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Effects of Drugs on Hyperactivity and Aggression Induced by Raphe Lesions in Rats

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YAMAMOTO, T. AND S. UEKI. *Effects of drugs on hyperactivity and aggression induced by raphe lesions in rats.* PHARMAC. BIOCHEM. BEHAV. 9(6) 821–826, 1978.—Midbrain raphe lesions in rats induce hyperactivity and aggressive behavior including muricide. Hyperactivity in raphe lesioned rats (raphe rats) was significantly suppressed by α-methyl-p-tyrosine (α-MT), tetrabenazine and neuroleptics such as chlorpromazine and haloperidol, but was reduced only with large doses of L-5-hydroxytryptophan (L-5-HTP). These results seem to suggest that hyperactivity in raphe rats is resulted from the activation of catecholaminergic system which is secondary to reduced serotonergic function. On the other hand, muricide in raphe rats was markedly inhibited by L-5-HTP, but was not suppressed by α-MT at doses which markedly reduced hyperactivity in raphe rats. The reduction of serotonergic function, therefore, seems to be directly attributable to muricide in raphe rats, indicating that the neural mechanism for inducing muricide is distinct from that for hyperactivity in raphe rats. In addition, muricide in raphe rats was different from that induced by olfactory bulbectomy with respect to the effects of antidepressants, and it would also be useful as a new model for evaluating the effect of antidepressants.

Raphe lesions Hyperactivity Muricide L-5-hydroxytryptophan Antidepressants

LESIONS of midbrain raphe nuclei markedly reduce serotonin (5-HT) levels in various brain regions [8, 10, 16]. The authors have previously reported that: (1) isolated housing commenced immediately after raphe nuclei lesions induced aggressive behavior including muricide; and (2) the pattern of this aggression distinctly differed from that evoked by septal lesions or olfactory bulbectomy [29]. Although muricide may occur at a low incidence spontaneously [11], it may also be precipitated by long-term isolation [6], local brain lesion [17,26], and specific types of drugs [22,25]. It was reported that antidepressants, stimulants and certain kinds of antihistamines selectively inhibited muricide when given in doses not eliciting marked behavioral changes [9]. Muricide has since been employed as a screening method for antidepressants. It is extremely interesting to know whether or not muricide in rats subjected to raphe nuclei lesions (raphe rats) is similarly inhibited by antidepressants. Furthermore, it has also been shown that raphe rats exhibit a marked increase in locomotor activity [27,28]. It remains unclear whether these two behavioral changes (aggression and hyperactivity) evoked by raphe lesions arise solely due to a decrease in cerebral 5-HT and if both phenomena are manifested via the same neural mechanism.

This study was therefore designed in an attempt to elucidate the mechanism by which the above behavioral alterations are caused by studying the effects of various drugs on aggression and hyperactivity in the raphe rat. Muricide induced by raphe lesions was contrasted with that caused by olfactory bulbectomy in an effort to investigate a difference in drug effect. In conjunction with these experiments, the utility of raphe rats in the evaluation of psychotropic drugs was assessed.

METHOD

Animals

Male Wistar King A rats (body weight 150–200 g at surgery) obtained from the Kyushu University Institute of Laboratory Animals were used. The rats were maintained under standardized conditions of temperature (22 ± 1°C) and light (7:00 a.m.–7:00 p.m.) throughout the experiment.

Surgical Procedure

The animals were anesthetized with sodium pentobarbital 40 mg/kg IP and placed on a stereotaxic instrument. Lesions of midbrain raphe nuclei were carried out by inserting an insulated, stainless steel wire, monopolar electrode of 0.4 mm in dia. (the tip of which has been cut from both sides), according to the rat brain atlas of König and Klippel [13] and applying a direct current of 3 mA for 15 sec. Either the medial raphe (frontal plane [F]: 0.16, saggital plane [S]: 0, horizontal plane [H]: –2.5) alone (m-R) or both the dorsal (F: 0.16, S: 0, H: 1.0) and medial raphe (dm-R) were lesioned.

Olfactory bulbectomy was performed by opening an approximately 1 mm hole in the skull and removing the olfactory bulbs bilaterally by suction (O.B. rats).

