP-INDUCED HEAD-TWITCHES IN FEMALE RATS

| Treatment | Number of head-twitch (mean ± SD) | | |
|---|---|---|---|
| | 30–32 min | 60–62 min | 90–92 min |
| Sham operation (N=9) | 3.0 ± 1.6 | 6.2 ± 3.0 | 2.7 ± 1.4 |
| d-R lesion (N=6) | 1.5 ± 1.1* | 1.0 ± 1.0‡ | 2.7 ± 2.2 |
| m-R lesion (N=6) | 2.0 ± 1.9 | 1.7 ± 1.0‡ | 2.3 ± 0.7 |
| dm-R lesion (N=5) | 1.2 ± 0.9* | 1.8 ± 2.2† | 0.6 ± 0.5† |
| PCPA 200 mg/kg IP (N=9) | 2.1 ± 1.7 | 5.9 ± 2.1 | 3.7 ± 3.4 |
| Methysergide 2 mg/kg SC (N=12) | 2.0 ± 1.6* | 1.3 ± 1.1‡ | 2.0 ± 1.5 |

Head twitches were counted for a 2-min period, three times (30, 60 and 90 min) after IP administration of L-5-HTP 100 mg/kg.

*=$p<0.05$, †=$p<0.01$, ‡=$p<0.001$, for the difference from the sham operation group, using Mann-Whitney U test.

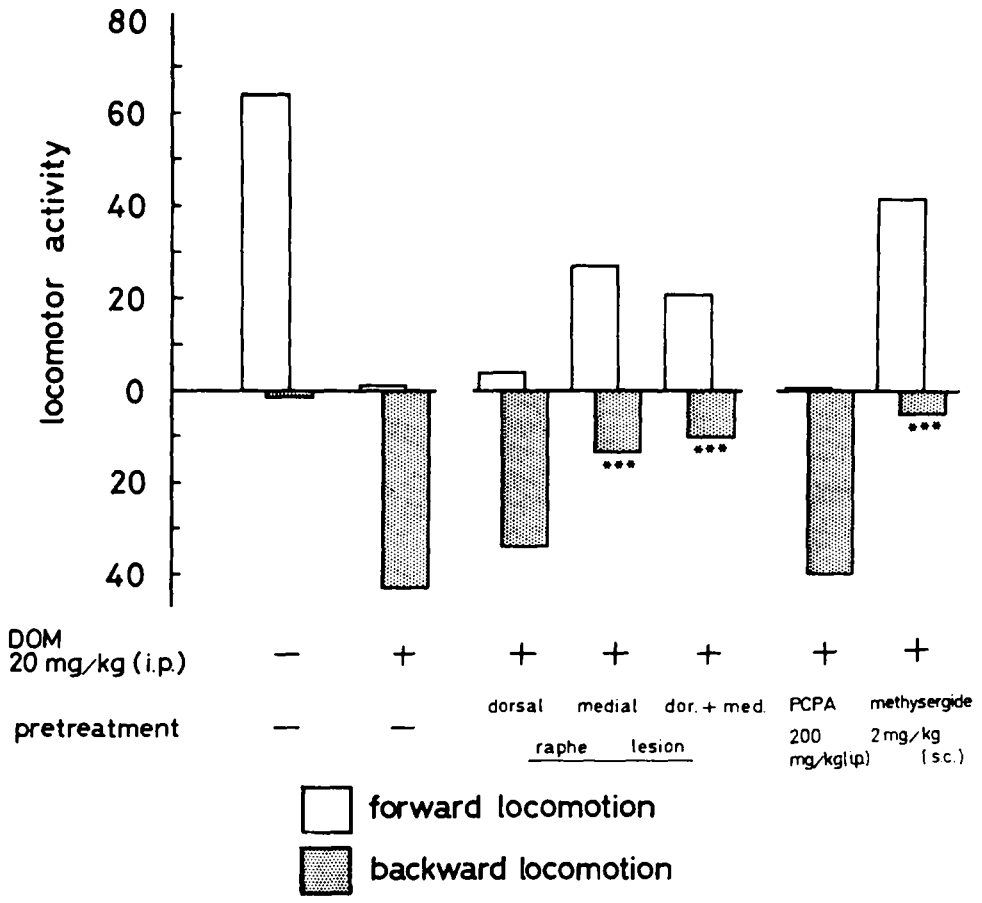


FIG. 4. Effects of midbrain raphe lesions, PCPA and methysergide on backward locomotion induced by DOM 20 mg/kg IP in female rats. The backward locomotion was measured for 3 min at 30 min after DOM administration. ***=$p<0.001$, for the difference from DOM-induced backward locomotion, using Mann-Whitney U test.

lesion (N=16) suppressed backward locomotion to 13.5 ± 9.9, and forward locomotion conversely increased to 26.7 ± 38.8. Backward locomotion was similarly inhibited (10.7 ± 9.5) by dm-R lesions (N=16), and forward locomotion was increased (19.2 ± 20.0). However, DOM-induced inhibition of rearing, preening, grooming and urination was not affected by any type of raphe lesion.

