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Differential Effect of Unilateral Amygdalar $GABA_A$ Receptor Agonist Injection on Low- and High-Anxiety Rats

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Abstract

The influence of γ-aminobutyric type-A ($GABA_A$) receptors agonist (muscimol hydrobromide, 0.1 μg/0.5 μl) injections into the right or left basolateral amygdala (BLA) on the behavior of high-anxiety (HA) and low-anxiety (LA) rats subjected to the elevated plus-maze (EPM) test was investigated. Anxiolytic-like effects (increase of open-arm entries and open-arm time) was revealed only after administration of muscimol into the left (but not right) amygdala of HA animals. No effect was observed upon administration of muscimol to LA rats. These findings suggest an important role in anxiety regulation of the amygdalar GABA levels, and the assumed GABA hemispheric lateralization.

Keywords

Anxiety, Basolateral Amygdala, $GABA_A$ Receptor, Muscimol Hydrobromide, Hemispheric Lateralization

1. Introduction

Anxiety is an emotional state accompanied by anticipation of a potential threat. The underlying mobilization of the organisms' reserves is of adaptive value. In addition to the anxiety as a state, the trait anxiety is observed in humans as stable characteristics of an individual [1] [2]. J. Gray referred to anxiety, together with impulsiveness, as to one of the most important features of a personality and thought that it reflected inter-individual differences in reactivity of the behavioral inhibition system [3]. Other authors also view anxiety as one of the major characteristics of individual behavior of animals [4]. Analysis of populations of various species reveals specimen with

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high- and low-anxiety levels, what allow to genetically breed lines of animals with different levels of anxiety [1] [5]-[7]. Study of the neurotransmitter mechanisms determining the high and low level of anxiety in animals and man is an important and incompletely understood problem. Investigation of the mechanisms is especially important for medicine, since man can develop pathological anxiety, including various anxiety disorders, such as panic attacks, phobia, generalized anxiety, etc. [8]. The possibility of the development and efficiency of treatment of anxiety disorders, as well as the effect of some anxiolytic agents, are known to be individual [9]-[12]. Moreover, animals with distinct coping strategies in negative situations show different vulnerability to alcohol and drug addiction, susceptibility to immunopathological diseases [13]-[15].

Today, convincing data have been accumulated in the literature proving that one of the key structures involved in rise and regulation of anxiety and fear is the amygdala [16] [17]. In humans, electrical stimulation of amygdala leads to feelings of fear and anxiety [18]. In animals, lesions or deactivation of this structure have been associated with deficit in freezing to conditioned stimulus and impairing unconditioned freezing [19]. It is proposed that basolateral (BLA) nuclei serves as a major integrator and relay center for the sensory information necessary for anxiety, whereas the central (CeA) is the main output for the autonomic and somatic components of fear reaction through major projections to other limbic regions [17] [20] [21]. Furthemore, there are data that animals with individual differences in coping have different level of amygdala activation as well as differ in the morphology of amygdala neurons [22]-[24]. Numerous data evidence the lateralization of the amygdala upon various emotional states in both animals and men [25]-[27].

A number of researches have provided evidence for an important role of GABAergic neurotransmission in the amygdala in modulating anxiety-related behaviors. For example, local injection of a specific $GABA_A$ receptor agonist muscimol in amygdala has been shown to result in the decrease of anxiety whereas injection of a specific $GABA_A$ receptor antagonist increases of anxiety in the elevated plus-maze and social interactions tests [28] [29]. Moreover, we have previously found that the right or left intra-amygdala infusions of the $GABA_A$ agonist and antagonist, differentially affect behavior of active or passive rabbits [30]. Based on the analysis of literature data, as well as our previous findings, we hypothesize that the level of GABA and, probably, its difference between the right and the left amygdala, may determine the differences in the anxiety levels in animals. The aim of the work is to study the role of amygdalar GABA in regulation of anxiety behavior in rats with high- and low-anxiety levels. Thus, the tasks of the work include: 1) discrimination of the high- and low-anxiety animals and analysis of their behavior; 2) comparison of the effect of local unilateral injection of a selective $GABA_A$ receptor agonist muscimol hydrobromide into amygdala on the behavior of high- and low-anxiety rats in the elevated plus-maze and; 3) comparison of the efficiency of injections into the right or left amygdala.

