GABA-ERGIC CORRELATES BETWEEN AGGRESSIVENESS AND SOCIABILITY IN ISOLATED MICE

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Much attention has been paid in recent years to gamma-aminobutyric acid (GABA) in connection with its role in the control of the key energy processes of the brain, and in the regulation of functional activity of the nigrostriatal and mesolimbic dopaminergic systems which exert subcortical control over locomotion and elementary forms of behavior [1, 5, 9]. Little is known about the role of GABA in the regulation of complex forms of behavior, especially intraspecific behavior. It is not clear to what extent facilitation or inhibition of GABA-ergic transmission may be specifically linked with an increase or decrease of sociability, aggressiveness, and sexual behavior.

The object of this investigation was to study the degree of change of intraspecific sociability and aggressive behavior in mice subjected to isolation, depending on modulation of GABA-ergic transmission by agonists and antagonists of GABA.

EXPERIMENTAL METHOD

Experiments were carried out on 42 male CC57W mice which were kept in isolation from their kin in individual cages for 12 weeks, with free access to food and water. The ethologic analysis of behavior of the aggressive isolated animal during interaction with its standard partner was carried out with the Ethograph–EC 1022 computer complex [3]. The cumulative number of acts for each category of behavior, and the mean probability of appearance of each act and posture throughout the experiment were calculated. All acts and postures were classified in motivation categories: sociability, aggressiveness, defense, sexual behavior, ambivalent behavior, and individual behavior [3, 8, 10]. The GABA agonist muscimol, the irreversible inhibitor of GABA transaminase (GABA-T) gamma-acetylene-GABA (GA-GABA), blockers of GABA receptors bicuculline and picrotoxin, and an inhibitor of GABA synthesis (inhibitor of glutamate decarboxylase) thiosemicarbazide were used. All preparations were injected intraperitoneally in a volume of 0.1 ml/kg body weight. The significance of the results was assessed by Wilcoxon's nonparametric T criterion for tied ranks.

EXPERIMENTAL RESULTS

The control experiments showed (Table 1) that as a result of isolation for 12 weeks the mice lost their intraspecific sociability, their aggressive behavior was sharply intensified, and the spectrum of their possible types of interaction was narrowed.

Activation of GABA-receptors by muscimol (0.2 mg/kg) had little effect on individual behavior but reduced the probability of attacking (Table 1). Muscimol in a dose of 0.5 mg/kg did not inhibit aggressive behavior completely, it did not stop manifestations of threatening, it reduced the likelihood of ambivalent acts and postures, and increased the likelihood of exhibition of forms of intraspecific sociability such as investigation of the body and sniffing the genitalia. These changes took place against the background of reduced individual activity and an increase in static postures. Muscimol in a dose of 1 mg/kg caused a switch from aggressive to defensive behavior (Table 1) and reduced individual behavior of active type (locomotion). The drug sharply inhibited intraspecific sociability.

The GABA inhibitor GA-GABA, in a dose of 50 mg/kg, caused some decrease in the frequency of attacking and manifestations of threatening (Table 1), increased the frequency of acts of sniffing the body and geni-

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TABLE 1. Change in Probability of Appearance of Different Types of Behavior in Isolated Mice under the Influence of GABA Agonists

Type of behavior	Control for muscimol	Muscimol (30 min)			Control for GA-GABA	GA-GABA (2 h)			GA-GABA 75 mg/kg (3 h) + picrotoxin 1 mg/kg (30 min)
		0.2 mg/kg	0.5 mg/kg	1.0 mg/kg		50 mg/kg	75 mg/kg	100 mg/kg	
Intraspecific sociability:									
sniffing the body	0,009	0,051*	0,108*	0,062	0,010	0,103*	0,168*	0,016	0,091*
sniffing the nose	0,004	0,001	—	—	—	—	—	0,012	—
sniffing the genitalia	0,036	0,048	0,043	0,003	0,032	0,088*	0,061		0,067
Aggressiveness:									
attacking	0,210*	0,111*	0,019	—	0,322*	0,174*	0,042	0,016	0,238*
threatening	0,066*	0,065*	0,051	0,023	0,116*	0,037	0,024	0,065*	0,067
Defense									
standing sideways	—	—	—	0,060*	—	—	—	0,049	—
vertical stance	—	—	—	0,017	—	—	—	0,012	—
Ambivalence:									
shaking the tail	0,103*	0,064	0,042	0,026	0,081	0,088	0,032	0,028	0,064
Individual behavior									
locomotion	0,175*	0,171*	0,137*	0,126*	0,163*	0,182*	0,291*	0,196*	0,282*
vertical stance	0,071	0,170*	0,120*	0,010	0,091	0,083	0,095	0,036	0,062
grooming	0,110*	0,037	0,006	—	0,085	0,074	0,038	0,008	0,045
sitting	0,192*	0,272*	0,488*	0,665*	0,102*	0,163*	0,241*	0,549*	0,069

Legend. Here and in Table 2, asterisk indicates most likely behavioral acts.

