Korean J. of Pharmacology
Vol. 23, No. 2, pp. 95-100,1987

Pharmacological Studies on Aggressive Behavior Induced by Three Different Regional Brain Lesions

Soon-Chul Lee[2], Tsuneyuki Yamamoto* and Showa Ueki*

College of Pharmacy, Chungnam National University, Daejeon 300, Korea
*Department of Pharmacology, Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan**

ABSTRACT

The effects of various drugs on muricide and hyperirritability induced by bilateral lesions of the nucleus accumbens septi (NAB) were investigated in comparison with those on aggression induced by midbrain raphe nuclei-lesioned rats (raphe) and olfactory bulbectomized rats (OB).

Muricide in NAB, raphe and OB rats were markedly suppressed by atropine. Muricide in NAB and raphe rats were significantly suppressed by L-DOPA, L-5-HTP, but muricide in OB rats was scarcely suppressed by L-DOPA and L-5-HTP. Hyperirritability in NAB, raphe and OB rats were significantly reduced by L-DOPA and haloperidol but not suppressed by atropine. On the other hand, muricide in NAB rats was markedly suppressed by antidepressants, particularily, nomifensine, clomipramine and desipramine. Muricide in raphe rats was markedly inhibited by nomifensine and clomipramine but only slightly inhibited by desipramine. Muricide in OB rats was markedly suppressed by imipramine. Hyperirritability in NAB, raphe and OB rats were slightly suppressed by antidepressants.

These results suggested that the pharmacological characteristics of aggression induced by NAB rats resembles that induced by raphe rats, but differs from that induced by OB rats. It is also suggested that employment of different types of experimentally induced muricide in rats can be useful for the evaluation of antidepressants.

Key Words: 1. This study was supported in part by research grants from the Korea Research Foundation, the Ministry of Education, the Republic of Korea.
2. To whom reprint requests should be addressed.

Abbreviation: NAB; nucleus accumbens septi, raphe; midbrain raphe nuclei, OB; olfactory bulbs, L-DOPA; l-dihydroxy phenylalanine, L-5-HTP; L-5-hydroxy tryptophan

INTRODUCTION

It is well known that aggression can be induced by various methods in rodents, i.e., long-term isolation (Valzelli & Garattini, 1972; Yen *et al.*, 1959). regional brain lesions (Brady & Nauta, 1953; Ueki *et al.*, 1972; Yamamoto & Ueki, 1977), certain drug treatment (Fujiwara & Ueki, 1978) and painful stimulation (Arzin, 1963), It is reported that bilateral stimulation of nucleus accumbens septi causes emotionality changes in the cat (Goldstein & Seigel, 1980) and bilateral lesion of that induced hyperkinesia and aggressiveness in the rat (Thomson, 1978). We also have previously reported that bilateral lesions of nucleus accumbens septi was result in aggressive behavior including muricide and hyperirritability in the rat (Lee *et al.*, 1980; Lee *et al.*, 1983), and that muricide in NAB rats results from increased cholinergic activity and reduced catecholaminergic and serotonergic activity (Lee & Ueki, 1986).

On the other hand, aggressions induced by various methods are useful for the evaluation of psychotropic drugs, especially, muricide has been

employed for screening antidepressants since it was selectively inhibited by these agents at doses which do not cause behavioral toxicity, such as ataxia (Horovitz *et al.*, 1965; Sofia, 1969b). Therefore, the present study was planned to elucidate the pharmacological characteristics as compared with the drug effects on aggression induced by three different regional brain lesions.

METHODS

Animals

The animals employed were male Wistar King A rats, weighing 200–300 g at the time of surgery. These animals were maintained at a room temperature of 22±1℃ and were given food and water ad libitum throughout the experimental period.

Surgical procedure

The animals were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and the head was fixed in stereotaxic instrument. Monopolar electrodes composed of stainless steel wire, 0.4 mm in diameter, insulated except for the last 0.5 mm of the tips, were inserted into nucleus accumbens septi. Lesions in both the caudal [anterior (A); 8.6, lateral (L); 1.5 ventral (V); −1.4] and rostral sites (A; 9.0, L; 1.0, V; −0.9) of the nucleus accumbens septi were induced according to König and Klippel's brain atlas (1963) in the rat, simultaneously (NAB rats). Lesions were made by applying DC of 3.0 mM for 15 second. Lesions of the midbrain raphe nuclei were carried out by the same manner as nucleus accumbens septi lesions. Lesions of both sites of the midbrain raphe nuclei, i.e., dorsal (A; 0.6, L; 0, V; −1.0) and median (A; 0.16, L; 0, V; −2.5) were made simultaneously (raphe rats). Olfactory bulbs were removed by suctioning through a hole made in the skull (OB rats). After the surgery, each animal was given an intramuscular injection of 300,000 units procain penicillin G.

