Pharmacology Biochemistry & Behavior, Vol. 26, pp. 351–355. Copyright © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

The Role of Brain Catecholamines in the Exhibition of Muricide Induced by Nucleus Accumbens Lesions and the Effect of Antidepressants in Rats

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Received 16 July 1986

AL-KHATIB, Iz. M. H., M. FUJIWARA, K. IWASAKI, Y. KATAOKA AND S. UEKI. *The role of brain catecholamines in the exhibition of muricide induced by nucleus accumbens lesions and the effect of antidepressants in rats.* PHARMACOL BIOCHEM BEHAV **26**(2) 351–355, 1987.—Changes in brain catecholamine content after lesioning the nucleus accumbens (ACC) and the effects of antidepressants were investigated using HPLC-ECD. ACC lesion reduced dopamine (DA) in the rostral caudate-putamen (r-CP), lateral hypothalamus (LH) and central amygdala (ACE). Imipramine (IMP) and nomifensine (NOM) increased DA in r-CP, caudal (c)-CP and basolateral amygdala. Mianserin (MIAN) and zimelidine (ZIM) increased DA only in c-CP. ACC lesion did not change DOPAC. Only IMP (in c-CP) and NOM (in r-CP and c-CP) increased DOPAC. Noradrenaline (NA) was decreased in c-CP and ACE after ACC lesion. IMP and ZIM displayed no effect on NA, while NOM increased NA in LH and frontal cortex (FC) and MIAN only in FC. These results suggest an important role for DA but not NA in the exhibition of muricide after ACC lesion, and in the antimuricide effect of antidepressants.

Rat Nucleus accumbens lesion Muricide Antidepressants Dopamine DOPAC Noradrenaline

NUCLEUS accumbens (ACC), a part of the mesolimbic dopamine (DA) system, has been known to mediate various animal behaviors including rotation, locomotion and feeding [12, 15, 19]. ACC lesions induce hyperemotionality and mouse-killing behavior (muricide), suggesting that ACC is involved in the neural mechanism of emotional behavior (1, 16, 18]. Muricide induced by ACC lesions is considered as a useful model for evaluating antidepressant drugs [2,18].

Our previous studies in olfactory bulbectomized rats indicated that catecholamines, especially noradrenaline (NA) and DA, in some specific brain areas played an important role in the exhibition of muricide and the antimuricide effect of antidepressants [11].

The present study was therefore undertaken to determine the changes of catecholamine content in various brain regions of rats in relation to the development of muricide following bilateral ACC lesions and the effect of some atypical antidepressants in comparison with that of imipramine. The brain regions were chosen according to our previous study [11] to provide more information about the changes induced by ACC lesion and to compare such changes with those induced by isolation and olfactory bulbectomy.

METHOD

Animals

Male Wistar King A rats, weighing 200–220 g at the start of the experiment, supplied by Kyushu University Institute of Experimental Animals, were used. Rats were housed 5 per cage (42×26×15 cm) for 2 weeks.

Before lesioning ACC, rats were placed in individual cages (20×21×17 cm) for one hour and a white male mouse (20–25 g) was put in each cage for muricide test. Only rats which did not kill the mice within 30 min after being in contact with them (50–80%) were used in this study. The rats were kept under standardized conditions of temperature (23±1°C), relative humidity (55±5%) and 12 hr light-dark cycles (lights on 07:00–19:00) with free access to food and water.

Lesioning of the Nucleus Accumbens

Rats anesthetized with sodium pentobarbital (40 mg/kg IP) were placed on a stereotaxic instrument, and monopolar stainless steel electrodes of 0.4 mm in diameter, insulated