Measurement of Locomotor Activity

The locomotor activity of m-R rats was measured for 1 hr

period by means of a photocell activity cage consisting of a circular floor with a dia. of 48.5 cm enclosed by a wall of 26 cm in height. Only rats displaying activity of at least 900 counts on Day 6 after m-R lesions were selected for the experiments on the following day. The incidence of such rats was approximately 80% of the animals subjected to medial raphe lesions.

Measurement of Aggressive Behavior

On Day 3 and Day 7 after dm-R lesions or on Day 5 and Day 7 after olfactory bulbectomy, muricide tests were conducted for a 15 min period. Only rats which exhibited muricide on both of these days were selected for use in the pharmacological experiments, commenced on Day 7 after surgery. The incidence of these rats was approximately 70% of the dm-R rats and approximately 80% of O.B. rats.

Aggressive behavior was measured as described previously [29]. In addition to muricide, the below-mentioned hyperemotional responses to stimuli (1)–(4) were scored as one of five levels (score 0–4). For response (5), the occurrence of vocalization was determined on an all-or-none basis. (1) Startle response to a standard quantity of air blown on the back; (2) Attack response to a rod presented in front of the snout; (3) Flight response to pinching the tail with a forceps; (4) Struggle response to capturing with a gloved hand; (5) Vocalization (squeal response) upon being caught.

Drugs

The drugs used in this study were: L-5-hydroxytryptophan (L-5-HTP), p-chlorophenylalanine (PCPA), methysergide hydrogenmaleinate, tetrabenazine hydrochloride, α-methyl-p-tyrosine (α-MT), phenoxybenzamine hydrochloride, apomorphine hydrochloride, L-dihydroxyphenylalanine (L-DOPA), methamphetamine hydrochloride, physostigmine sulfate, atropine sulfate, chlorpromazine hydrochloride, haloperidol hydrochloride, imipramine hydrochloride, chloroimipramine hydrochloride, and desipramine hydrochloride. PCPA and α-MT were suspended in 0.5% carboxymethylcellulose. The other drugs were dissolved in physiological saline. All drugs were administered in a volume of 0.2 ml/100 g body weight. α-MT was administered p.o.; all other drugs were injected IP.

Locomotor activity was measured over a 1 hr period commencing at the following times after treatment: 15 min in the methysergide and apomorphine groups; 30 min in the L-5-HTP, L-DOPA and methamphetamine groups; 2 hr in the tetrabenazine group; 4 hr in the α-MT group; 48 hr in the PCPA group; and 1 hr in all other groups. Aggression tests were performed at 4 hr after treatment in the α-MT group and 1 hr after treatment in all other groups.

The rats employed in these pharmacological tests were reused after a 5–7 day rest period. However, tests were not repeated in rats receiving α-MT, tetrabenazine and PCPA due to their property of inhibiting cerebral amine synthesis.

RESULTS

Activity Experiments

Locomotor activity during a 1 hr period in intact rats (n=8) was recorded at 646.3 ± 63.5 counts (mean ± SE). On Day 6 after surgery, m-R rats (n=10) showed a remarkable degree of hyperactivity (1884.9 ± 270.3 counts). On the following day, activity decreased somewhat to 1410 ± 104.1 counter. However, even this activity in m-R rats remained significantly higher level as compared with that in intact rats. This activity level on Day 7 was used as control for pharmacological investigations.

Hyperactivity in m-R rats was not significantly altered by 10 mg/kg (n=10), 50 mg/kg (n=10) or 100 mg/kg (n=9) of L-5-HTP (Fig. 1). However, the maximum dose of 200 mg/kg (n=7) remarkably suppressed activity to 364 ± 142.8 counts (two-tailed Mann-Whitney U test, $p<0.002$). Administration of 100 mg/kg of PCPA (n=6), an inhibitor of 5-HT synthesis, induced a further increase in hyperactivity in m-R rats, but the degree was not significant. A dose of 300 mg/kg of PCPA (n=4) did not produce any marked activity-related changes and hyperactivity was even inhibited in some m-R rats. The 5-HT receptor blocker methysergide, 5 mg/kg, did not appreciably influence activity in m-R rats (n=8). In contrast, hyperactivity in m-R rats was remarkably suppressed by tetrabenazine, 40 mg/kg (n=8), and α-MT, 200 mg/kg (n=6) (both $p<0.002$), as illustrated in Fig. 2. Similarly, hyperactivity was significantly inhibited by administration of chlorpromazine 5 mg/kg (n=5), and haloperidol, 0.5 mg/kg (n=8) (both $p<0.002$). Phenoxybenzamine, 10 mg/kg (n=5), suppressed m-R rat hyperactivity by about 50%, but this degree was not significant.