Testing procedure

The rats were tested for muricide before the surgery. Only rats which did not kill mice within 15 min after they were introduced into the home cage were used. After the surgical procedure, the rats were housed in individual cages 20×17×17 cm with wire-mesh walls and were tested for muricide 2, 4 and 7 days after brain lesioning. Only rats which exhibited muricide on 3 consecutive test days were used for drug experiments. In the hyperirritability, the 3 responses of the rats to given stimuli such as air blowing on the back (startle), presentation of a rod (attack) and handling (struggle), were scored in each item, ranging from 0 and to 4, according to the same rating scale as employed in the previous study (Lee *et al.*, 1983).

Drugs

The drugs used in this experiment were L-dihydroxyphenylalanine (L-DOPA; Sigma), Ro 4-4602 (Roche), L-5-hydroxytryptophan (L-5-HTP; Kyowa Hakko), atropine sulfate (Iwaki), haloperidol (Injection; Dainippon), imipramine hydrochloride (CIBA-GEIGY), nomifensine hydrogen maleate (Hoechst-Japan), clomipramine hydrochloride (CIBA-GEIGY), desipramine hydrochloride (CIBA-GEIGY), L-DOPA, L-5-HTP and nomifensine were suspended 0.5% carboxymethyl cellulose. The other drugs were dissolved in distilled water. All the drugs were administered in a fixed volume of 0.1 ml/100 g body weight and were injection intraperitoneally.

Statistical analysis

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

RESULTS

Table 1 illustrates the effects of various drugs on muricide induced by NAB, raphe and OB rats. Atropine, at relative low doses, produced a significant inhibition of muricide in NAB, raphe and OB rats, with ED50's of 9.4 (3.5−25.2), 14.1 (7.1-28.2) and 12.0 (6.7-21.6)mg/kg, respectively. Haloperidol (2 mg/kg), at relative high dose, produced a significant inhibition of muricide in NAB rats, with ED50's of 2.3 (1.4-3.9)mg/kg. Muricide in raphe rats and OB rats was markedly inhibited at lower doses than in NAB rats by

Table 1. ED50's values of various drugs on muricide induced by three different brain lesions in rats

Drug (mg/kg)	Muricide					
	NAB rats		Raphe rats		OB rats	
Atropine	9.4	(3.5 – 25.2)	14.1	(7.1 – 28.2)	12.0	(6.7 – 21.6)
Haloperidol	2.3	(1.4 – 3.9)	0.4	(0.3 – 0.7)	0.7	(0.3 – 1.6)
L-DOPA	12.0	(3.4 – 42.6)	25.0	(10.0 – 62.5)	100 <	
L-5-HTP	50.0	(37.6 – 66.5)	25.6	(3.1 – 224.5)	122.5	(32.0 – 272.0)

Table 2. Effects of haloperidol on aggressive behavior induced by three different brain lesions

Treatment	Dose (mg/kg i.p.)	Emotional response			
		Muricide (%)	Startle (Mean ± S.D.)	Attack (Mean ± S.D.)	Struggle (Mean ± S.D.)
NAB rats	Control	9/9 (100)	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***
Raphe rats	Control	8/8 (100)	2.0 ± 0.5	2.1 ± 0.6	2.6 ± 0.7
	0.2	6/8 (75)	1.5 ± 0.4	1.6 ± 0.6**	1.2 ± 0.3***
	0.5	5/9 (55.6)*	1.7 ± 0.7	1.3 ± 0.3**	1.2 ± 0.5***
	1.0	1/8 (12.5)***	1.3 ± 0.5**	1.4 ± 0.5*	1.1 ± 0.2***
OB rats	Control	8/8 (100)	2.7 ± 0.8	2.5 ± 0.5	3.3 ± 0.7
	0.2	6/8 (75)	2.7 ± 0.4	2.4 ± 0.9	1.9 ± 0.4***
	0.5	5/9 (55.6)*	2.2 ± 0.8	1.3 ± 0.4***	1.6 ± 0.6***
	1.0	3/8 (37.5)*	1.5 ± 0.7***	1.8 ± 0.8**	1.9 ± 0.6***

