SPONTANEOUS AND "SEPTAL" MODELS OF MURICIDAL BEHAVIOR: REGIONAL ACTIVITY OF ENZYMES CONTROLLING BRAIN ANGIOTENSIN AND BRADYKININ METABOLISM

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UDC 57.082.26:616.89-008.444.9-092.9

KEY WORDS: brain; muricidal behavior; angiotensin converting enzyme; kinin degrading activity

Muricidal behavior is regarded as a variant of the aggressive, predatory behavior of rats which is sufficiently widespread under natural conditions [10]. Muricidal behavior is manifested in a certain percentage of noninbred and inbred laboratory rats or it can be obtained experimentally by local destruction of certain brain regions. Recent attempts to demonstrate the particular features of neurophysiological responses in spontaneously muricidal rats (SMR) and in rats with surgical lesion of the lateral hypothalamus and septum pellucidum did not yield definite results [2, 3]. Different responses to electric shock were found in four different models of muricidal rats [11]. Some difference in responses to antidepressants and emotiogenic stimuli was found in spontaneously and bulbectomized muricidal rats [14]. Despite certain functional differences in the models described, the final form of the aggressive response, namely muricidal behavior, was stereotyped. However, it is not clear whether the biochemical mechanisms of muricidal activity are the same in different models of this form of aggressive behavior.

Previously the writers found characteristic changes in angiotensin converting and kinin degrading activities in certain brain zones of muricidal rats, obtained by local injury to the septal zone [1].

This paper describes an attempt to compare two different forms of aggressiveness, obtained by selection from a general population of animals, and of "septal" rats, i.e., surgically produced muricidal rats.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing initially 140-160 g. The animals were kept in individual cages measuring 32 × 15 × 15 cm on the standard animal house diet with food and water ad lib. Individuals with a spontaneous muricidal response were selected as a first step from the general group of rats. The remaining, nonmuricidal animals, were subjected to electrolytic destruction of the periseptal zone by the method described previously [1]. A rat was considered to be muricidal if, in the course of 4 min, it attacked a victim (an albino mouse weighing 15-20 g), biting it in the region of the head and neck. Selection was carried out for 1 month until stable parameters of muricidal behavior appeared. The criteria of muricidal behavior were the fraction of muricidal rats compared with the general group of test animals, the latent period before attacking a mouse, and the length of time the muricidal rat held its victim. Testing was repeated every 3-7 days. The experimental material thus consisted of four groups of animals: 1) intact, 2) SMR, obtained by selection from the general group; 3) "septal" rats which did not develop muricidal behavior; 4) "septal" muricidal rats. By the time of sacrifice of the animals and biochemical testing, the rats were 3 months old. Activity of angiotensin converting enzyme (ACE) and total kinin-degrading activity (KDA) was determined in homogenates of individual brain zones isolated by the method in [9]. During determination of ACE activity [8] hippuryl-histidyl-leucine was used as the substrate. KDA was determined by the method in [12], based on spectrofluorometric detection of bradykinin, after its separation from the enzyme reaction

Research Institute of Medical Enzymology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR S. S. Debov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 104, No. 7, pp. 45-49, July, 1987. Original article submitted April 29, 1986.

0007-4888/87/0007-0927$12.50

TABLE 1. ACE and KDA Activity in Brain Zones of Muricidal Rats (M ± m)

Brain zone	Group of animals			
	1) intact (n = 4)	2) spontaneously muricidal (n = 6)	3) "septal" non-muricidal (n = 6)	4) septal muricidal (n = 7)
	ACE			
Pituitary	3,76±0,55	5,44±0,86	6,27±0,68	5,40±0,90
Olfactory bulb	0,72±0,07	0,97±0,09	0,93±0,23	0,80±0,07
Cerebellum	3,11±1,06	2,84±0,58	2,85±0,33	3,44±0,50
Midbrain	2,84±0,24	1,20±0,26*	3,60±0,48	3,87±0,54
Hypothalamus + thalamus	3,56±0,99	1,16±0,29*	2,14±0,09	1,75±0,14
Corpus striatum	3,38±0,49	4,06±0,32	3,38±0,52	4,17±1,14
	KDA			
Pituitary	3,37±0,15	2,97±0,10	3,61±0,27	4,66±0,05*
Olfactory bulb	3,03±0,01	2,56±0,14	1,94±0,09**	1,98±0,08
Cerebellum	1,92±0,17	2,06±0,02	1,77±0,02	2,52±0,10*
Midbrain	0,78±0,11	0,94±0,04	0,95±0,06	1,03±0,03
Hypothalamus + thalamus	1,55±0,22	1,94±0,17	2,10±0,06**	2,99±0,13*
Corpus striatum	2,28±0,08	2,49±0,04	1,98±0,12	2,69±0,24*

Legend. Activity expressed in nanomoles of His-Leu/min/mg protein; *p < 0.05 between groups 1 and 2, and between groups 3 and 4; **p < 0.05 between groups 1 and 3. Here and in Table 2: n) number of animals. KDA expressed in nanomoles bradykinin/min/mg protein.

