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Pharmacological Studies on Aggressive Behavior Induced by Lesions of the Nucleus Accumbens Septi in Rats

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Abstract □ Bilateral lesion of nucleus accumbens septi (NAB), one of the mesolimbic nuclei, resulted in hyperirritability and muricide including mouse eating behavior in rats.

The effects of various drugs on hyperirritability and muricide induced by NAB lesion were investigated in rats.

Hyperirritability in NAB rats was significantly reduced by L-DOPA, L-5-HTP, major and minor tranquilizers but not reduced by MA, ATP and imipramine-like antidepressants.

On the other hand, muricide in NAB rats was significantly suppressed by L-DOPA, L-5-HTP, major and minor tranquilizers, furthermore, selectively suppressed by MA, ATP and antidepressants.

These results suggested that the neural mechanism for inducing muricide is distinct from for hyperirritability in NAB rats, and that muricide in NAB rats is resulted from the increasing of cholinergic activity and reduction of dopaminergic and serotonergic activity.

Keywords □ Nucleus accumbens septi, Muricide, Hyperirritability, Antidepressants.

Nucleus accumbens septi (NAB) has been considered to be an important site of control for motionality because the NAB has massive fiber onnection with related areas of aggression such as eptal area, preoptic area and lateral hypothlamus (1, 2, 3).

It might therefore be proposed that bilateral sions of the NAB would cause changes in notionality and it was reported that bilateral imulations of the NAB cause changes in notionality in the cat (4). We also have previsly reported that bilateral lesions of NAB result- in aggressive behavior including muricide and ouse-eating behavior (5, 6).

It is well known that aggression induced by vari- s method. *i.e.*, long-term isolation (7, 8), local ain lesions (9, 10, 11), pharmacological treatnt (12) and painful stimulation (13) in laboray animals. These aggression have their respece characteristics and advantages in their usefulss for drug evaluation. Especially, muricide has en employed as a screening method for antidessants since it was selectively inhibited by antidepressants at nondebilitating doses or below neuro-toxicity.

The present study, therefore, was planned to examine the effects of drugs on aggression of NAB rat, in the hope of evaluating the relevance of utilizing this model of aggression for drug screening.

EXPERIMENTAL METHODS

Animals

The animals employed were male Wister King A rats, weighing 200-300g at the time of surgery, supplied by Kyushu University Institute of Laboratory Animals.

These animals were maintained at a room temperature of 22±1℃ and were given food and water ad libitum throughout the experimental period. Illumination was provided by an automatically controlled 12-hour light/dark cycle (lights on at 07 : 00, off at 19 : 00).

Surgical procedure

The animals were anesthetized with sodium

pentobarbital (40mg/kg i.p.) and the head was fixed in a stereotaxic instrument. Monopolar electrodes composed of stainless steel wire of 0.4mm in a diameter insulated except for the last 0.5mm of the tips were inserted into the NAB. Lesions of both site of NAB, *i.e.*, caudal site of NAB [anterior (A);8.6, lateral (L);1.5, ventral (V);-1.4] and rostral site of NAB [(A):9.6, (L);1.0, (V);-0.9] were made according to König and Klippel's brain atlas (14) in the rat, simultaneously. Lesions were made by applying DC of 3.0mA for 15 second. Sham operated rats underwent the same surgical procedure except for applying DC.

After the surgery, each animal was given an intramuscular injection of procaine penicillin G.

Testing procedure

The rats were tested for mouse-killing response before the surgery. Only those rats with not killed mice within 15 minutes after presentation were used. After the surgical procedure, the rats were housed in individual cages (20×17×17) with wire -mesh walls and were tested for their mouse-killing behavior 2, 4 and 7 days after lesioning. Only those rats which exhibited muricide on consecutive 3 test days were used for drug experiment.

The three responses of these rats to given stimuli such as presentation of a rod (attack), air blowing on the back (startle) and handling (struggle), were scored in each item, ranging from 0 and 4, according to the same rating scale and muricide was tested the same method as employed in the previous study (6).