haloperidol. L-DOPA was injected 30 min after Ro 4-4602 50 mg/kg. Muricide was not inhibited by Ro 4-4602 alone, though a slight muscle relaxation was observed. L-DOPA combined with Ro 4-4602 produced a significant inhibition of muricide in NAB rats at doses over 10 mg/kg. The ED 50's of muricide inhibition for L-DOPA was 12.0 (3.4-42.6)mg/kg. Muricide in raphe rats was significantly suppressed by L-DOPA at doses of 30mg/kg and 50 mg/kg in dose dependently. Muricide in OB rats was not suppressed by L-DOPA even though at very high doses over 100 mg/kg. L-5-HTP also suppressed muricide in NAB rats in a dose-dependent manner, and showed a significant inhibition at doses over 50 mg/kg. The ED50's of muricide inhibition for L-5-HTP was 50.0 (37.6-66.5) mg/kg. Muricide in raphe rats was markedly suppressed by L-5-HTP and ED50's of muricide inhibition for L-5-HTP was 25.6 (3.1 -224.5)mg/kg. Muricide in OB rats was suppressed by L-5-HTP at high doses. The ED50's of muricide inhibition for L-5-HTP was 122.5 (32.0 -272.0) mg/kg.

Table 2 illustrates the effects of haloperidol on aggression induced by NAB, raphe and OB rats. Hyperirritability in NAB rats was markedly suppressed by haloperidol in a dose dependent manner. Hyperirritability in raphe and OB rats was significantly suppressed by haloperidol at doses over 0.2 mg/kg.

Table 3 illustrates the effects of L-DOPA on aggression induced by NAB, raphe and OB rats. In NAB rats, the startle response score was not at all reduced by L-DOPA. The attack and the struggle response score were markedly decreased by L-DOPA at doses of 30 mg/kg, but not dose-dependently. In raphe rats, the startle response score was also not at all reduced by L-DOPA. The attack and the struggle response score were markedly suppressed by L-DOPA at doses of 10 mg/kg. The startle response score in OB rats was not reduced by L-DOPA at any doses used, whereas

Table 3. Effects of L-DOPA on aggressive behavior induced by three different brain lesions in rats

Treatment	Dose (mg/kg i.p.)	Emotional response			
		Muricide (%)	Startle (Mean ± S.D.)	Attack (Mean ± S.D.)	Struggle (Mean ± S.D.)
NAB rats	Control	9/9 (100)	2.3 ± 0.6	2.0 ± 0.6	2.7 ± 0.8
	10	5/9 (44.4)*	1.9 ± 0.5	1.6 ± 0.3	2.3 ± 0.6
	30	3/8 (37.5)*	2.7 ± 0.5	1.4 ± 0.3***	1.7 ± 0.7***
	50	3/9 (33.3)*	2.2 ± 0.6	1.6 ± 0.2	2.1 ± 0.8*
Raphe rats	Control	8/8 (100)	2.2 ± 0.6	2.4 ± 0.7	2.4 ± 0.9
	10	6/8 (75)	2.2 ± 0.5	1.2 ± 0.2***	1.3 ± 0.5**
	30	4/8 (50)*	2.3 ± 0.3	1.7 ± 0.3*	2.0 ± 0.7
	50	3/8 (37.5)*	2.1 ± 0.2	2.0 ± 0.2	2.0 ± 0.4
OB rats	Control	9/9 (100)	2.4 ± 0.4	2.6 ± 0.4	3.6 ± 0.6
	10	6/8 (75)	1.9 ± 0.6	1.9 ± 0.5***	2.2 ± 0.5**
	30	7/9 (77.8)	2.2 ± 0.3	1.7 ± 0.3***	2.7 ± 0.4***
	100	6/8 (75)	2.1 ± 0.5	1.9 ± 0.4**	2.3 ± 0.6***

Table 4. ED50's values of various antidepressants on muricide induced by three different brain lesions in rats

Drug (mg/kg)	Muricide					
	NAB rats		Raphe rats		OB rats	
Nomifensine	4.2	(1.6 – 11.1)	4.0	(1.6 – 10.2)	8.2	(3.9 – 17.2)
Imipramine	17.8	(8.9 – 35.6)	17.8	(4.1 – 41.0)	11.0	(4.3 – 28.1)
Clomipramine	9.0	(6.4 – 12.6)	10.0	(4.5 – 22.4)	27.5	(16.7 – 45.5)
Desipramine	9.6	(3.5 – 26.5)	25.1	(14.4 – 43.9)	18.4	(17.7 – 19.1)

Table 5. *Effects of nomifensine on aggressive behavior induced by three different brain lesions*