TABLE 2. Protein Concentration (in mg/mg tissue) in Different Brain Zones of Muricidal Rats (M ± m)

Brain zone	Group of animals			
	1) intact (n = 4)	2) spontaneously muricidal (n = 6)	3) "septal" non-muricidal (n = 6)	4) septal muricidal (n = 7)
Pituitary	0,534±0,007	0,470±0,073	0,566±0,044	0,599±0,060
Olfactory bulb	0,094±0,010	0,207±0,025*	0,139±0,008	0,363±0,056*
Cerebellum	0,134±0,007	0,131±0,006	0,125±0,011	0,124±0,008
Midbrain	0,114±0,004	132±0,005	0,118±0,005	0,144±0,007*
Hypothalamus + thalamus	0,099±0,011	0,146±0,012*	0,135±0,016	0,144±0,007
Corpus striatum + basal ganglia	0,166±0,023	0,152±0,032	0,142±0,007	0,174±0,032*

Legend. *p < 0.05 between groups 1 and 2 and between groups 3 and 4.

products on a cellulose phosphate column. Protein was determined by Lowry's method. The following reagents were used: hippuryl-histidyl-leucine and histidyl-leucine were obtained from Serva, West Germany, cellulose phosphate from Sigma, USA, o-phthaleic dialdehyde and fluorescamine from Serva, West Germany, and bradykinin from the All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR.

EXPERIMENTAL RESULTS

Parameters of aggressive behavior of the SMR and septal rats differed considerably. In animals of group 1 the portion with muricidal behavior gradually increased up to a maximum of 25.7% on the 26th day of testing (Fig. 1). Parameters of the aggressive response during this time changed successively: the mean time of the first attack decreased from 204 sec to 1.4 sec, the time of holding the victim increased from 7.1 to 16.2 sec, and the time of a second attack was reduced from 132 to 1.1 sec. In septal rats (Fig. 2) these values were much less marked. Of 100 rats undergoing the operation, and not hitherto exhibiting spontaneous aggressiveness, only eight showed persistent muricidal behavior. The other parameters of the aggressive response also indicate a considerable difference between these two models: the time of the first and second attacks were initially shorter in septal rats than in SMR and reached maximal values 2 weeks after injury to the septal zone. The time course of the change in time of holding the victim was similar for these two models. This type of selection

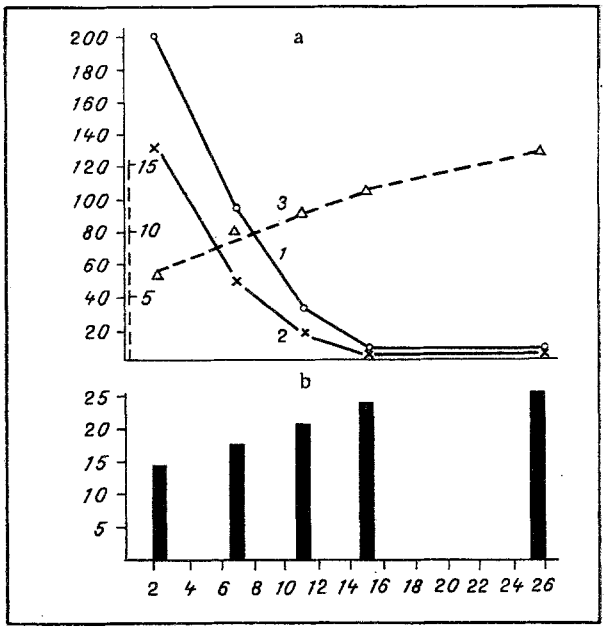

Fig. 1. Time course of changes in parameters of aggressive behavior in SMR. Here and in Fig. 2: abscissa, time of experiment (in days); ordinate: a) parameters of muricidal response (in sec). 1) Latent period until first attack; 2) latent period until second attack; 3) time of holding victim. b) Fraction of muricidal animals (in %).