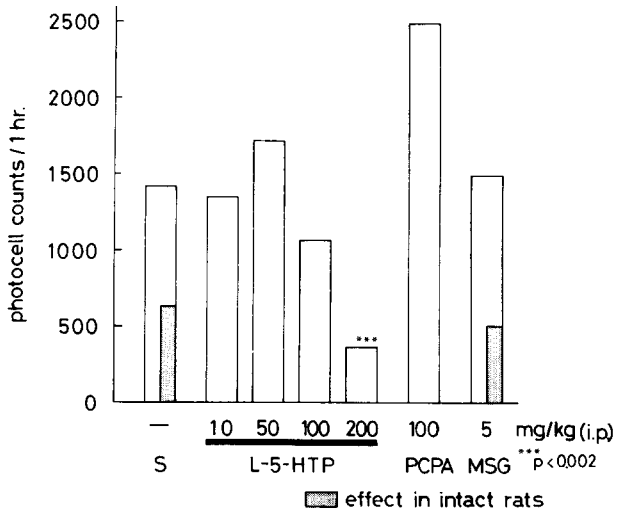

FIG. 1. Effects of serotonergic drugs on hyperactivity induced by lesions of the medial raphe nuclei in rats. S: saline, L-5-HTP: L-5-hydroxytryptophan, PCPA: p-chlorophenylalanine, MSG: methysergide.

Intact rats (n=7) administered 10 mg/kg of apomorphine exhibited a significant increase in activity to 1681.0 ± 233.9 counts ($p<0.002$) in comparison to control level in the intact rat. However, equivalent doses of apomorphine in m-R rats did not further potentiated hyperactivity. L-DOPA at a dose of 100 mg/kg similarly did not affect hyperactivity in m-R rats. Administration of methamphetamine 1 mg/kg to intact rats (n=6) increased activity to 1685 ± 236.9 counts, approximately three times that of control. When an equivalent dose of methamphetamine was given to m-R rats (n=7), hyperactivity increased by four-fold to 5537.1 ± 405.4 counts. Physostigmine 0.5 mg/kg did not appreciably alter hyperactivity in m-R rats. However, atropine 10 mg/kg markedly

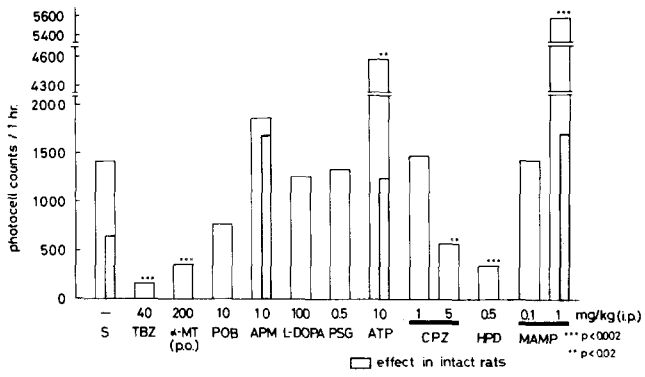

FIG. 2. Effects of various drugs on hyperactivity of the rat with medial raphe lesions. S: saline, TBZ: tetrabenazine, α-MT: α-methyl-p-tyrosine, POB: phenoxybenzamine, APM: apomorphine, L-DOPA: L-dihydroxyphenylalanine, PSG: physostigmine, ATP: atropine, CPZ: chlorpromazine, HPD: haloperidol, MAMP: methamphetamine.

increased hyperactivity in m-R rats (n=7) by about threefold to 2095.7 ± 729.1 counts. Intact rats given equivalent doses of atropine only showed a mild tendency to increase locomotor activity with a count of 1248.0 ± 287.8 ($p<0.10$).

