Metabolism of Biogenic Amines in Rat Brain during Pilocarpine-Induced Aggression

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Quantitative distribution of bioactive substances in the brain of aggressive rats was studied. The norepinephrine/serotonin ratio increased in the temporal and parietal lobes, hypothalamus, and hippocampus of killer rats. The open filed behavior of aggressive rats is characterized by a long latency period, low locomotor activity, and slow movements. Exposure to constant darkness aggravated abnormal behavioral characteristics of aggressive rats. Serotonin content in the hypothalamus and visual cortex of these rats decreased by 75 and 76%, respectively.

Key Words: *aggression; pilocarpine; serotonin; norepinephrine*

Evaluation of stress factors causing aggression and associated with motivational and emotional behavioral reactions is the urgent problem of neurobiology. Each form of aggressive behavior is mediated by specific psychophysiological system and neurochemical mechanism. Biochemical mechanisms of aggression, topographic distribution of aggressive centers in the brain, and metabolism of biogenic amines during aggressive behavior are extensively studied [12]. However, the actual biochemical mechanisms of aggression remain unclear.

There are various forms of aggression. Predatory behavior is the most common form of aggression, which differs in the topography of reactions and specificity of trigger stimuli. This form of aggression is studied on the model of killer rats.

Despite considerable advantages of functional neurochemistry, the cause-effect relationships between psychological and neurochemical processes are poorly understood. It remains unclear whether the changes in monoamine metabolism in the brain cause aggression, serve as its neurochemical correlates, or reflect adaptive processes in the brain tissue. Previous studies showed that changes in the vascular tone during emotional strain and stress are mediated by physiological amines, *e.g.*, serotonin [4].

Here we evaluated changes in biogenic amine content in various brain structures in aggressive rats and studied the metabolism of serotonin and its metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) in the brain of aggressive animals under phase shift conditions.

MATERIALS AND METHODS

Experiments were performed on outbred albino rats weighing 230-250 g. Naturally aggressive animals were selected as described elsewhere [10]. Pilocarpine in a dose of 12.5 mg/kg [11] was administered subchronically to derive killer rats. Animal behavior was studied in a computerized open field [5]. Biogenic amines were measured by high-performance liquid chromatography using a Waters electrochemical detector. Catecholamines were isolated from tissue extracts with aluminate [9].

The results were analyzed by Student's *t* test.

RESULTS

In aggressive rats the latency of exit from the central area and number and time of ambulations were lower

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TABLE 1. Quantitative Distribution of Biogenic Amines in Various Brain Structures during Pharmacological and Natural Aggressions (μg/g, *M*±*m*)

Brain structure		Control	Aggression	
			pilocarpine-induced	natural
Midbrain	dopamine	0.32±0.04	0.52±0.03**	0.80±0.13
	norepinephrine	0.48±0.02	1.20±0.18**	0.68±0.21**
	serotonin	0.50±0.05	0.25±0.02*	0.35±0.06**
Hypothalamus	dopamine	0.58±0.05	0.73±0.04*	0.95±0.07*
	norepinephrine	1.45±0.08	2.83±0.20*	2.24±0.13**
	serotonin	1.12±0.09	0.45±0.06*	0.62±0.02
Hippocampus	dopamine	0.61±0.09	0.74±0.04*	0.85±0.02**
	norepinephrine	0.75±0.06	1.18±0.12**	1.12±0.17**
	serotonin	0.48±0.04	0.28±0.06**	0.24±0.03**

Note. *p<0.01 and **p<0.05 compared to the control.

than in control animals. Aggressive rats were characterized by slower movements and required more time for crossing squares (3.5 cycles over 0.7 sec compared to 6 cycles over 0.8 sec in nonaggressive animals).

The incidence and duration of freezing behavior cycles in aggressive rats were higher than in control animals (6 and 47.4% *vs*. 4 and 16.3%, respectively).

Aggressive rats differed in their exploratory activity and stereotyped behavior. The number of peripheral rearing postures decreased by 5 times, while the mean cycle took 9.8-fold more time than in the control. No central rearing postures were seen in aggressive rats. The number of grooming reactions in aggressive rats was higher than in controls (1.1 and 1.0, respectively).

Previous studies showed that predatory aggression is induced by stimulation of the lateral hypothalamus and is associated with the activation of neuronal pathways entering the midbrain [6]. Neurons in the midbrain central gray matter control predatory aggression. The hippocampus is also involved in the regulation of predatory aggression [3]. In our experiments the most pronounced changes in the distribution of norepinephrine, dopamine, and serotonin were found in these brain structures (Table 1).

In the midbrain of aggressive rats containing a considerable amount of dopaminergic and noradrenergic neurons the content of norepinephrine increased by 2.5 times, while serotonin concentration was 2-fold lower than in control animals. The contents of these neurotransmitters underwent considerable changes in the hippocampus and lateral hypothalamus.