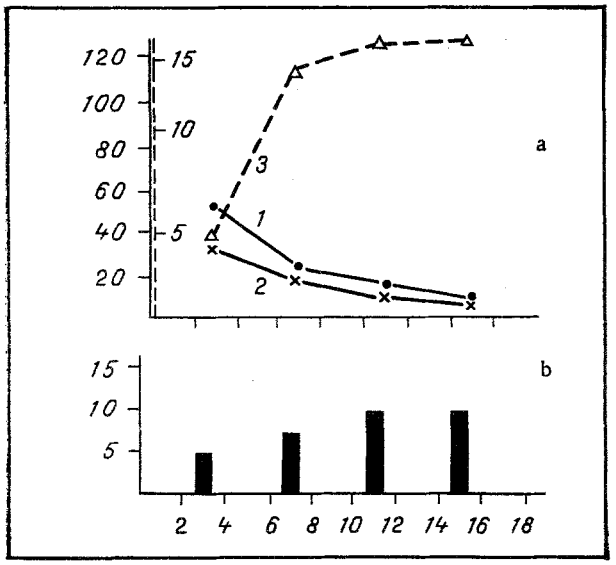

Fig. 2. Time course of changes in parameters of aggressive behavior in muricidal rats after electrolytic destruction of the periseptal zone.

shows that within the same population of noninbred rats, besides spontaneously muricidal rats, aggressive and muricidal animals can also be obtained by surgical means. The two groups have initially different characteristics of their muricidal response. However, in the course of testing for muricidal behavior, these parameters gradually equalized in the SMR and septal rats.

The biochemical experiments showed equally clearly that the models of muricidal behavior also have differences in their distribution of ACE and KDA activity in the brain regions. ACE activity was found to be reduced by 50-66% in the midbrain and thalamo-hypothalamic region of SMR compared with intact rats (Table 1). However, KDA in SMR did not differ from that in intact animals in any of the brain regions studied. In the case of septal rats it was found that their ACE activity did not change significantly in any of the brain zones,

whereas KDA activity, conversely, increased in the pituitary, cerebellum, thalamo-hypothalamic zone, and corpus striatum: these changes amounted to 22.5, 29.8, 29.8, and 26.4% respectively of the corresponding values in nonmuricidal rats undergoing the same operation ($p < 0.05$). Thus significant differences in changes in activity of the enzyme systems involved in angiotensin and kinin metabolism in the brain were found in the spontaneous and "septal" models of muricidal activity.

It was next shown that during the development of muricidal behavior there is a change in the protein concentration in individual brain zones (Table 2). An increase in protein concentration was observed in the thalamo-hypothalamic region and, in particular, in the olfactory bulbs (more than doubled) of the SMR compared with intact rats. The protein concentration in septal rats was increased even more in the olfactory bulbs. These facts are particularly interesting for evaluation of the role of the olfactory bulbs in connection with the presence of muricidal behavior, for after publication of [10], bulbectomy has been used as one of the simplest and most effective methods of modeling aggressive behavior. However, the results of the present investigation relating to protein concentration cannot be directly linked with the changes in ACE activity and KDA which we found. If the functional significance of the results is estimated as a whole, it can be concluded that whereas the presence of spontaneous muricidal activity is coupled with a reduction of angiotensin II formation, mainly in the midbrain and thalamo-hypothalamic region, aggressiveness in "septal" rats is linked with increased destruction of kinins in the majority of brain regions investigated. Ultimately, all of the models of muricidal activity we have examined were characterized by a fall in the level of regulatory peptides in particular brain zones. Previously the writers found similar regional changes in ACE activity and KDA in the general group of surgically produced muricidal rats [1]. The subdivision into spontaneous and "septal" models adopted in this paper enabled the specificity of changes in ACE and KDA to be determined for each one separately. Initial information [5, 13] on the participation of the peripheral renin system in the aggressive behavior of mice did not appear sufficiently convincing. Considering the association between the central physiological effects of angiotensin II and serotonin and the catecholamines, and between those of bradykinin and dopamine — groups of mediators involved in the regulation of muricidal activity [4, 6, 7, 15], it can be concluded that these polypeptides are elements of the integral regulatory chain of formation and maintenance of certain types of aggressive behavior. There is thus no doubt that, by turning our attention to angiotensin (in SMR) or kinin (in septal rats) mechanisms of regulation of muricidal behavior, we are concerned with only individual links of a more complex neurochemical chain. Meanwhile, an attempt was made in [11] to link the "bulbectomized" model of muricidal behavior with participation predominantly of the catecholamine component, whereas muricidal behavior induced by injury to the nuclei raphe was linked with the serotonin system. These data, together with the results of the present investigation, suggest that particular models (variants) of muricidal activity may be linked with different leading mediator systems of the brain.

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