PHARMACOLOGY AND TOXICOLOGY

Effect of Intranasal Administration of γ-Aminobutyric Acid on Intraspecies Aggression of Male Mice

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Intranasal administration of γ-aminobutyric acid (GABA) modifies the behavior of male mice in the intraspecies aggression model. Low doses of GABA (0.5 mg/kg) considerably decrease the number of attacks for several days. Systemic administration of GABA in high doses (100 mg/kg) induces short-term changes in the aggressiveness of male mice. It is hypothesized that intranasally administered GABA enters the central nervous system without crossing the blood-brain barrier.

Key Words: *γ-aminobutyric acid; intranasal administration; aggressive behavior; blood-brain barrier*

Intranasal (IN) administration is the most effective route for some pharmacological substances, primarily for neuropeptides. The mechanism by which these substances enter the brain so far remains unknown. It was suggested that they are transported via the blood vessels of respiratory epithelium [7]. However, it was demonstrated that IN administered ^{125}I-histone is accumulated in olfactory bulbs [2]. This im-plies that other mechanisms operate upon accumulation of this protein in the central nervous system (CNS), for instance, axoplasm transport in the peripheral region of the olfactory analyzer [8]. It was shown that radio-labeled histone readily crosses the blood-brain barrier (BBR) irrespective of adminis-tration route [2].

Our objective was to estimate the ability of the inhibitor neurotransmitter GABA to cross the BBR and exert central effect upon IN administration. The effect was assessed in the intraspecies aggression model (territorial aggression), which is a convenient tool for investigation of GABA agonists/antagonists [4]. Systemic administration of GABA was used as the control.

MATERIALS AND METHODS

Experiments were performed on 210 adult male albino mice aged 2-2.5 months. The intraspecies aggression model was employed [4]. At the same daytime, an "intruder" (other male) was placed into the cage of a "resident", and the number of attacks of the resident toward the intruder during a 5-min period was calculated. The results obtained 24 h before administration of GABA served as the control. GABA (Reanal) was administered intranasally in a single dose of 0.1, 0.3, 0.5, 1, or 10 mg/kg or intraperitoneally in a dose of 10 or 100 mg/kg. GABA was dissolved in physiological solution for the warm-blooded animals, the effect of which was examined in a special series of experiments. The mice were tested 15 min after administration of GABA; this time is sufficient for crossing the BBR by a pharmacological agent after IN administration [2]. The test was repeated after 24 h and sometimes after 2, 3, and 10 days. The data of these tests were compared with those obtained in intact mice. The percent of changes in the parameters of the

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TABLE 1. Number of Attacks of Resident toward Intruder after Administration of GABA (*M±m*)

Administration route	Dose, mg/kg	Test after administration of GABA					
		24 h before	15 min	24 h	2 days	3 days	10 days
Intranasal	0.1	27.81±2.36	29.04±2.57	24.76±1.74	—	—	—
	0.3	24.76±1.77	25.61±2.22	21.05±3.58	—	—	—
	0.5	23.55±1.89	18.25±2.26*	16.68±1.91*	—	21.68±2.38	—
	1.0	45.43±3.52	29.33±3.53*	23.93±3.06*	25.13±3.36*	31.53±2.64*	42.8±2.54
	10.0	30.13±3.72	15.27±2.76*	11.40±3.24*	17.60±2.21*	21.35±1.90*	32.8±3.42
Intraperitoneal	10	42.93±1.19	43.75±2.25	—	—	—	—
	100	38.29±2.01	26.74±2.18*	36.91±1.28	—	—	—

Note. *$p<0.001$ in comparison with the data obtained 24 before administration of GABA.

aggression reaction was determined, and the significance of differences was evaluated by the *t* test.

RESULTS

Upon IN or intraperitoneal administration, physiological solution used for GABA dissolution did not modify the parameters of aggression of male mice. Intraperitoneal administration of GABA in low doses had no effect on the behavior of mice. A transient insignificant decrease in the number of attacks was observed at 100 mg/kg GABA (Table 1). The parameters of aggressive reaction were restored 24 h after systemic administration of GABA.

After IN administration, GABA produced a different effect on aggressive behavior of male mice. Fifteen minutes after administration in low doses (0.1 and 0.3 mg/kg) it had no effect on aggression and slightly inhibited it after 24 h (the differences were statistically insignificant, Table 1). In a higher dose (0.5 mg/kg) GABA significantly decreased (by 28%) the number of attacks 15 min after administration, the effect being preserved for 24 h, and normal aggressiveness was restored on the 3rd day (Table 1). The increase in GABA dose led to potentiation and prolongation of its inhibitory effect on aggressiveness. The effect was preserved for 10 days after administration of GABA in a dose of 10 mg/kg. The number of attacks decreased by 35-62% in comparison with the control at various terms of the test.

Thus, after IN administration GABA produces fast and prolonged effect on the CNS, which in our model is manifested as reduced aggressiveness. These findings imply that IN administered GABA crosses the BBR, as evidenced by the fact that GABA inhibited aggressiveness in smaller doses than upon systemic administration. Presumably, after IN administration GABA is rapidly accumulated in the olfactory bulbs similar to ^{125}I-histone [2]. GABA may enter the olfactory bulbs via the system of fast axonal transport of amino acids in the olfactory nerve bundles. This type of transport has been demonstrated for other amino acids in peripheral olfactory system, i.e., between olfactory receptors and olfactory bulbs [8]. The olfactory bulbs are the first component of the CNS in which the signal triggering aggressive behavior is formed [3,5]. Inhibitory neurotransmission is the major function of GABA in the CNS. The olfactory bulb contains considerable amounts of GABAergic synapses in different neuronal structures [6]. These synapses were identified in the olfactory nerve—mitral cell system, where they are probably involved in the inhibition of the information flow that determines the realization of aggressive behavior of male mice from the receptors to other structures of the olfactory analyzer. The effects of GABA-agonists entering CNS upon systemic administration have been described [4]. However, it remains unclear whether after IN administration exogenous GABA acts at the synaptic level or becomes involved in other mechanisms. Our findings indicate that GABA, and probably other neurotransmitter amino acids, can be administered intranasally in order to modify various functions of the CNS.

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