Treatment	Dose (mg/kg i.p.)	Emotional response			
		Muricide (%)	Startle (Mean ± S.D.)	Attack (Mean ± S.D.)	Struggle (Mean ± S.D.)
NAB rats	Control	8/8 (100)	2.4 ± 0.6	2.0 ± 0.3	3.1 ± 0.7
	1	6/8 (75)	2.5 ± 0.8	1.3 ± 0.3**	3.1 ± 0.7
	5	4/8 (50)*	2.4 ± 0.4	1.4 ± 0.2**	2.9 ± 0.7
	10	2/9 (22.2)**	2.6 ± 0.3	1.3 ± 0.4**	3.2 ± 0.5
Raphe rats	Control	8/8 (100)	2.1 ± 0.4	1.9 ± 0.7	2.5 ± 0.8
	1	6/8 (75)	2.3 ± 0.4	2.0 ± 0.7	1.9 ± 0.4*
	5	2/9 (22.2)***	2.3 ± 0.4	1.5 ± 0.3*	2.0 ± 0.6
	10	2/8 (25)***	2.1 ± 0.5	1.4 ± 0.3**	1.9 ± 0.7*
OB rats	Control	8/8 (100)	2.1 ± 0.3	2.4 ± 0.5	2.8 ± 0.6
	5	8/8 (100)	2.2 ± 0.3	1.6 ± 0.2**	2.4 ± 0.6
	7	4/7 (57.1)	2.3 ± 0.3	1.6 ± 0.3**	2.9 ± 0.3
	10	4/8 (50)*	2.3 ± 0.3	1.7 ± 0.3***	2.6 ± 0.2
	20	3/9 (33.3)***	2.2 ± 0.4	1.3 ± 0.4***	3.0 ± 0.6

the attack and the struggle response score were significantly decreased by L-DOPA at all doses of 10, 30 and 100 mg/kg.

Table 4 illustrates the effects of various antidepressants on muricide induced by NAB, raphe and OB rats. Muricide in NAB rats was markedly inhibited by various antidepressants. Particularily, nomifensine inhibited muricide at lower dose than did the other antidepressants. Imipramine, clomipramine and desipramine also produced a significant inhibition of muricide. In raphe rats, antidepressants produced muricide inhibition of similar potency to those in NAB rats, with the exception of desipramine. Although muricide in OB rats was inhibited by antidepressants, the effects were generally weak in potency as compared with in NAB rats, with the exception of imipramine.

Table 5 illustrates the effects of nomifensine on aggression induced by NAB, raphe and OB rats. The startle and struggle response score in NAB rats were not at all suppressed by nomifensine at any doses used, but the attack response score was significantly suppressed. The startle response score in raphe rats was not reduced by nomifensine at any doses used, but the attack response score and the struggle response score were inhibited. In OB rats, nomifensine was produced the hyperirritability inhibition of similar potency to those in NAB rats.

DISCUSSION

We previously revealed some behavioral characteristics in aggression of NAB rats in comparison with that of raphe and OB rats (Lee *et al.*, 1983). The main purpose of this investigation was to clarity the quantitative difference in drug effects between the three different brain lesions, i.e., nucleus accumbens septi, midbrain raphe nuclei and olfactory bulbs.

Muricide in NAB rats was markedly suppressed by atropine, L-DOPA and L-5-HTP. Muricide in raphe rats was also markedly suppressed by L-DOPA and L-5-HTP as well as NAB rats, whereas muricide in OB rats was only slightly suppressed by L-DOPA and L-5-HTP. We previously reported that aggression induced by NAB lesions closely resembled that of the rats with lesions of the midbrain raphe nuclei, containing serotonergic cell bodies, display hyperirritability, muricide, mouse-eating behavior. It was also reported that NAB lesions significantly reduced dopamine level (Lee, 1984) and serotonin content (Lorens *et al.*, 1970) in the telencephalon in rats.

Therefore, present results consisted that antimuricidal effects in NAB rats and raphe rats resulted from decreased cholinergic activity and increased dopaminergic and serotonergic activity, but pharmacological characteristics on aggression in OB rats somewhat differs from that in NAB rats and raphe rats.

There were many reports that antidepressants selectively block muricide in both spontaneous killer rat and OB rats. Muricide in NAB rats markedly suppressed by a dopamine uptake blocker nomifensine, a 5-HT uptake blocker, clomipramine and a noradrenaline uptake blocker, desipramine. As illustrated Table 4, the order of potency of antimuricidal effect in NAB rats was nomifensine > clomipramine > desipramine > imipramine. In raphe rats, the order of potency of antimuricidal effect was nomifensine > clomipramine > imipramine > desipramine, whereas in OB rats that was nomifensine > imipramine > desipramine > clomipramine. Hyperirritability induced by three different brain-lesioned rats was slightly suppressed by antidepressants.