Drugs

The drugs used in this experiment were; L-dihydroxy phenylalanine (L-DOPA). Ro 4-4602, L -5-hydroxytryptophan (L-5-HTP), atropine sulfate (ATP), chlorpromazine hydrochloride (CPZ), haloperidol (HPD), diazepam (DZP), nitrazepam (NZP), imipramine hydrochloride (IMP), nomifensine (NOF), clomipramine hydrochloride (CIP), desmethylimipramine hydrochloride (DMI), maprotyline (MPT), methamphetamine hydrochloride (MA), L-DOPA, L-5-HTP, DZP, NZP and NOF were suspended in 0.5% carboxymethyl cellulose and MA was dissolved in physiolgical saline. The others were dissolved in distilling water. All drugs were administered in a volume of 0.1ml/100g body weight and were injected intraperitoneally.

Histology and Statistical analysis

After completion of all experiments, the animals were anesthetized with ether, and their brains were perfused with 10% formalin through the carotid arteries.

The brain was removed, fixed and 50-60μ frozen sections were prepared and stained with cresyl violet. The site and extent of the brain lesions were verified histologically.

The results were statistically analyzed from using Fisher's exact probability test for the incidence of muricide and two-tailed Mann-Whitney U test for the emotional responses.

RESULTS

Effect of L-DOPA

Muricide in NAB rats was does-dependently suppressed by L-DOPA (Fig.1.). L-DOPA was injected after 30 min followed Ro 4-4602 50mg/kg. Rats showed muscle relaxation by Ro 4-4602 but not inhibited in muricide. L-DOPA provided a significant effect in does of more of 10mg/kg. ED50 of muricide inhibition was 12.0 (3.4-42.6) mg/kg. The startle response score was not significantly suppressed by L-DOPA and the attack response score was significantly suppressed only at a dose of 30mg/kg ($p<0.005$). The struggle response score was markedly suppressed by L -DOPA 30mg/kg ($p<0.005$), and 50mg/kg ($p<0.05$) (Fig.1).

Effect of L-5-HTP

Muricide in NAB rats was dos -dependently suppressed by L-5-HTP (Fig.2). L-5-HTP provided a significant effect in dose of 50mg/kg ($p<0.05$) and 100mg/kg ($p<0.005$). ED50 of muricide inhibition was 50.0 (37.6-66.5)mg/kg. The startle reponse score was significantly suppressed by L-5-HTP 20mg/kg (score;1.7±0.4, mean ±S.D.) and 100mg/kg (score;1.4±0.2, $p<0.05$). The attack response score was significantly inhibited in all rats by L-5-HTP. The struggle response score was markedly suppressed by L -5-HTP 50mg/kg (score;2.0±0.5, $p<0.05$) and 100mg/kg (score;1.7±0.6, $p<0.005$) (Fig.2).

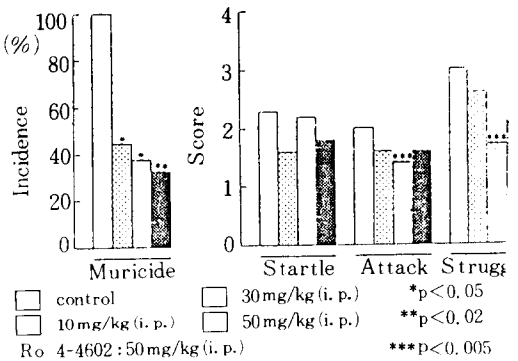
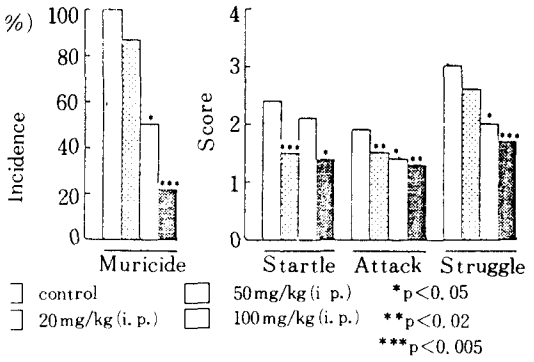