TABLE 1

CHANGES IN BRAIN DOPAMINE CONTENT (ng/mg TISSUE) FOLLOWING LESION OF NUCLEUS ACCUMBENS AND THE EFFECT OF ANTIDEPRESSANTS

	Treatment	N	r-CP	c-CP	VMH	LH	AME	ACE	ABL	FC
Intact	Saline (Nonkiller)	8	6.152 ±0.238	3.520 ±0.126	1.069 ±0.202	0.333 ±0.057	0.066 ±0.015	0.439 ±0.036	0.151 ±0.019	0.031 ±0.007
	Saline (Killer)	4	7.261 ±0.714	3.941 ±0.333	0.760 ±0.328	0.349 ±0.110	0.043 ±0.013	0.280 ±0.064	0.148 ±0.028	0.034 ±0.008
ACC Killer	Saline	10	4.984* ±0.201	3.115 ±0.235	0.925 ±0.166	0.159* ±0.014	0.047 ±0.014	0.168* ±0.036	0.098 ±0.019	0.030 ±0.033
	Imipramine (30 mg/kg)	5	8.938‡ ±0.483	8.681‡ ±0.581	0.931 ±0.369	0.245 ±0.081	0.058 ±0.014	0.074 ±0.020	0.201† ±0.036	0.044 ±0.009
	Nomifensine (15 mg/kg)	5	11.924§ ±1.147	8.648‡ ±1.343	0.524 ±0.217	0.211 ±0.057	0.030 ±0.015	0.063 ±0.042	0.358‡ ±0.064	0.048 ±0.006
	Zimelidine (15 mg/kg)	5	4.789 ±0.642	5.718† ±0.474	0.578 ±0.260	0.228 ±0.043	0.032 ±0.010	0.124 ±0.015	0.070 ±0.011	0.038 ±0.004
	Mianserin (15 mg/kg)	5	5.802 ±1.376	9.403‡ ±0.999	1.232 ±0.427	0.208 ±0.079	0.026 ±0.015	0.095 ±0.014	0.166 ±0.050	0.040 ±0.006

N=number of rats per group. Values are mean ± S.E. *$p<0.01$ vs. intact killer. †$p<0.05$, ‡$p<0.01$, §$p<0.001$ vs. saline treated ACC rats.

TABLE 2

CHANGES IN BRAIN DOPAC CONTENT (ng/mg TISSUE) FOLLOWING LESION OF NUCLEUS ACCUMBENS AND THE EFFECT OF ANTIDEPRESSANTS

	Treatment	N	r-CP	c-CP	VMH	LH	AME	ACE	ABL	FC
Intact	Saline (Nonkiller)	8	1.005 ±0.076	0.800 ±0.048	0.075 ±0.010	0.043 ±0.012	0.040 ±0.012	0.220 ±0.040	0.050 ±0.003	0.020 ±0.001
	Saline (Killer)	4	1.342 ±0.302	0.920 ±0.115	0.064 ±0.008	0.040 ±0.001	0.032 ±0.010	0.120 ±0.002	0.045 ±0.001	0.020 ±0.001
ACC Killer	Saline	10	1.289 ±0.200	0.716 ±0.080	0.056 ±0.008	0.040 ±0.001	0.030 ±0.006	0.080 ±0.010	0.040 ±0.002	0.018 ±0.003
	Imipramine (30 mg/kg)	5	1.805 ±0.134	1.538† ±0.149	0.041 ±0.005	0.040 ±0.001	0.031 ±0.003	0.090 ±0.004	0.038 ±0.001	0.010 ±0.001
	Nomifensine (15 mg/kg)	5	2.371* ±0.350	1.586† ±0.207	0.040 ±0.002	0.040 ±0.001	0.028 ±0.002	0.080 ±0.004	0.040 ±0.001	0.026 ±0.003
	Zimelidine (15 mg/kg)	5	0.997 ±0.125	0.644 ±0.050	0.043 ±0.004	0.040 ±0.001	0.020 ±0.002	0.055 ±0.005	0.040 ±0.001	0.020 ±0.002
	Mianserin (15 mg/kg)	5	1.179 ±0.261	0.707 ±0.020	0.085 ±0.004	0.038 ±0.001	0.018 ±0.008	0.075 ±0.010	0.040 ±0.001	0.020 ±0.002

*$p<0.05$, †$p<0.01$ vs. ACC rats.

except for 0.5 mm at the tips, were implanted in the rostral and caudal ACC according to the rat brain atlas of König and Klippel [14]. The stereotaxic coordinates were for the rostral ACC: anterior (A)=9.6, lateral (L)=1.1, horizontal from the skull surface (H)=7.1, and for the caudal ACC; A=8.6, L=1.5, H=7.5. Lesions were induced by applying DC current of 3 mA for 20 sec through the electrodes. A reference electrode was placed in the rat's body. After the surgery, penicillin 150,000 I.U. was injected IM to prevent infection and isolated housing was commenced.