2. Experimental Procedures

2.1. Animals

Fifty male Wistar rats (350 - 450 g) were obtained from the campus of Biomedical Technology Scientific Centre of RAMS. Rats were housed in a temperature controlled vivarium (22˚C ± 2˚C) under a 12-h light/dark cycle (lights on at 08.00 h) with food and water ad libitum. Animals were kept 5 per cage before surgery and individually, after cannula implantation. Rats were handled for about 3 min each day prior to behavioral testing. All experimental procedures were conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) on the protection of animals used for scientific purposes. The study was approved by the Ethics Committee of the Institute of Higher Nervous Activity and Neurophysiology of RAS. Enough animals were used to ensure reliability of the result, and every effort was made to minimize animal suffering.

2.2. Behavioral Testing

Behavior of the rats was tested in the elevated plus-maze, one of the most widely used experimental models for anxiety studies [31]-[33]. The plus-maze was constructed from black-colored wood and consisted of two opposing open arms (10 × 50 cm each, with 2-mm rims) perpendicular to two opposing closed arms (10 × 50 cm each, with 40-cm side walls), all joined the central area measuring 10 × 10 cm. The closed arms had no end walls. The maze was elevated to a height of 50 cm from the floor. Each rat was placed in the middle of the central area facing the open arm and allowed 5 min of free exploration. The behavioral parameters were scored as follows: number of open arm entries, open arm time, distance moved, total duration of moving, velocity, number of left

and right turns, number of centre crossing, number of rearings, number of head dipping, number of looking out to open arms, number of fecal boli and urination acts, as well as the duration and number of grooming. Rats were sorted by the number of entries in the open arms of the plus-maze, and split at the median into high-(HA) (n = 29; number of entries 0 or 1) and low-anxiety (LA) (n = 21; number of entries >1) groups.

An "EthoVision 3.1" (Noldus Information Technology b.v., 2003) integrated system was used for automatic recording and analysis of movement and behavior. Additionally, behavior in the maze was recorded by a video camera linked to a monitor.

2.3. Stereotaxic Surgery and Microinjections

About 4 - 5 weeks after the first (trial 1) exposure to the elevated plus-maze, 27 animals (HA, n = 15; LA, n = 12) were anesthetized intraperitoneally with chloral hydrate (400 mg/kg), and restrained in a stereotaxis, and the incisor bar was adjusted so that the heights of lambda and bregma were equal. The stainless steel guide cannula (23 gauge) with injection cannula (30 gauge, dental needle, Ni-pro) were implanted bilaterally in basolateral amygdala according to Paxinos and Watson [34]. Stereotaxic coordinates for cannula placement were: −2.8 mm posterior to bregma, ± 4.8 mm lateral to the sagittal suture, and 8.5 mm ventral to bregma. The guide cannula was fixed to the skull with acrylic dental plastic. The injection cannula was taken out and dummy cannula (30 gauge, dental needle, Ni-pro) was inserted in the guides to prevent contamination. After the surgery, animals were singly housed and allowed 1 week to recover from the surgery before the experiments.

For microinfusion, the dummy cannula was removed from the guide cannula, and a 30 gauge injection cannula, extending 1.0 mm from the tip of the guide cannula, was inserted. The injection cannula was connected with polyethylene tubing to a 10-µl Hamilton syringe. Muscimol hydrobromid (SIGMA) was dissolved in 0.9% saline. Mean muscimol dose leading to anxiolytic-like effect was based on the literature data [28]. Muscimol (0.1 µg/0.5 µl, SIGMA) or saline (control, 0.5 µl) was injected into the right or left basolateral amygdala of HA and LA rats over 2 min. The displacement of an air bubble inside the polyethylene tubing was used to monitor the microinjection. After infusion, the cannula was left in place for an additional minute to allow diffusion of the solution and to reduce the possibility of reflux. Rats were tested in the elevated plus-maze 10 min after the injections.

Each animal received both muscimol and saline. Each rat was tested in the EPM four times (trial 2, 3, 4 and 5) under treatment conditions with inter-trial interval of at least 48 hours. Trials with injection of muscimol and saline in the left or right amygdala interchanged. Thus, some animals received saline before the trial 2 or 4, others before the trial 3 or 5 on EPM. For some animals injections started with the right BLA, for others with left BLA.

Ten control/non-surgerized HA and LA rats were tested in the EPM four times (trial 1, 2, 3 and 4) without any treatment with inter-trial interval of 48 h to replicate experimental conditions used in the drug study.