On the other hand, hyperactivity in dm-R rats (n=7) was recorded at 2896.9 ± 555.1 counts. This activity was even more remarkable than in m-R rats. This high level of hyperactivity was also significantly suppressed by administration of α-MT 200 mg/kg (n=7). L-5-HTP at a dose of 100 mg/kg (n=7) attenuated activity to 1842.9 ± 373.5 counts, but this was not significantly different from control ($p<0.10$).

Aggressive Behavior Experiments

Muricide persisted without any signs of abatement in dm-R and O.B. rats even after repeating the test. In addition, it was noticed that some of dm-R rats not only killed a mouse, but also bit repeatedly and even ate body parts of it within test period of 15 min [29]. Such a mouse-eating behavior was scarcely observed in O.B. rats. In both types of rats, the startle response score decreased when the test was repeated. Marked increases in the attack response score of dm-R rats were not observed at any time after surgery. The flight and struggle response scores in dm-R rats were 3.1 ± 0.2 (mean ± SE) and 2.0 ± 0.2, respectively. Similarly, the attack, flight and struggle response scores in O.B. rats were 3.1 ± 0.1, 3.1 ± 0.1 and 3.0 ± 0.2, respectively. Furthermore, the squeal response was positive in all dm-R and O.B. rats.

Effect of L-5-HTP

Muricide in dm-R rats was dose-dependently inhibited by L-5-HTP (Table 1). L-5-HTP provided a significant effect in doses of ≥50 mg/kg, and muricide was suppressed in all rats receiving 200 mg/kg (Fisher's exact probability test: both $p<0.005$). ED50 of muricide inhibition was 25.6 (3.1–224.5) mg/kg (calculated by the method of Litchfield and Wilcoxon). Even in rats in which muricide was not suppressed by L-5-HTP, mouse-eating behavior was inhibited. The flight response was significantly suppressed by L-5-HTP only at a dose of 100 mg/kg, resulting in a score of 2.4 ± 0.2 (mean ± SE) ($p<0.05$, two-tailed Mann-Whitney U test). The struggle response score was also markedly suppressed by L-5-HTP 100 mg/kg (score: 2.0 ± 0.2, $p<0.05$) and 200 mg/kg (score: 1.5 ± 0.2, $p<0.05$). The squeal response was suppressed by 66.7% only at the maximal dose of 200 mg/kg.

Muricide in O.B. rats was also dose-dependently suppressed by L-5-HTP. However, significant levels of suppression were only obtained at a dose of 200 mg/kg ($p<0.01$). ED50 of muricide inhibition was 125.5 (32.0–272.0) mg/kg, equivalent to about five times the dose required in dm-R rats. The marked attack response in O.B. rats was significantly suppressed by administration of 100 mg/kg (score 1.9 ± 0.2, $p<0.002$) and 200 mg/kg (score 1.4 ± 0.3, $p<0.002$) of L-5-HTP. In addition, significant inhibition of flight response was produced by administration of 200 mg/kg (score 2.3 ± 0.3, $p<0.05$). The struggle response was significantly suppressed at a dose of 100 mg/kg (score 2.0 ± 0.4, $p<0.05$) and was similarly suppressed at 200 mg/kg (score 2.2 ± 0.4), though not significant ($p<0.10$). The squeal response was 62.5% suppressed only at the maximal dose of 200 mg/kg.

Effect of Imipramine

Muricide in dm-R rats was significantly suppressed by administration of ≥10 mg/kg of imipramine. The effect of imipramine was dose-dependent (Table 2). ED50 was calculated to be 17.8 (4.1–41.0) mg/kg. The struggle response tended to be inhibited by 5 mg/kg of imipramine ($p<0.10$).

TABLE 1

THE EFFECT OF L-5-HYDROXYTRYPTOPHAN ON MURICIDE IN DM-R RATS AND O.B. RATS

treatment	mg/kg (IP)	incidence of suppressed muricide dm-R rat (%)	O.B. rat (%)
L-5-HTP	10	3/8 (37.5)	—
	50	6/9 (66.7)*	2/8 (25.0)
	100	8/12 (66.7)*	3/7 (42.9)
	200	9/9 (100.0)*	5/8 (62.5)†
ED50 (95% confidence limits)		25.6 (3.1–224.5)	122.5 (32.0–272.0)

* $p<0.005$, † $p<0.01$

Significantly different from the pre-drug value in the same group by Fisher's exact probability test.