Experimental Procedure and Drugs

One week after ACC lesions, rats were tested for muricide. Muricide was regarded as positive when rat killed a mouse within 3 min after introduction into the rat's individual cage. Groups of ACC-lesioned rats exhibiting muricide (ACC rats) were given either drugs (N=5 for each drug) or physiological saline (N=10). A group of intact rats (N=12), housed in isolation cages for one week, received only saline and served as control for ACC rats. Antidepressants used in this study were imipramine HCl (IMP, Sigma), nomifensine maleate (NOM, Hoechst), mianserin HCl (MIAN, Organon) and zimelidine HCl (ZIM, Fujisawa). All drugs were administered IP. The vehicles used were physiological saline for IMP, MIAN and ZIM, and 0.5% carboxymethylcellulose (CMC) for NOM. The dose of

TABLE 3

CHANGES IN BRAIN NORADRENALINE CONTENT (ng/mg TISSUE) FOLLOWING LESION OF NUCLEUS ACCUMBENS AND THE EFFECT OF ANTIDEPRESSANTS

	Treatment	N	r-CP	c-CP	VMH	LH	AME	ACE	ABL	FC
Intact	Saline	8	0.204	0.202	1.417	2.042	0.246	0.396	0.389	0.353
	(Nonkiller)		±0.039	±0.018	±0.074	±0.115	±0.038	±0.039	±0.018	±0.034
	Saline	4	0.386	0.271	1.898*	2.020	0.603†	0.652	0.381	0.299
	(Killer)		±0.115	±0.015	±0.138	±0.109	±0.183	±0.119	±0.037	±0.035
ACC	Saline	10	0.139	0.152§	1.769	1.836	0.439	0.286‡	0.314	0.257
Killer			±0.026	±0.022	±0.192	±0.124	±0.088	±0.045	±0.044	±0.025
	Imipramine	5	0.119	0.180	1.896	2.011	0.358	0.290	0.416	0.299
	(30 mg/kg)		±0.015	±0.016	±0.085	±0.175	±0.081	±0.038	±0.097	±0.019
	Nomifensine	5	0.154	0.120	1.708	2.477¶	0.336	0.179	0.547	0.346¶
	(15 mg/kg)		±0.038	±0.037	±0.238	±0.303	±0.019	±0.039	±0.166	±0.024
	Zimelidine	5	0.074	0.198	1.470	1.870	0.526	0.248	0.261	0.268
	(15 mg/kg)		±0.015	±0.031	±0.060	±0.019	±0.114	±0.030	±0.003	±0.024
	Mianserin	5	0.132	0.137	2.245	1.606	0.264	0.164	0.276	0.343¶
	(15 mg/kg)		±0.036	±0.036	±0.159	±0.232	±0.185	±0.045	±0.018	±0.023

*$p<0.05$, †$p<0.01$ vs. intact nonkiller; ‡$p<0.05$, §$p<0.01$ vs. intact killer; ¶$p<0.05$ vs. saline treated ACC rats.

each drug was chosen according to the dose-response curve for antimuricide action obtained in our previous study [2].

Brain Tissue Sampling and Catecholamine Assay

One hour after IP administration of either saline or drugs, rats were tested for muricide and soon decapitated. The brain was quickly removed, placed on ice-cooled glass stage, and dissected by a microknife according to the atlas of König and Klippel [14]. Sections of 2 mm thickness were grasped at the coordinates A=4–6. The following nuclei were dissected at A=4; the ventromedial hypothalamus (VMH), lateral hypothalamus (LH). medial (AME), central (ACE) and basolateral amygdala (ABL). The rostral (r-CP) and caudal parts (c-CP) of the caudate-putamen were dissected at the coordinates A=8 and A=6 respectively. The frontal cortex (FC) was dissected at the central part, A=11.

Catecholamines were determined using HPLC-ECD according to the method of Felice *et al.* [7] with minor modifications [11].

Statistical Analysis

Data were analyzed for uniformity of variance by Bartlett's test. Significances of the changes with the treatments were determined by Student's *t*-test in case of uniform variances, and Duncan's new multiple range test in case the variances were not uniform, using NEC computer-9801F.

RESULTS

After isolated housing for one week, 4 out of 12 intact rats exhibited muricide. No difference in DA content between the intact killer and nonkiller rats was detected in all brain areas studied, although DA was decreased in VMH, AME and ACE and increased in r-CP, but these changes were not significant (Table 1).

Lesioning of ACC induced muricide in 30 out of 36 rats. In ACC rats exhibiting muricide, DA content was significantly decreased in r-CP, LH and ACE. DA content tended to decrease in ABL but insignificantly. Antidepressants, at the doses studied, suppressed muricide of all ACC rats. IMP (30 mg/kg IP) and NOM (15 mg/kg IP) significantly increased DA contents in r-CP, c-CP and ABL in ACC rats, while MIAN (15 mg/kg IP) and ZIM (15 mg/kg IP) increased DA only in c-CP (Table 1). The decreased DA content in LH tended to be reversed by antidepressants. The DA content in ACE was further decreased by all antidepressants in ACC rats, though insignificantly. No significant change in DA content was produced by antidepressants in the other brain areas studied.