Fig.1. Effect of L-DOPA on aggressive behavior in nucleus accumbens septi lesione rats.



ig.2. **Effect of L-5-HTP on aggressive behavior in nucleus accumbens septi lesioned rats.**

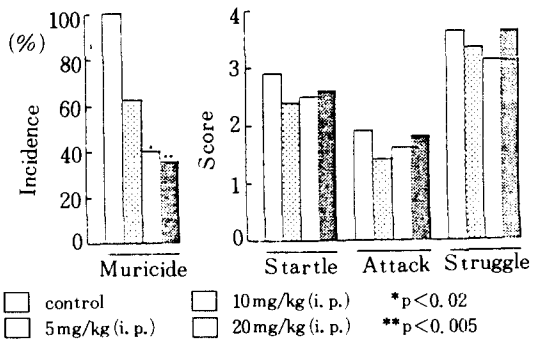


Fig.3. Effect of atropine on aggressive behavior in nucleus accumbens septi lesioned rats.

Effect of ATP

Muricide in NAB rats was does-dependently uppressed by ATP (Fig.3). ATP provided a sigificant effect in does of more over 10mg/kg. :D50 of muricide inhibition was 9.4 (3.5-25.2) ıg/kg. However, startle, attact and struggle esponse score were not effected in all does of ATP.

ffects of major tranquilizers

Muricide in NAB rats was dose-dependently hibited by CPZ (Table I). However, significant vels of suppression were only obtained at the aximal dose of 20mg/kg. ED50 of muricide inhition was 13.0 (7.1-23.7) mg/kg. The startle sponse score was significantly suppression by ?Z 10mg/kg and 20mg/kg (all $p<0.02$). The tack response score also significantly suppressed ' CPZ 10mg/kg and 20mg/kg (all $p<0.05$). The ruggle response score was significantly suppressed in all doses of cpz.

Muricide in NAB rats dose-dependently inhibited by HPD (Table I) and significant levels of suppression were 2mg/kg ($p<0.05$) and 5mg/kg ($p<0.005$). ED50 of muricide inhibition was 2.3(1.4-3.9) mg/kg. The startle response score was significantly suppressed by HPD 2mg/kg ($p<0.02$) and 5mg/kg ($p<0.002$). In addition, significant inhibition of the struggle score was produced in all doses of HPD.

Effects of minor tranquilizers

Muricide in NAB rats was dose-dependently inhibited by DZP (Table II). DZP showed a significant effect in doses of more of 10mg/kg. ED50 of muricide inhibition was 10.2(6.7-15.6) mg/kg. The startle response score was significantly suppressed by DZP in doses of more of 5mg/kg. The attack response score was significantly inhibited by DZP 10mg/kg and 20mg/kg (all $p<0.02$). The

able I. Effects of CPZ and HPD on aggressive behavior in nucleus accumbens septi lesioned rats.

rugs	Doses (mg/kg, i. p)	Emotional responses			
		Muricide (%)	Startle (mean±S. D)	Attack (mean±S· D)	Struggle (mean±S. D)
PZ	Control	8/8 (100. 0)	2. 3±0. 4	1. 9±0. 5	3. 4±0. 5
	5	6/8 (75. 0)	1. 9±0. 7	1. 7±0. 4	1. 6±0. 6***
	10	6/9 (66. 7)	1. 2±0. 3***	1. 3±0. 4**	1. 2±0. 3***
	20	3/9 (33. 3)***	1. 2±0. 3***	1. 2±0. 3**	1. 3±0. 6***
PD	Control	9/9 (100. 0)	2. 6±0. 6	2. 0±0. 5	3. 0±1. 0
	1	8/9 (88. 9)	2. 1±0. 7	1. 6±0. 4	1. 8±0. 8*
	2	4/9 (44. 4)*	1. 6±0. 4**	1. 3±0. 3***	1. 5±0. 6*
	5	1/9 (11. 1)***	1. 3±0. 4***	1. 1±0. 2***	1. 2±0. 4***

$p<0.05$ ** $p<0.02$ *** $p<0.005$

Table II. Effects of DZP and NZP on aggressive behavior in nucleus accumbens septi lesioned rats.