2.4. Histology

Upon the completion of the behavioral experiments, animals were deeply anaesthetized with intraperitoneal overdose of chloral hydrate (1000 mg/kg). The animals were decapitated 10 - 20 min after the injection, brains were removed and maintained in 10% formalin solution for 2 - 3 days. Serial 180 µm coronal brain sections were cut with a freezing microtome. Cannulae placements were reconstructed on stereotaxic atlas templates from Paxinos and Watson [34].

2.5. Data Analysis

Statistical analysis was performed using Statistica 8.0 (StatSoft). The data are presented as means ± SEM. One-way ANOVA was used to analyze the compared groups for various behavioral measures taken from the plus-maze during the first trial without any injections. Factorial ANOVA was used to assess the effects of muscimol injected into left or right basolateral amygdala on the behavior of HA and LA rats in EPM as well as to analyze the behavior of rats during repeated testing in EPM with/without the infusion of saline into the amygdala. Significance of the differences in the ANOVA ($p < 0.05$) was assessed by Fisher LSD *post hoc* test.

3. Results

3.1. Selection of High-Anxiety (HA) and Low-Anxiety (LA) Animals

After the first EPM trial, 50 Wistar rats were sorted by the number of open arm entries and split at the median

into HA (n = 29; number of entries 0 or 1) and LA (n = 21; number of entries >1) animals. Behavioral parameters of high- and low-anxiety rats during the first trial on elevated plus-maze are shown in **Table 1**. LA rats spent more time and entered more frequently in the open arms of the maze than HA rats ($p < 0.05$). Rate of movement, distance moved, movement duration, number of center crossing, rearing, and head dipping were significantly higher in LA than in HA rats ($p < 0.05$). Number of fecal boli in closed arms was lower in LA as compared to HA animals ($p < 0.05$).

Thus, LA rats were showing lower anxiety, higher locomotor and exploration activity, but lower emotionality than HA rats.

3.2. Localization of Cannulae Tips in the Amygdala

Histological examination confirmed that from the total of 54 cannulae (2 per rat) 35 were located in basolateral amygdala (18 in HA (9 right/9 left) and 17 in LA (8 right/9 left) rats); 4, in central amygdala; 2, in basomedial amygdala; 7, on the central/basolateral amygdala line; and 6, out of amygdala (**Figure 1**). Localization of the cannulae tips had no significant differences in HA and LA rats. Only the data from 12 HA and 11 LA rats with injection sites located inside the basolateral amygdala were included in the analysis.

3.3. The Behavior of Intact/Non-Operated Rats and Animals during Repeated Tests in EPM upon Saline Injection in BLA

Taking into account that repeated testing on EPM altered baseline behavior [31], we carried out an analysis of the behavior of intact/non-surgerized rats at four sequential trials on EPM. We have shown that the number of entries and time spent in open arms decreased in LA rats at the second trial compared with the first; the values for subsequent trials (3 and 4) remained the same as for the second trial (**Figure 2**, Control). No changes in the behavior of HA animals were detected for trials 1 through 4. In another group (Saline) animals received saline

Table 1. Behavioral parameters of high- and low-anxiety rats in the first trial on elevated plus-maze.

Behavioral parameters			Groups		
			HA n = 29	***LA*** n = 21	*p*
Anxiety	Number of open arm entries		0.52 ± 0.15	2.85 ± 0.18	*0.000
	Time spent in the open arms (s)		16.72 ± 5.6	47.09 ± 6.58	*0.001
Locomotor activity	Distance moved (cm)		890.44 ± 46.53	1283.24 ± 54.68	*0.000
	Velocity (cm/s)		2.99 ± 0.16	4.32 ± 0.19	*0.000
	Movement duration (s)		157.11 ± 5.97	201.64 ± 7.01	*0.000
	Number of central platform crossing		4.24 ± 0.44	8.19 ± 0.51	*0.000
	Coefficient of motor asymmetry		0.02 ± 0.09	0.03 ± 0.11	0.952
Exploratory behavior/risk assessment	Rearing		5.45 ± 0.67	9.33 ± 0.79	*0.001
	Head dipping		3.69 ± 0.73	9.10 ± 0.85	*0.000
	Looking out to open arms		6.90 ± 0.87	9.05 ± 1.03	0.117
	Duration of looking out to open arms (s)		29.69 ± 3.80	35.45 ± 4.46	0.331
Autonomic indices	Number of fecal boli per minute[1]	Open arms	0.76 ± 0.49	0.33 ± 0.36	0.485
		Closed arms	0.26 ± 0.06	0.06 ± 0.07	*0.029
	Number of urination acts per minute[1]	Open arms	2.80 ± 1.17	2.20 ± 0.89	0.691
		Closed arms	0.20 ± 0.07	0.27 ± 0.08	0.502
Detour behavior	Grooming		2.03 ± 0.40	1.67 ± 0.47	0.551
	Grooming duration		31.32 ± 6.64	17.52 ± 7.72	0.183

