Brain Content of 5-Hydroxytryptamine and 5-Hydroxyindoleacetic Acid and Immune Response in Aggressive C57Bl/6J Mice

L. B. Devoino, E. L. Al'perina, E. K. Podgornaya,* O. V. Polyakov,* G. V. Idova, and R. Yu. Il'yuchenok*

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Catabolism of 5-hydroxytryptamine in the midbrain raphe nuclei of aggressive C57Bl/6J mice increased after 10 and 20 days of confrontations. Both catabolism and concentration of 5-hydroxytryptamine increased in the dopaminergic nuclei A11, A10, A9, and in the amigdala. The level of 5-hydroxyindoleacetic acid in the A9 and raphe nuclei decreased after 20 days of confrontations, which coincided with manifestation of the immune response.

Key Words: *aggression; 5-hydroxytryptamine; brain structures; immune response*

Various forms of zoosocial behavior are associated with different immune responses [1,4,13]. Our previous data on CBA and C57Bl/6J mice showed that aggressive behavior increased the number of rosette- and plaque-forming cells in the spleen during immunization [4,6]. However, this immunostimulation in C57Bl/6J mice required longer confrontation compared to CBA mice [1].

It is known that some types of zoosocial behavior modulate activity of neurotransmitter systems, in particular 5-hydroxytryptamine (5-HT) and dopamine (DA) [14]. At the same time, the 5-HT and DA brain systems are involved in immune response regulation: they stimulate or suppress immunogenesis [6,12]. It can be assumed that the intensity of the immune response associated with certain behavior depends on activity of the brain neurotransmitter systems. There is accumulating evidence that aggressive behavior depends on DA-ergic activity [3,14]. However, recent reports show that the 5-HT system is also involved [10]. This can explain delayed stimulation of the immune response in aggressive C57Bl/6J mice compared to CBA mice, since these strains considerably differ in the initial level and brain distribution of neurotransmitters, and activity of relevant metabolic and catabolic enzymes [9]. In this study, we analyzed alterations in 5-HT metabolism in different brain structures after different periods of confrontations to reveal the metabolic pattern of 5-HT providing immunostimulation in aggressive C57Bl/6J mice.

MATERIALS AND METHODS

The study was carried out on 2.5-3-month-old C57Bl/6J mice weighing 23-24 g. The animals were maintained under standard vivarium conditions. Aggressive behavior was provoked using the model of sensory contact [8]. Two mice were placed into a metal cage separated with a transparent removable wall with small openings which allowed animals to see and perceive each other without physical contacts (distant sensory contact). Aggression was tested daily for 10 or 20 days. To this end the wall was removed for 10 min, after that some animals were decapitated, while others were immunized with sheep erythrocytes (5×10^8, intravenously). The immune response was measured on

Laboratory of Neurochemical Modulation, *Laboratory of Mechanisms of Memory Regulation, Institute of Physiology, Siberian Division of Russian Academy of Medical Sciences; **Laboratory of Dielectric Layers, Institute of Inorganic Chemistry, Siberian Division of Russian Academy of Medical Sciences, Novosibirsk

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TABLE 1. Content of 5-HT and 5-HIAA (ng/g Tissue) in Aggressive C57Bl/6J Mice *(M±m)*

Brain structure	5-HT			5-HIAA		
	controls	aggressors		controls	aggressors	
		10 days	20 days		10 days	20 days
Frontal cortex	162.1±3.2	247.0±5.1*	200.0±4.2*+	55.3±1.2	61.10±0.94*	40.5±1.0*+
Amigdala	239.5±6.5	494.4±8.9*	667.5±27.4*+	76.5±1.9	68.9±1.2**	162.5±4.7*+
Hippocampus	648.0±13.7	697.0±15.6***	600.0±12.4***+	200.0±4.1	151.5±2.5*	171.7±4.4*+
Raphe nuclei	1037.5±27.4	906.0±19.4*	599.0±18.8*+	29.5±0.6	599.0±12.3*	197.5±6.0*+
A11	211.5±4.3	600.0±13.9*	757.0±17.6*+	59.0±1.5	67.7±2.0**	197.5±4.0*+
A10	163.3±4.2	453.0±10.4*	576.0±10.3*+	44.3±1.0	44.3±0.9	121.6±3.8*+
Nucleus accumbens	359.5±7.2	235.3±3.1*	407.2±7.8*+	70.4±1.7	24.9±0.6*	251.0±7.2*+
A9	179.6±3.5	357.0±15.6*	459.5±10.2*+	34.0±1.0	252.9±7.6*	173.9±3.5*+
Caudate nucleus	150.0±3.6	72.5±2.3*	150.2±2.7+	80.9±2.1	35.2±0.7*	19.5±1.3*+
Hypothalamus	402.0±8.8	207.0±0.6*	415.0±8.7+	147.0±5.4	10.0±0.3*	201.5±3.7*+