Therefore, we suggested that the neural mechanism for inducing muricide is different from that for inducing hyperirritability in three kinds of brain-lesioned rats.

REFERENCES

Azrin NH, Hutchinson RR, Hake DF: *Pain-induced fighting in the squirrel monkey. J Exp Anal Behav 6: 620-621, 1963*

Brady JV, Nauta WJH: *Subcortical mechanism in emotional behavior: Affective changes following septal forebrain lesion in the albino rat. J Comp Physiol Psychol 46: 339-346, 1953*

Goldstein JM, Seigel J: *Suppression of attack behavior in cats by stimulation of ventral tegmentum area and nucleus accumbens. Brain Res 183: 181-192, 1980*

Horovitz SP, Pagozzino PW, Leaf RC: *Selective block of rat-mouse killing by antidepressants. Life Sci 4: 1909-1912, 1965*

König JFR, Klippel RA: *The rat brain: A stereotaxic atlas of the forebrain and lower part of the brain stem. Baltimore, Williams and Wilkins, 1963*

Lee SC, Showa Ueki: *Pharmacological studies on*

aggressive behavior induced by lesions of the nucleus accumbens septi in rats. Arch Pharm Res pp169-174, 1986

Lee SC, Yamamoto T, Ueki, S: *Characteristics of aggressive behavior induced by nucleus accumbens septi lesions in rats. Behav and Neural Biol 37: 237-245, 1983*

Lorens SA, Sorensen JP, Harvery JA: *Lesions in the nuclei accumbens septi of the rat; Behavioral and neurochemical effects, Journal of comparative and physiological psychology 73: 284-290, 1970*

Fujiwara M, Ueki S: *Muricide induced by single injection of $\triangle^9$-tetrahydrocannabinol. Physiol Behav 21: 581-585, 1978*

Rebert Thomson: *A behavioral atlas of the rat. Oxford Univesity, 1978*

Sofia RD: *Structure relationship and potency of agents which selectively block mouse-killing (muricide) behavior in rats. Life Sci 8: 1201-1210, 1969*

Yamamoto T, Ueki S: *Characteristics in aggressive behavior induced by midbrain raphe lesions in rats. Physiol Behav 19: 105-110, 1977*

Ueki S, Nurimoto S, Ogawa N: *Characteristics in emotional behavior of the rat with bilateral olfactory bulb ablations. Folia Psychiat Neurol Jap 26: 229-239, 1972*

Valzelli L, Garattini S: *Biochemical and behavioral changes induced by isolation in rats. Neuropharmacol 11: 17-22, 1972*

Yen CY, Stanger L, Millman N: *Attractive suppression of isolation-induced aggressive behavior. Arch Int Pharmacodyn 123: 179-185, 1959*

=국문초록=

서로 다른 뇌 부위 손상으로 인한 공격성에 대한 약물학적 연구

충남대학교 약학대학 약학과 및 구주대학 약학부 약물학교실

이순철, S. 우에끼, T. 야마모토

본 연구는 측좌각, 봉선핵 및 후구 등 서로 다른 뇌 부위의 손상으로 야기된 공격성에 대한 약물의 효과를 비교 검토하여 다음과 같은 결과를 얻었다.

1. 측좌각, 봉선핵 및 후구 손상으로 야기된 muricide는 atropine으로 억제되었으나 hyperirritability는 억제되지 않았다.
2. 측좌각, 봉선핵 손상으로 인한 muricide는 L-DOPA, L-5-HTP에 의하여 현저히 억제되었으나 후구 손상으로 인한 muricide는 거의 억제되지 않았다.
3. 측좌각, 봉선핵 및 후구 손상으로 인한 muricide는 항우울제에 의하여 현저히 억제되었다. 특히 측좌각 및 봉선핵 손상으로 인한 muricide 억제에는 nomifensine과 clomipramine이 효과적이었으며 후구 손상으로 인한 muricide 억제에는 imipramine이 가장 효과적이었다. 그러나 hyperirritability는 항우울제에 의하여 거의 억제되지 않았다.

이상의 결과에서 측좌각 손상으로 인한 공격성의 약물학적 특징은 후구보다는 봉선핵 손상으로 인한 공격성과 유사하였으며 muricide 억제에 대한 항우울제의 효과가 서로 다른 것을 이용하여 항우울제의 작용평가에 도움이 될 것으로 사료된다.