*$p < 0.05$, significant differences between HA and LA groups; n, number of rats per group. Data are mean ± SEM. [1]Number of fecal boli and urination acts per minute were calculated using the following formula: number of urination acts (fecal boli) in open (closed) arms/open (closed) arms time × 60.

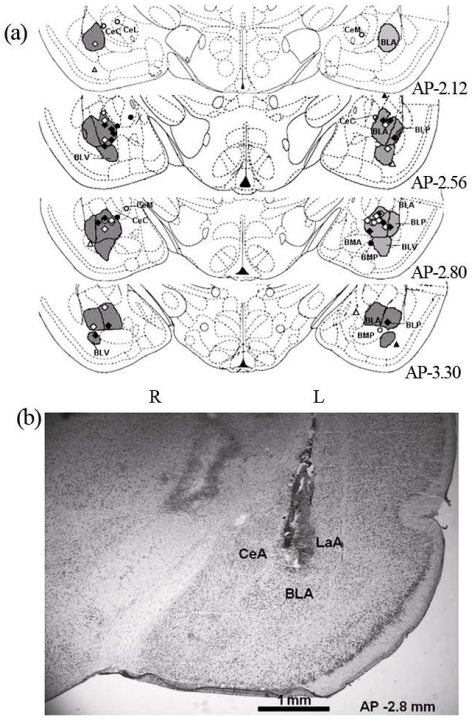

Figure 1. (a) Schematic diagram representing cannulae tips location according to the coordinates of Paxinos and Watson [34]. R, right hemisphere; L, left hemisphere. The diamonds represent the location of cannula tips in basolateral amygdala, circles, in the amygdala, but not the basolateral nucleus, and triangles, location of cannulae tips outside the amygdala. Black figures represent the location of cannula tips in the brain of low-anxiety rats (LA) and white, in the brain of high-anxiety rats (HA). BLA, BLP, BLV, anterior, posterior, and ventral parts of basolateral amygdala, BMP, anterior and posterior parts of basomedial amygdala, CeC, CeL, CeM, capsular, lateral, and medial parts of central amygdala. Dark area represents basolateral nucleus of amygdala. AP indicates coordinates relative to bregma. (b) Representative photomicrograph of micro-injections into the basolateral nucleus of the amygdala. CeA, BLA and LaA, central, basolateral and lateral nuclei of the amygdala respectively. Scale bar represents 1000 μm.

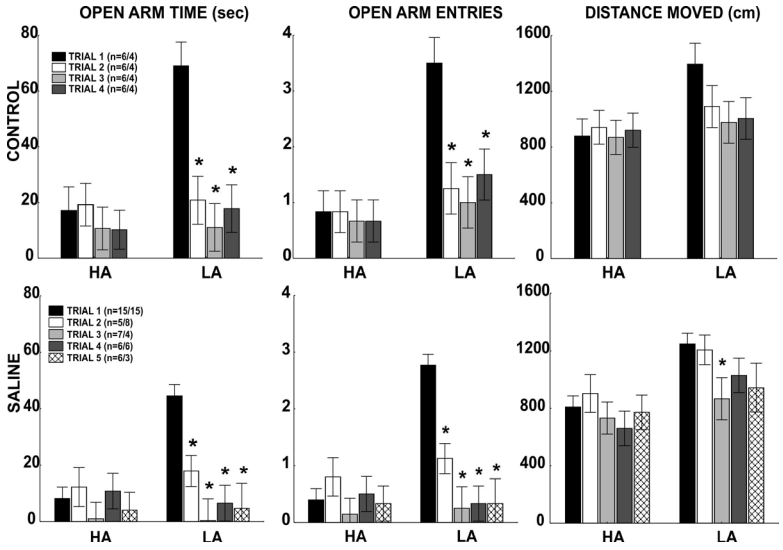

Figure 2. Behavioral parameters of HA and LA rats measured at sequential trials in the elevated plus-maze (EPM). Control, intact non-operated rats; Saline, animals after the saline injection in BLA. Trial 1 in Saline, first trial without saline injection. n, number of high-/low-anxiety rats in each trial. Data are presented as mean ± SEM. $^{*}p < 0.05$, significant differences compared to first trial.