Table 2 shows that there is no difference in DOPAC content in isolation-killer and nonkiller rats. Lesions of ACC did not change DOPAC significantly. On the other hand, DOPAC was increased in c-CP by IMP, and in both c-CP and r-CP by NOM. ZIM and MIAN did not change DOPAC content. Neither ACC lesions nor antidepressants changed DOPAC/DA ratios significantly.

Table 3 shows that NA content is increased significantly in VMH and AME after one week of isolated housing only in the rats exhibiting muricide. Moreover, NA content was decreased in c-CP and ACE after ACC lesions without changes in VMH and AME. IMP and ZIM displayed no significant effect on the NA content in all brain areas. On the other hand, NA content was increased by NOM in LH and FC, but only in FC by MIAN.

DISCUSSION

The present study showed that ACC lesion preferentially decreased DA content in r-CP, LH and ACE, while NA was decreased in c-Cp and ACE. These effects are expected to be corollary to the destruction of the dopaminergic and noradrenergic neurons in ACC with subsequent decrease in the "availability" of both DA and NA. Since ACC lesions did not change DOPAC/DA ratios, it is also possible to suggest that ACC lesions did not affect DA release or metabolism.

The neural mechanisms involved in the exhibition of muricide by ACC rats seem to be different from those in other muricide models such as isolation-induced muricide, in which DA was not changed and NA was increased in VMH and AME (the present study); and muricide of olfactory bulbectomized rats in which NA was increased in VMH, LH and AME, while DA was decreased in LH [11]. These differences are probably due to the differences in the biochemical properties of ACC and the olfactory bulbs and the biochemical changes corollary to isolation.

Because of the vast etiological factors involved in human depression, the biochemical changes in the depressives are also known to be different. Apart from the well established importance of NA and serotonin in depression, there is a growing evidence for the possible importance of DA in depression; DA dysfunction [20,23], decreased DA synthesis [3,13] and decreased DA storage [23] were reported in the depressive patients. Since lesion of specific brain region is expected to lead mainly to decrease of the neurotransmitter abundant in that region, it is logical to examine the effect of antidepressants on muricide induced by various manipulations in order to correlate the biochemical properties of the antidepressants and their effects in each muricide model (possibly analogous to some aspects of human depression). Of the antidepressants examined NOM is a potent DA reuptake blocker [4,10] and displays a direct effect on DA receptors [8]. IMP has a 10-fold greater action on serotonin reuptake than NA and on the latter 8-fold more than DA reuptake [9] and its effect on DA reuptake is 100 times less than NOM [5], but it increases tyrosine concentration [17] and also displays some effect on DA receptors [8]. The increased DA in r-CP, LH and ACE produced by NOM could be related to its potent dopaminergic activities. The increased DA produced by IMP was less than NOM, an effect could be due to the weak effect on DA by IMP compared with NOM.

On the other hand, ZIM and MIAN displayed less prominent effect on DA content and even the increase in DA content produced by both drugs was not related directly to their antimuricide activity. This result could be reverted to the fact that both ZIM and MIAN possess only weak dopaminergic properties, and both drugs reportedly increase DA in striatum only at high doses [6,22], an effect could result from their sedative effects [6]. As to the effect on NA, MIAN increased NA in FC. This effect could be due to blockade of α_2-adrenoceptor and increase in NA synthesis by MIAN [5]. However, ZIM which has a 50-fold greater action on serotonin uptake than NA [21] did not change NA content.

It can be suggested that decreased DA content in r-CP, LH and ACE is related to the exhibition of muricide by ACC rats and there seems to be a correlation between the dopaminergic properties of the antidepressants and reversal of decreased DA content induced by ACC lesion especially in r-CP. This effect is involved in the activity of NOM and IMP. However, this effect is not the sole mechanism by which the antidepressants suppress muricide of ACC rats because ZIM and MIAN also suppressed the muricide.

ACKNOWLEDGEMENTS

This study was supported by the Grant-in-Aid for Scientific Research from Japanese Ministry of Education, Science and Culture. We thank Hoechst-Japan, Fujisawa and Organon-Japan for the generous supply of nomifensine, zimelidine and mianserin respectively.

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