Drugs	Doses (mg/mk, i. p)	Emotional ponses			
		Muricide (%)	Startle (mean±S. D)	Attack (mean±S. D)	Struggle (mean±S. D)
DZP	Control	8/8 (100. 0)	2. 5±0. 6	2. 0±0. 3	3. 1±0. 8
	5	8/9 (88. 9)	2. 2±0. 5**	1. 6±0. 2	2. 6±0. 7
	10	3/8 (37. 5)*	1. 7±0. 7**	1. 4±0. 4**	2. 4±0. 7**
	20	2/8 (25. 0)***	1. 5±0. 5**	1. 4±0. 3**	1. 7±0. 6**
NZP	Control	8/8 (100. 0)	2. 5±0. 7	1. 7±0. 4	3. 0±0. 8
	2	6/8 (75. 0)	1. 8±0. 6	1. 2±0. 3**	1. 8±0. 6***
	5	5/8 (62. 5)	1. 4±0. 4***	1. 2±0. 3**	1. 4±0. 7***
	10	1/7 (14. 3)***	1. 3±0. 3***	1. 1±0. 2**	1. 3±0. 6***

* $p<0.05$ ** $p<0.02$ *** $p<0.005$

struggle response score was also markedly suppressed by DZP 10mg/kg and 20mg/kg (all $p<0.02$).

Muricide in NAB rats was does-dependently suppressed by NZP (Table II). However, significant levels of suppression were only obtained at a dose of 10mg/kg. ED50 of muricide inhibition was 5. 0(2. 9-8. 4)mg/kg. The startle response score in NAB rats was significantly suppressed by NZP 5mg/kg and 10mg/kg (all $p<0.005$). The attack response score was also markedly suppressed by NZP 2mg/kg, 5mg/kg and 10mg/kg (all $p<0.02$). The struggle response score was also significantly suppressed in all rats by NZP (all $p<0.005$).

Effects of antidepressants

Fig.4 and Fig.5 illustrate the effects of various antidepressants on NAB rats. Muricide in NAB rats was dose-dependently inhibited by IMP (Fig.4). ED50 muricide inhibition was 17. 5(8. 9-35. 6)mg/kg. However, the startle, attack and struggle response score were not at all significantly suppressed by IMP (Fig.5). Muricide in NAB rats was dose-dependently suppressed by NOF (Fig.4). ED50 of muricide inhibition was 4. 2(1. 6-11. 1) mg/kg. The startle response score was not inhibited by NOF. The attack response score was significantly suppressed by NOF 1mg/kg (score;1. 3±0. 3, $p<0.005$), 5mg/kg (score;1. 4±0. 2, $p<0.005$) and 10mg/kg (score;1. 3±0. 4, $p<0.005$). The struggle response score was not at all inhibited by NOF (Fig.5). Muricide in NAB rats was dose-dependently suppressed by CIP (Fig.4). ED50 of muricide inhibition was 9. 0(6. 4-12. 6)mg/kg. The startle response score was not significantly reduced at any dose by CIP. The attack response score was significantly suppressed only at a dose of

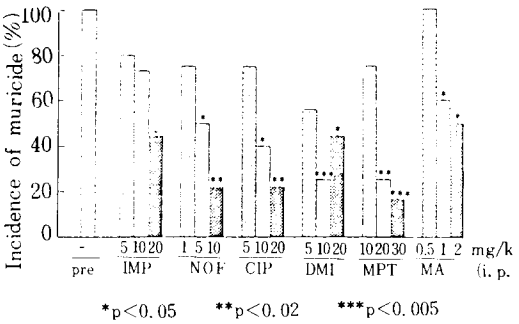


Fig.4. Effects of various antidepressants o muricide in nucleus accumbens sept lesioned rats.