starting with the 2nd trials. The reduction of open arm entries and open arm time in LA rats of saline group was revealed at 2, 3, 4 and 5 trials compared with the first (without saline) (**Figure 2**, Saline). However, no differences were identified for trials 2 through 5. The number and duration of open arm entries, as well as distance moved, were not changed in HA rats of saline group over trials 1 to 5. Thus, the analysis of the behavior of rats during repeated testing in EPM with/without the infusion of saline into the amygdala showed that, starting with the 2nd trials, the behavior of animals did not change significantly. These data afforded us not to take into account the number of trials in the EPM to determine the effect of muscimol compared with saline as well as not to use control group with shame-surgerized rats.

3.4. Effects of Intra-BLA Injection of Muscimol on the Anxiety Behavior of HA and LA Rats

Figure 3 shows the effect of saline and muscimol injections on the behavior of LA and HA rats subjected to EPM. *Post hoc* analysis showed that the increase of GABA transmission in the basolateral amygdala caused by left-side muscimol injections (but not right-side) significantly increased the number of open arm entries (Fisher LSD; $p = 0.015$) (**Figure 3**) and open arm time values (Fisher LSD; $p = 0.001$) (**Figure 3**) in HA, but not LA rats. No significant change in the behavior of LA rats after injections of muscimol in either left or right BLA was observed. Application of muscimol had no significant effect on locomotor (**Figure 3**) and exploratory activity, number of fecal boli, urination acts, grooming, as well as grooming duration, in both LA and HA rats (Fisher LSD, $p > 0.05$). Thus, injection of muscimol in the left BLA (but not right) decreased anxiety behavior only in HA rats.

4. Discussion

In the work, rats were split at the median into HA and LA groups based on the number of entries in the open arms of the plus-maze. Statistical analysis of two groups for others behavioral measures taken from the plus-maze during the first trial was revealed that LA rats were showing higher locomotor and exploration activity, but lower emotionality than HA rats. In support of our findings, it had been shown that rats with less anxious

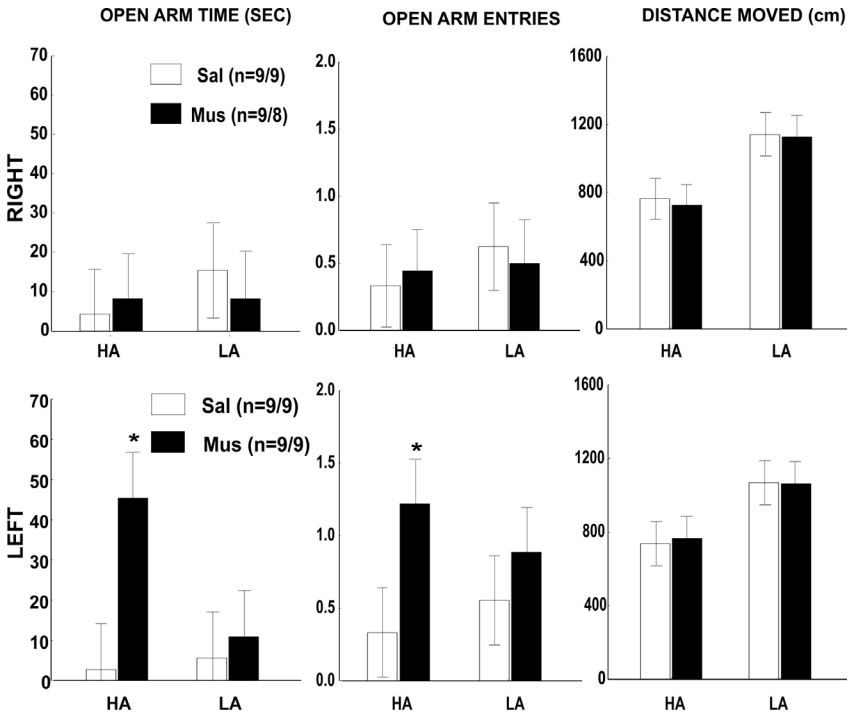

Figure 3. The effect of right or left intra-BLA microinjection of muscimol (Mus) or saline (Sal) on the behavior of HA and LA rats in the elevated plus-maze. n, number of trials with muscimol or saline in groups of high-/low-anxiety rats. Data are presented as mean ± SEM. $^{*}p < 0.05$, significant differences saline injections (Sal).