TABLE 2
THE EFFECT OF IMIPRAMINE ON MURICIDE IN DM-R RATS AND O.B. RATS

treatment	mg/kg (IP)	incidence of suppressed muricide dm-R rat (%)	O.B. rat (%)
imipramine	5	2/9 (22.2)	3/10 (30.0)
	10	4/10 (40.0)*	4/8 (50.0)*
	20	6/9 (66.6)‡	5/8 (62.5)†
ED50 (95% confidence limits)		17.8 (4.1–41.0)	11.0 (4.3–28.1)

* $p<0.05$, † $p<0.01$, ‡ $p<0.005$

This inhibitory effect was not augmented by increases in dosage. In fact, some rats conversely showed higher scores than control following administration of larger doses (10–20 mg/kg). The effect of imipramine on the flight response was similar. The squeal response was suppressed by 44.4% at a dose of 5 mg/kg, but enhancement of effect was not achieved by increasing the dosage.

Muricide in O.B. rats was likewise suppressed in a dose-dependent manner. ED50 for inhibition of muricide was 11.0 (4.3–28.1) mg/kg (Table 2). Significant suppression of the attack response in O.B. rats was produced by 5 mg/kg (score 1.8 ± 0.2), 10 mg/kg (score 1.6 ± 0.2) and 20 mg/kg (score 1.7 ± 0.2) (all $p<0.002$). The flight response was inhibited by doses of 10 mg/kg (score 2.2 ± 0.2, $p<0.002$) and 20 mg/kg (score 2.2 ± 0.2, $p<0.02$). In contrast, the struggle response score increased proportionally to dosage, attaining a significantly elevated score of 3.8 ± 0.2 at a dose of 20 mg/kg ($p<0.002$). The squeal response was not appreciably affected by any of the doses of imipramine administered.

Effect of Chlorimipramine

Chlorimipramine significantly suppressed muricide in dm-R rats in doses of ≥10 mg/kg ($p<0.005$). Its ED50 was 10.0 (4.5 ± 22.4) mg/kg (Table 3). The flight response was also inhibited by chlorimipramine; the score was significantly reduced to 1.7 ± 0.2 by administration of 10 mg/kg ($p<0.02$). However, chlorimipramine did not produce marked change in the squeal response in raphe rats.

Muricide in O.B. rats was likewise suppressed by chlorimipramine. Its ED50 was 27.5 (16.7–45.4) mg/kg, equivalent to about three times the dose necessary for inhibition of muricide in dm-R rats (Table 3). The struggle response was appreciably suppressed by 10 mg/kg (score 1.3 ± 0.1), 20 mg/kg (score 1.5 ± 0.1) and 30 mg/kg (score 1.3 ± 0.1) of chlorimipramine (all $p<0.002$). There were no marked effects on any other hyperemotional responses.

Effect of Desipramine

Muricide in dm-R rats was suppressed dose-dependently by desipramine. Its ED50 was 25.1 (14.4–43.9) mg/kg (Table 4). Although the flight response tended to be inhibited by 10 mg/kg of desipramine ($p<0.10$), the intensity of this effect was not heightened by further increases in dosage. The struggle and squeal responses were similarly not appreciably affected by desipramine.

In sharp contrast, desipramine, strongly suppressed muricide in O.B. rats, with an ED50 of 3.3 (1.8–5.9) mg/kg. The inhibitory effect of desipramine in O.B. rats was thus about 8 times more potent than in dm-R rats (Table 4). No appreciable inhibitory effect was observed, however, on the other hyperemotional responses in O.B. rats. Conversely, the flight response was significantly augmented by administration of 1.5 mg/kg (score 3.6 ± 0.3, $p<0.05$).