Note. *p<0.001, **p<0.01, and ***p<0.05 compared to the control; +p<0.001 compared to aggressors after 10 daily confrontations.

day 5 after immunization by counting the number of rosette- and plaque-forming cells in the spleen [7,11]. Control group comprised mice without confrontation experience housed individually 5-7 days before the end of the experiment. 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in the frontal cortex, amigdala, A9, caudate nucleus, A10, nucleus accumbens, A11, and hypothalamus were determined by HPLC with the electrochemical detection (LKB) [2]. The data were processed statistically using Studen's t test.

RESULTS

Twenty days of daily confrontations enhanced 5-HT catabolism in the raphe nuclei of aggressive C57Bl/6J mice without elevating its level, while both the content and catabolism of 5-HT increased in the A11, A10, A9, amigdala, and nucleus accumbens, the DA-ergic structures receiving 5-HT projections from the raphe nuclei. Accumulation of the 5-HT in the projection zones and its decreased content in the raphe nuclei probably result from more intense axonal transport of HT in aggressive mice. The level of 5-HT in A9, the nuclear part of the nigrostriatal DA-ergic system increased with increasing the number of confrontations, while the content of 5-HIAA after 20 daily confrontations decreased almost 2-fold compared to the 10-day level suggesting 5-HT accumulation (probably due to its deposition and reduced synaptic release) and, therefore, the reduced activity of the 5-HT system in this structure. In the caudate nucleus, the terminal zone of the nigrostriatal DA system, the level of 5-HT and 5-HIAA did not differ from the control after either 10 or 20 days of confrontations.

We also determined the 5-HIAA/5-HT ratio characterizing 5-HT catabolism and synaptic activity. Only in the raphe nuclei and A9 involved in immunomodulation [6,12] 5-HT catabolism markedly enhanced after 10 daily confrontations (0.66 *vs.* 0.03 in the control, p<0.001 and 0.71 *vs.* 0.19 in the control, p<0.001 for the raphe nuclei and A9, respectively) decreased after 20 confrontations (0.33 and 0.38 in the raphe nuclei and A9, respectively, p<0.001). The immune response was also activated at this period (after 20

TABLE 2. Confrontation-Induced Changes in the Number of Rosette- and Plaque-Forming Cells in Aggressive C57Bl/6J Mice after Immunization with Sheep Erythrocytes (*M±m*, n=11-19)

Index	Control	Aggressors	
		10 days	20 days
The number of cells forming: rosettes/10^3 cells	31.3±1.2	30.7±0.5	50.0±1.6*
plaques/10^6 cells	184.3±15.8	205.4±11.0	245.7±21.3**
The number of plaque-forming cells per spleen	19,435.3±1815.3	24,480.7±1697.4	27,348.5±3361.8**

Note. *p<0.001 and **p<0.05 compared to the control.

daily confrontations, Table 2) and therefore immunostimulation coincided with the reduced activity of the midbrain raphe nuclei and A9.

Thus, aggressive behavior increases the level of 5-HT and its metabolite 5-HIAA in some brain structures of C57Bl/6J mice indicating activation of 5-HT metabolism. At the same time, stimulation of the immune response manifests itself only after 20 days of confrontations coinciding with the reduction of 5-HIAA level in the A9 and raphe nuclei, which attenuates 5-HT-ergic inhibitory effects on the DA system and enables predominance of DA activity. This interplay between the 5-HT and DA systems is supported by the data on increased content of DA metabolites in the A9 of aggressive C57Bl/6J mice after 20 days of confrontations [5].

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