5mg/kg by CIP. The struggle response score wa significantly suppressed only at the maximal dos of 20mg/kg by CIP (Fig.5). Muricide in NA rats was significantly inhibited by DMI (Fig.4) ED50 of muricide inhibition was 9. 6(3. 5-26. mg/kg. The startle response score was significant suppressed by DMI 5mg/kg (score;2. 4±0. 4, p 0. 05) and 20mg (score;2. 1±0. 5, $p<0.02$). Th attack response score was also significantly su preseed by DMI 5mg/kg (score;1. 4±0. 2, p< 05) and 20mg/kg (score;1. 4±0. 2, $p<0.02$). Th struggle response score was dose-dependently su pressed by DMI (Fig.5). However, significa levels of suppression was only obtained at a dose 20mg/kg (score;2. 3±0. 4, $p<0.02$). Muricide NAB rats was also significantly inhibited by MP (Fig.4). ED50 of muricide inhibition was 13. 8(5-22. 3)mg/kg. The startle response score was n significantly reduced at any dose of MPT.

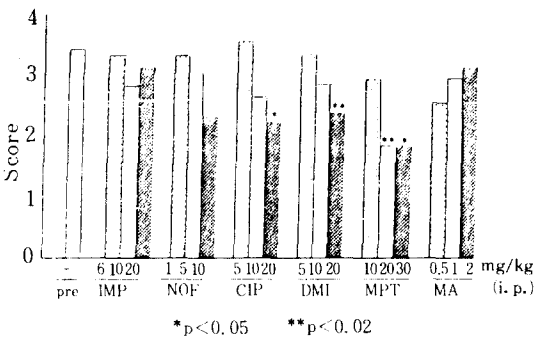


Fig.5. Effects of various antidepressants on struggle response in nucleus accumbens septi lesioned rats.

The attack response score was significantly suppressed in dose of 20mg/kg (score;1. 5±0. 1, $p<0.02$). The struggle response score was significantly suppressed in doses of 20mg/kg (score;1. 7±0. 6, $p<0.02$) and 30mg/kg (score;1. 7±0. 7, $p<0.05$) (Fig.5).

Muricide in NAB rats was dose-dependently suppressed by MA (Fig.4). ED50 of muricide inhibition was 1. 7(0. 8-3. 3)mg/kg. However, the startle, attack and struggle responses score were not significantly reduced at any doses of MA (Fig. 5).

DISCUSSION

The authors, in the previeus investigation, analyzed the aggressive behavior of the NAB-lesioned rats in comparision with that of the raphe nuclei -lesioned rats or olfactory bulbectomized rats and revealed some characteristics in aggression of the NAB-lesioned rats.

The purpose of the this investigation was to clarify the pharmacological characteristics of aggressive behavior of the NAB rats.

Hyperirritability in NAB rats was remarkebly suppressed by L-DOPA, L-5-HTP, major and minor tranquilizers but not reduced by ATP. On the other hand, muricide in NAB rats was significantly suppressed by L-DOPA, L-5-HTP, major and minor tranquilizer and ATP. These results suggested that a reduction of cholinergic activity and an increase of dopaminergic or serotonergic activity in capable of inhibition muricide induced by NAB lesion. It is also suggested that the neural mechanism for inducing muricide is distinct from that for hyperirritability in NAB rats.

Muricide has been employed as a screening method for antidepressants because Horovitz *et. al.*, (15), Sofia and Malick *et. al* (16) have reported that antidepressants, antihistamines and CNS stimulants selectivily block the muricide behavior of either the spontaneous killer rats or the O.B. rats.

This study was therefore examined in an attempt to elucidate the characteristics by studing the effect various antidepressants on muricide induced by NAB lesion. Muricide in NAB rats was significantly suppressed by IMP, NOF, CIP and MA. These results suggested that muricide in NAB rats is selectively inhibited by antidepressants and it can be as useful for the evaluation of various antidepressants since the effectiveness on the muricide induced by NAB lession differ from each other as well as various brain-lesioned animal models.

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