Effect of Atropine

Muricide in dm-R rats was also suppressed by atropine, showing an ED50 of 14.1 (7.1–282.2) mg/kg (Table 5). The flight response was significant suppressed by atropine 10 mg/kg (score 1.9 ± 0.2, $p<0.001$). However, this suppressive effect was not dose-dependent. The struggle response was significantly attenuated by doses of 5 mg/kg (score 2.3 ± 0.2, $p<0.002$) and 10 mg/kg (score 2.3 ± 0.3, $p<0.05$). On the other hand, the maximal dose of 20 mg/kg conversely produced a significant increase in score of the response (score 3.6 ± 0.2, $p<0.05$). There were no appreciable changes in the squeal response.

Muricide in O.B. rats was also suppressed by atropine, but this effect was not dose-dependent. Its ED50 was 12.0 (6.7–21.6) mg/kg (Table 5). The attack response was significantly attenuated by doses of 10 mg/kg (score 2.4 ± 0.2, $p<0.02$) and 20 mg/kg (score 2.3 ± 0.2, $p<0.002$). The flight response was significantly inhibited by doses of 5 mg/kg (score 1.7 ± 0.2, $p<0.002$) and 10 mg/kg (score 2.5 ± 0.2, $p<0.02$). However, at a dose of 20 mg/kg, some O.B. rats conversely showed an increase in the score of flight response. The struggle and squeal responses of O.B. rats were not significantly changed at any doses of atropine.

TABLE 3
THE EFFECT OF CHLORIMIPRAMINE ON MURICIDE IN DM-R RATS AND O.B. RATS

treatment	(mg/kg IP)	incidence of suppressed muricide dm-R rat (%)	O.B. rat (%)
chlorimipramine	5	2/9 (22.0)	1/10 (10.0)
	10	7/10 (70.0)‡	2/10 (20.0)
	20	5/10 (50.0)*	3/10 (30.0)
	30		6/10 (60.0)†
ED50 (95% confidence limits)		10.0 (4.5–224)	27.5 (16.7–45.5)

* $p<0.05$, † $p<0.01$, ‡ $p<0.005$

TABLE 4

THE EFFECT OF DESIPRAMINE ON MURICIDE IN DM-R RATS AND O.B. RATS

treatment	mg/kg (IP)	incidence of suppressed muricide dm-R rat (%)	O.B. rat (%)
desipramine	3	—	5/10 (50.0)*
	5	—	6/9 (66.7)†
	10	2/7 (28.6)	—
	20	5/15 (33.3)	8/10 (80.0)‡
	40	7/10 (70.0)†	—
ED50 (95% confidence limits)		25.1 (14.4-43.9)	3.3 (1.8-5.9)

* $p<0.05$, † $p<0.01$, ‡ $p<0.005$

TABLE 5

THE EFFECT OF ATROPINE ON MURICIDE IN DM-R RATS AND O.B. RATS

treatment	mg/kg (IP)	incidence of suppressed muricide dm-R rat (%)	O.B. rat (%)
atropine	5	4/10 (33.3)	1/7 (14.3)
	10	3/10 (30.0)	10/15 (66.7)‡
	20	6/9 (66.7)‡	7/12 (58.3)‡
ED50 (95% confidence limits)		14.1 (7.1-28.2)	12.0 (6.7-21.6)

‡$p<0.005$

Effect of α-MT

Four hours after the administration of α-MT 200 mg/kg, muricide was suppressed only in 2 of 10 dm-R rats. Other hyperemotional responses were similarly not appreciably affected by α-MT administration.

α-MT did not suppress muricide in any O.B. rats. The flight, struggle and squeal responses were likewise not appreciably affected. Only the attack response was significantly inhibited to a score of 2.2 ± 0.4 ($p<0.05$).