behavor in open field, light-dark test and elevated plus-maze were showing higher locomotor and exploration activity, but lower emotionality compared to more anxious rats [1] [35].

Administration of muscimol increased the number of entries and time spent in the open arms of the EPM, indicating that the drug showed anxiolytic-like behaviors without affecting locomotor activity. In agreement with our data regarding anxiolytic effect of muscimol, it had been reported that intra-amygdala injection of the drug increased the percentage of open arm time and open arm entries [28], decreased duration of tonic immobility in guinea pigs [36] and produced anxiolytic-like effects in the social interaction test [29].

It is interesting to note that introduction of muscimol causes significant changes in the behavior of only high-anxiety rats, producing no effects on the behavior of low-anxiety animals. There are data that systemic injection of midazolam (a benzodiazepine that reinforces transmission at $GABA_A$ receptors) significantly enhances the inhibition of an aversive context-induced freezing response observed during the extinction session only high (HR) anxiety rats [37]. According to our hypothesis, the fact may be in connection with the differences in GABA transmission in the amygdala between these two groups of animals. Probably, the lower level of GABA transmission in the amygdala of high-anxiety rats is compensated for upon introduction of the $GABA_A$ receptor agonist muscimol, which results in statistically significant changes in the behavior of this group of animals. Our hypothesis is in agreement with some literature facts. Mice deficient in GAD65 exhibits increased anxiety-like responses in both the open field and elevated zero maze assays [38]. Rats with artificially elevated number of GABAergic neurons are found to spend more time in the open arms of the elevated plus-maze [39]. The level of GABA receptors containing $\alpha 5$ and $\gamma 1$ subsunits is lower in the central and medial amygdala of high anxiety-related behavior (HAB) mice than in mice with normal anxiety-like behavior (NAB). Furthemore, marker for neuronal activity (FosB) is increased in principal neuron of the basolateral amygdala of HAB mice, reflecting activation of excitatory neurons [7]. Rats with low freezing response in the contextual fear test have higher GABA concentration in the basolateral amygdala if compares to the rats with high freezing response in the contextual fear test [6].

In the work, we find that statistically significant differences in the behavior of high-anxiety rats are observed only upon left-side administration of the agent. There are literature data stating that right-side, but not left-side injection of muscimol in the amygdala leads to impaired acquisition of continuous multiple-trial inhibitory-avoidance [40]. Following each extinction session infusions of GABAergic antagonist bicuculline into the right but not left BLA significantly enhances extinction of contextual fear [41]. Moreover, there literature data demonstrate lateralization of the effect anxiolytic drug on brain activity [42]-[44]. Earlier, in the experiments on rabbits we also observe the inequality of the effect of the $GABA_A$ receptor agonist upon introduction into the right and left amygdala, however, in contrast to rats, muscimol causes higher effect upon introduction in the right amygdala in passive rabbits, decreasing percent of freezing on loud sound [30]. Probably, the differences between the results of the current study and the literature data are due to differences in experimental conditions and the animals used. It is interesting to note that hemispheric asymmetries are revealed in amygdala activity in emotion [25]-[27]. These data allow the assumption that there is a hemispheric laterality in functioning of GABAergic system of the amygdala and its potential involvement in determination of the level of anxiety. Several literature facts support the assumption. The number of GABA binding sites was found to be higher in cortex and hippocampus of the left hemisphere in rats, while the opposite asymmetry was observed in the thalamus [45]. A consistently higher level of GABA contents in rat brain was observed in the right-hand substantia nigra and nucleus accumbens, and in the left-hand ventral tegmentum, ventromedial thalamus and caudate nucleus [46].

Thus, the findigs suggest an important role in anxiety regulation of the amygdalar GABA levels, and the assumed GABA hemispheric lateralization.

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