Killing of one rat by another is associated with changes in the ratio between neurotransmitters in various brain structures, but not with variations in the concentration of individual substances [1].

In aggressive rats the norepinephrine/serotonin ratios in the midbrain, lateral hypothalamus involved in the formation of motivational and emotional states [7], and hippocampus possessing multisensory functions [3] increased by 5, 5.3, and 2.7 times, respectively (Table 2).

We compared quantitative changes in biogenic amines during pilocarpine-induced and natural aggressions. In naturally aggressive animals the catecholamine/serotonin and norepinephrine/serotonin ratios underwent similar, but less pronounced changes compared to rats with pilocarpine-induced aggression. Behavioral reactions typical of rats with pilocarpine-induced aggression were attenuated or even absent in naturally aggressive animals (*e.g.*, steady state, crawling, and rapid breathing). These data indicate that the change in biogenic amine content is an important, but not the sole factor that determines killing of animals.

TABLE 2. Norepinephrine/Serotonin and Catecholamine/Serotonin Ratios during Pharmacological and Natural Aggressions (*M*±*m*)

Brain structure	Nonaggressive state	Aggression	
		pilocarpine-induced	natural
Midbrain	0.91±0.06 1.52±0.11	4.63±0.28* 6.68±0.21*	1.80±0.22* 3.05±0.18*
Lateral hypothalamus	1.15±0.22 1.72±0.24	6.08±0.32* 7.79±0.31*	3.42±0.29 4.72±0.34
Hippocampus	1.50±0.08 2.72±0.13	4.12±0.15* 6.53±0.18*	3.18±0.18* 5.53±0.21*

Note. *p<0.05 compared to controls.

TABLE 3. Distribution of Serotonin and 5-HIAA in Brain Structures (μmol/g, *M*±*m*)

Brain structure		Nonaggressive rats	Nonaggressive rats in darkness	Aggressive rats in darkness
Midbrain	serotonin	0.889±0.039	0.823±0.083*	0.418±0.066*
	5-HIAA	0.594±0.061	0.675±0.078*	1.028±0.043*
Hippocampus	serotonin	0.465±0.041	0.432±0.068*	0.185±0.049*
	5-HIAA	0.518±0.032	0.560±0.09	0.951±0.121**
Lateral hypothalamus	serotonin	1.212±0.081	1.140±0.115**	0.302±0.088**
	5-HIAA	0.930±0.074	0.982±0.110**	1.766±0.207
Visual cortex	serotonin	0.598±0.028	0.581±0.089*	0.143±0.056*
	5-HIAA	0.434±0.046	0.461±0.048*	0.645±0.052*

Note. *$p<0.01$ and **$p<0.05$ compared to nonaggressive rats.

Since the content of serotonin involved in the formation of aggressive behavior decreases during nighttime [8], we studied the effect of pilocarpine on the metabolism of serotonin and its metabolite 5-HIAA in various brain structures in aggressive animals during phase shift.

The rats were divided into 3 groups. Group 1 animals were kept under natural light/dark regimen. Group 2 rats were housed in constant darkness. Group 3 animals were kept in constant darkness and transformed into killer rats [11].

Aggressive rats kept in darkness became behaviorally passive: the time of freezing increased, central rearing activity was absent, and number of peripheral rearing postures decreased to a minimum. Group 2 animals retained high locomotor activity, and the incidence of grooming reactions was much higher than in the control.

Previous studies showed that long-term exposure to darkness changes the pattern of activation of serotoninergic neurons [1]. In these animals serotonin conversion into melatonin in the pineal gland and visual and motor cortices is intensified. These changes depend on the diurnal rhythm and correlate with environmental lighting conditions. It was demonstrated that the rate of dark-time melatonin synthesis is maximum during nighttime [2].

In rats kept in darkness serotonin concentration in the midbrain with ascending serotoninergic pathways decreased by 7% (Table 3). In the visual cortex that associates all ascending pathways from the retina serotonin content changed insignificantly, while 5-HIAA concentration increased by 6%. Serotonin content decreased in the hypothalamus and hippocampus.

In group 3 rats serotonin contents in the lateral hypothalamus (center of predatory aggression), hippocampus, and midbrain decreased by 75, 53, and 60%, respectively, compared to the control.

Serotonin content in the visual cortex increased by 76% in rats subjected to phase shift. Pronounced changes in serotonin content in various brain structures of rats kept in darkness indicate that serotonin conversion into melatonin is intensified during the nighttime.

Our results indicate that during aggression induced by 12.5 mg/kg pilocarpine the norepinephrine/serotonin ratio increases in the hypothalamus, hippocampus, and midbrain of killer rats. In aggressive rats exposed to constant darkness in the content of serotonin in the midbrain, hypothalamus, and visual cortex decreased. Changes in serotonin content and behavioral profile of animals indicate aggravation of pathological aggression.

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