DISCUSSION

In this study, hyperactivity induced by midbrain raphe lesions was suppressed by L-5-HTP and, conversely, potentiated by PCPA 100 mg/kg. However, since (1) high doses of L-5-HTP (200 mg/kg) were required to achieve suppression and (2) high doses of PCPA (300 mg/kg) conversely inhibited hyperactivity, it seems difficult to attribute hyperactivity in raphe rats merely to a decrease in cerebral 5-HT content. Based on the recent findings that high doses of L-5-HTP markedly reduce cerebral NA content [2], suppression of hyperactivity in raphe rat by high doses of L-5-HTP may also bear some relationship with diminished adrenergic activity in the brain. In fact, hyperactivity in raphe rats was also markedly inhibited by administration of α-MT and chlorpromazine in the present study. Furthermore, remarkable inhibition of hyperactivity was likewise obtained with tetrabenazine, known to cause depletion of both NA and 5-HT. Judging from these findings, it is suggested that hyperactivity in the raphe rat is due to activation of the catecholaminergic system, resulted from suppression of the serotonergic function. This hypothesis is supported by the findings of Kostowski *et al.* [14] that raphe lesions markedly increase NA turnover rate. Moreover, since PCPA 316 mg/kg causes a decrease in the content of cerebral NA in addition to 5-HT [12], hyperactivity in the raphe rat is conversely postulated to decrease. On the other hand, based on the observation that raphe lesions markedly reduce the ACh content of the forebrain [20]. Anticholinergic agents will increase spontaneous locomotor activity [18,24] and, conversely, cholinergic agents reduce it [21]. In this point, hyperactivity in raphe rats appears to be linked to decrease in ACh. However, this is unlikely because hyperactivity was not suppressed by physostigmine. Therefore, reduced ACh levels apparently seem to be a secondary effect of hyperactivity. The participation of a cholinergic mechanism on hyperactivity induced by raphe lesions appears to be minimal.

The dopamine receptor stimulant apomorphine accentuated locomotor activity in the intact rat similar to methamphetamine. However, it did not have an appreciable effect on activity in the raphe rat, unlike methamphetamine. Therefore, among the catecholamines, NA seems to play a more important role than DA in the increase of locomotor activity in the raphe rat.

Muricide in raphe rats was inhibited by low doses of L-5-HTP without suppressing the other hyperemotionality and ataxia, and was not suppressed by α-MT. Accordingly, muricide in the raphe rats is considered to be directly evoked by a decrease in cerebral 5-HT content and thereby be mediated by a neural mechanism distinct from that involved in the manifestation of hyperactivity. Although muricide was suppressed by L-5-HTP even in O.B. rats, the dose required for suppression was approximately 5 times that capable of inhibiting muricide in raphe rats. Muricide of spontaneous killer rats is similarly inhibited by L-5-HTP [15], but doses higher than those required for inhibition of muricide in the raphe rats are necessary. Although muricide can be induced by various methods, the underlying mechanism leading to muricide appears to be qualitatively different depending on the method of induction. This was also made evident from the difference in the effects of desipramine and chlorimipramine. Namely, chlorimipramine, more potently inhibiting 5-HT uptake rather than NA [3,5], exerted a greater degree of inhibition on muricide in the raphe rats than in the O.B. rats. Conversely, desipramine, more potently inhibiting NA uptake rather than 5-HT [4], inhibited muricide to a greater extent in the O.B. rats. These findings are of extreme interest when considered in conjunction with the report of Carlsson *et al.* [4] that NA is principally involved in the psychomotor activation and increase in drive in the clinically depressed state, whereas 5-HT plays the main role in the brightening of mood, judging from the differences in amine uptake inhibition of antidepressants. Employment of different types of experimentally-induced muricide may therefore potentially provide a method capable of accurately predicting the clinical effects of antidepressants to the extent of being able to pinpoint the above specific actions in man. In this sense, muricide in the raphe rats is expected to serve as a new experimental model capable of aiding in the evaluation of antidepressant drugs. Hyperemotionality except muricide, especially defensive aggression in dm-R rats and O.B. rats was augmented by antidepressants even when given in doses which suppressed muricide. This demonstrates that the mechanism eliciting muricide is distinct from that involved in other forms of hyperemotionality, particu-

larly defensive aggression. Such an effect of antidepressants was also observed by Nurimoto *et al.* [19] in the rats with lesions in the olfactory bulbs and olfactory tubercles. Furthermore, higher doses of antidepressants were necessary to suppress defensive aggression in septal rats as compared with the dosage which inhibited muricide induced by long-term isolation in rats [23]. In addition, it was shown that doses of antidepressants capable of inhibiting predatory attack did not suppress the defensive-hissing response induced by hypothalamic stimulation in cats and the rank order of potency for this inhibition was similar to the rank of potency for blocking ^{3}H-5-HT uptake (chlorimipramine > imipramine > desipramine). These reports support the conclusion of this study.

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