DOM-induced backward locomotion was also not af-

fected by pretreatment with 200 mg/kg of PCPA (N=12), but methysergide pretreatment (N=9) produced remarkable inhibition of backward locomotion, while forward locomotion increased to 41.7 ± 34.2 (Fig. 4). At the same time, rearing similarly increased to 7.2 ± 7.3, indicating a tendency towards recovery to control level. Moreover, urination, which completely disappeared after the administration of DOM, was seen in 8 of 10 rats. However, preening, grooming and defecation were not suppressed.

## DISCUSSION

It has been reported that most hallucinogens inhibit the firing rate of raphe nuclei neurons [1,2]. Some hallucinogens act as post-synaptic 5-HT receptor agonists [4], while others augment 5-HT synthesis and release [9]. It is extremely interesting to speculate which action of hallucinogens are most intimately related to the manifestation of head-twitch.

The results of the present investigation demonstrated that signs of head-twitch were not induced solely by raphe nuclei lesions and that hallucinogens could produce head-twitch even in raphe lesioned rats. Therefore, the mechanism of hallucinogen-induced head-twitch does not appear to involve an action of 5-HT cell bodies.

Freedman *et al.* [9] reported that LSD increased brain 5-HT and decreased 5-HIAA, while mescaline and DOM increased both 5-HT and 5-HIAA. In addition, the dynamics of hallucinogen-induced changes in 5-HT have been reported to differ depending on the region of the brain examined [5,23]. Therefore, hallucinogens which produced head-twitch do not necessarily cause similar changes in brain 5-HT dynamics. Accordingly, it is highly unlikely that head-twitch can be explained in terms of a secondary action mediated by endogenous 5-HT in the nerve terminal. This is supported by the fact that hallucinogen-induced head-twitch was not inhibited by PCPA treatment and raphe lesions, which produce significant decreases in brain 5-HT concentration [13,17]. Hallucinogen-induced head-twitch was suppressed by the 5-HT receptor blocker methysergide. This implies that head-twitch is mediated by an action of hallucinogens as 5-HT receptor agonists. The increased incidence of head-twitch evoked by raphe lesions or PCPA treatment may be attributed to 5-HT receptor supersensitivity. It is of extreme interest that head-twitch was increased only by m-R lesion and not by d-R lesion. This finding suggests that in the midbrain raphe, the region controlled by ascending 5-HT pathways originating in the m-R serves as an important site of action in the production of hallucinogen-induced head-twitch.

In the present investigation, $\Delta^9$-THC, possessing potent hallucinogenic activity, did not induce head-twitch. Although hallucinogenic activity has been reported to be correlated with the manifestation of head-twitch [6], we would like to point out that this phenomenon is not invariably induced by all hallucinogens.

L-5-HTP-induced head-twitch was significantly inhibited by all three types of raphe lesions. This may be ascribed to a 5-hydroxytryptophan (5-HTP) decarboxylase deficit arising from the destruction of 5-HT cell bodies [15], thereby impeding the conversion of 5-HTP to 5-HT.

DOM-induced backward locomotion was reversed by treatment with methysergide. A tendency toward reversal was similarly produced by m-R and dm-R lesions. In this respect, backward locomotion is apparently mediated by a mechanism distinct from that eliciting head-twitch. However, unlike the results obtained with raphe lesions, DOM-induced backward locomotion was not suppressed by PCPA treatment, known to markedly reduce brain 5-HT levels by inhibiting tryptophan hydroxylase [13]. Therefore, it seems unlikely that the inhibition of DOM-induced backward locomotion results from a decrease in 5-HT neural activity. On the other hand, locomotor activity was remarkably increased by m-R or dm-R lesions, but was not changed by either d-R lesion or PCPA treatment [12, 17, 25]. The conversion of DOM-induced backward locomotion to forward locomotion may simply be due to marked hyperactivity. Rearing, used as an another index of exploratory behavior, was inhibited by DOM, but this DOM-induced inhibition of rearing was not antagonized by any type of raphe lesion. In this respect, the effect of methysergide differed from those of raphe lesion. methysegide antagonized not only backward locomotion but also inhibition of rearing induced by DOM. This fact also indicates that the disappearance of DOM-induced backward locomotion due to raphe lesions was not caused by antagonizing the action of DOM, but rather resulted from a behavioral shift elicited by lesion induced hyperactivity.

## ACKNOWLEDGEMENTS

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