TABLE 2. Changes in Probability of Appearance of Different Types of Behavior in Isolated Mice under the Influence of GABA Antagonists

Type of behavior	Control for thiosemicarbazide and picrotoxin	Thiosemicarbazide (1 h)		Picrotoxin 1 mg/kg (15 min)	Control for bicuculline	Bicuculline 1 mg/kg (15 min)
		1 mg/kg	3 mg/kg			
Intraspecific sociability:						
sniffing the body	0,007	0,007	0,002	0,007	0,012	0,011
sniffing the nose	0,009	0,008	—	—	0,007	0,002
sniffing the genitalia	0,009	0,010	0,013	—	0,022	—
Aggressiveness:						
attacking	0,162*	0,273*	0,269*	0,314*	0,288*	0,254*
threatening	0,110*	0,048	0,049	0,130*	0,126*	0,128*
Sexual behavior:						
attempted copulation	—	0,021	—	—	—	—
copulation	—	0,003	0,003	—	—	—
Ambivalence:						
shaking the tail	0,073	0,075	0,053	0,093	0,081	0,118*
Individual behavior						
locomotion	0,162*	0,168*	0,204*	0,152*	0,170*	0,124*
vertical stance	0,092	0,103*	0,114*	0,067	0,089	0,064
grooming	0,098	0,067	0,078	0,065	0,076	0,010
sitting	0,164*	0,141*	0,130*	0,134*	0,185*	0,278*

talia, but did not significantly change individual behavior. GA-GABA in a dose of 75 mg/kg caused a further decrease in aggressiveness and an increase in intraspecific sociability. In a dose of 100 mg/kg, GA-GABA caused maximal inhibition of aggressive behavior and sociability 1-2 h after its administration, accompanied by activation of defensive behavior (Fig. 1; Table 1). However, by the time of stabilization of a high GABA level in the CNS (about 4 h after administration) aggressiveness in the isolated animals began to recover gradually. This is evidence that the compensatory mechanisms responsible for integration of aggressive behavior are activated sufficiently rapidly, and an increase in the GABA level in the CNS alone is insufficient to give rise to prolonged and effective blocking of aggression by GABA-T inhibitors. Nevertheless, when both muscimol (1 mg/kg) and GA-GABA (100 mg/kg) were used, temporary activation of inhibitory GABA-ergic mechanisms led to dissociation between interdependent (aggression–defense) behavioral responses: Inhibition of behavior requiring active orientation and intricately coordinated movements (attacking) was inhibited and responses requiring immobilization and primitive movements (defense) were enhanced.

Bicuculline, which blocks GABA receptors, in low doses (0.5 mg/kg) increased the number of attacks on the partner (Fig. 2), but an increase in the dose of 1.0-1.5 mg/kg led to some decrease in aggression and to a sharp decrease in intraspecific sociability. In a dose of 2 mg/kg, bicuculline caused convulsions in the isolated mice. Picrotoxin (1 mg/kg) increased aggressiveness in the isolated animals but did not change intraspecific sociability depressed by the isolation factor (Table 2). Picrotoxin restored aggressiveness and threatening in mice previously treated with GA-GABA (75 mg/kg) and prevented the activating action of GA-GABA on intraspecific sociability (Table 1).

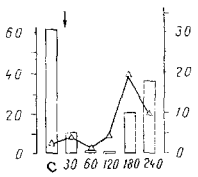

Fig. 1

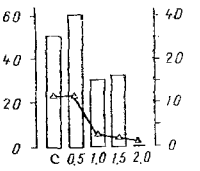

Fig. 2

Fig. 1. Dynamics of effect of GA-GABA (100 mg/kg) on aggressiveness and sociability in isolated mice. Abscissa, time (in min); ordinate: left – cumulative number of attacks (unshaded columns), right – number of acts of intraspecific sociability (triangles). C) Control. Arrow indicates time of injection of drug.

Fig. 2. Action of bicuculline on aggressiveness and sociability in isolated mice. Abscissa, dose (in mg/kg). Remainder of legend as to Fig. 1.

Thiosemicarbazide (1 and 3 mg/kg) increased the probability of attack, depressed sociability, and sharply increased individual motor activity. In a dose of 1 mg/kg the drug caused attempts at copulation with the male (homosexual behavior). With an increase in the dose of 3 mg/kg motor activity was enhanced and this effect was reduced (Table 2).

Changes in behavior arising in mice after prolonged isolation may be linked with a deficiency of GABA-ergic inhibitory mechanisms, for GABA antagonists can exacerbate the effects of isolation. Isolation sharply lowers the threshold for convulsions in mice, and this also may be due to GABA deficiency. The results of the present investigations show that GABA deficiency may be manifested in the form of multiple pathology of behavior, not only aggressive, but also sexual (when thiosemicarbazide is used). If GABA deficiency is really the pathogenetic link responsible for the pathology of behavior in isolated animals (hyperaggressiveness, hyperreactivity), making good the deficiency ought to restore normal behavior. In fact, the use of GABA analogs (β-phenyl-γ-aminobutyric acid, 4-phenylpyrrolidone-2, hydroxybutyrate) can restore normal behavior to aggressive [4] and frightened [2] isolated animals. The use of agonists of GABA receptors alone caused something resembling a restorative effect (muscimol in a dose of 0.5 mg/kg). Large doses of muscimol depressed aggressive behavior nonselectively. High affinity of muscimol in vitro [7] does not guarantee the effectiveness of the drug at the behavioral level as an agent selectively compensating for the GABA deficiency. The sufficiently selective making good of the GABA deficiency by blocking GABA-T in isolated animals shows that intraspecific sociability against the background of depressed aggressive behavior can be selectively but temporarily restored.

Modulation of the activity of GABA-ergic transmission by neuropharmacological agents thus shows that GABA antagonists strengthen aggressiveness and reduce sociability, whereas GABA agonists are variously capable of restoring intraspecific sociability and depressing aggressiveness in mice after prolonged isolation.

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