The Functional Role of Monoanimergic and Aminoacidergic Mechanisms of the Locus Coeruleus in Anxiety States of Different Aversive Origins

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It is well known that the locus coeruleus (LC), the main intracerebral adrenergic substrate, modulates various anxiety states [2,8,9]. Indeed, the effect on rats of aversive stress of nonuniform modality stimulates the synthesis of enzymes of the catecholaminergic cycle in LC [5] or activates its neurons [4]. On the other hand, the selective degeneration of ascending projections of noradrenergic LC neurons, caused by the neurotoxin 6-hydroxydopamine, or its electrolytic decomposition blocks the avoidance reaction induced by the anxiety factor [11]. It can also intensify zoosocial contacts among animals [8,10], which are an indication of an anxiogenic effect [8]. This effect can likewise result from a microinjection of a bicuculine antagonist (antagonist of the $GABA_A$-receptors) [13] directly into the LC. But the adrenergic and GABA-ergic effects of the locus coeruleus are probably not the only factors in anxiety states, as transmitter functions in the LC are also carried out by dopamine [12], serotonin, and α-aminoglutaric acid [6]. The role of the last two substances has not yet been investigated.

The purpose of the present study was to analyze the functional role in anxiety states of different aversive origins of mezaton, an α-adrenomimetic substance that stimulates the effect of norepinephrine, as well as the role of other neurotransmitters: dopamine (DA), serotonin (5-OT), GABA, and L-glutamic acid (GA), which were locally injected into the locus coeruleus.

MATERIALS AND METHODS

Experiments were carried out on 18 mongrel pubertal male rats weighing 270-360 g. The anxiety state was modeled by using the "illuminated site" and "threatening situation" avoidance methods [3]. Capillary tubes were implanted into the LC of the animals under ether anesthesia along the stereotaxic coordinates [1]: AP-8,8; L-1,1; H-6,6. The following solutions (1 μl of 1-2% concentrations) were introduced through the microinjection system of the conditioned animals: mezaton, DA, GABA, GA (10 μl), and 5-OT (serotonin-creatinine sulfate, 20 μg). After 5 min the rats were placed in an experimental stand. There, as in previous experiments [3], determinations were made with the aid of decatrons of the changes in the behavior parameters. These parameters would indicate an anxiolytic or an anxiogenic effect.

In control experiments 1 μl of 0.9% NaCl was injected into the LC of the animals. The results were analyzed by standard variational statistics methods. After the completion of the experiments the animals were euthanized under ether anesthesia. Verification

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TABLE 1. Effect of Monoamines and Amino Acids Introduced into the Locus Coeruleus on Anxiety States in Tests of Avoidance of an "Illuminated Site" (Numerator) and a "Threatening Situation" (Denominator) ($M \pm m$, $n=5$)

Substance	Dose, μg	Time during which rats remained in illuminated sector, sec	Motor activity (number of intersected squares atbase of illuminated sector)	Strenght of motivation for staying in dark sector, arbitrary units
NaCl (0.9%)	1 μl	3.2±0.44	5.4±0.25	0.54±0.06
		2.0±0.32	5.2±0.49	0.55±0.06
Dopamine	10	5.2±0.58*	6.6±0.40*	0.42±0.03
		2.2±0.33	5.4±0.40	0.54±0.06
Serotonin	20	6.2±0.44*	6.4±0.40	0.43±0.06
		4.6±0.60*	5.6±0.25	0.43±0.06
GABA	10	2.8±0.49	5.6±0.25	0.56±0.06
		4.2±0.58*	6.0±0.32	0.44±0.07
L-Glutamic acid	10	5.4±0.51*	6.2±0.20*	0.44±0.06
		2.6±0.78	5.4±0.40	0.51±0.06
Mezaton	10	3.2±0.49	5.4±0.40	0.50±0.05
		4.4±0.51*	6.0±0.32	0.44±0.03
Phentolamine hydrochloride	10	5.0±0.45*	6.2±0.37	0.41±0.04
		2.2±0.49	5.2±0.50	0.56±0.06

Note. The asterisk indicates values where $p...0.05$.

of the microinjection capillaries in the LC was carried out in morphological control experiments.

RESULTS

The morphological control experiments showed that the substances investigated affected the LC neurons. The microinjections of transmitter substances or their simulators into the LC revealed the different roles played by LC neurochemical systems in anxiety states of different aversive origin.

As can be seen from the data summarized in Table 1, the anxiety state motivated by fear [3] was resistant to chemical stimulation of the LC with GABA and mezaton, which had no notable effect on the avoidance parameters of the "illuminated site". On the other hand, local injection of DA, 5-OT, and GA into the LC produced a distinct antiaversive effect, manifested in a statistically significant increase in the time during which the rats remained in the illuminated sector. This anti-anxiety effect was not related to a motor deficiency in the performance of the acquired behavior, because 5-OT did not inhibit motor activity in the experimental animals, while DA and GA significantly stimulated it ($p<0.05$). The data presented in Table 1 show that in the formation of the fear motivation the neuronal matrix of anxiety engaged not the GABA-ergic and adrenergic, but the DA-, 5-OT-, and glutamatergic transmitter components of the LC, which are functionally important in negative emotional states. This conclusion accords with the experimental results which show that antagonists of the NMDA-glutamate receptors have an anxiolytic effect in that they decrease the number of passages from the illuminated to the darkened sector [14]. This conclusion is also consistent with investigations showing that damage to the noradrenergic system of the locus coeruleus has no effect on attentiveness, habituation, motor activity, or anxiety [2, 8].

When the rats could freely choose an illuminated or dark chamber, chemical stimulation of the LC with DA or GA did not influence the anxiety state formed as a result of a different biologically significant aversive effect [3] (the avoidance response on the part of the rats which were "spectators" against the background of the painful stimulation of the rats which were "victims"). On the other hannd, 5-OT, GABA, and mezaton counteracted the anxiety state. This anxiolytic effect was a selective one, that is, in "threatening situation" avoidance tests the transmitters in question or their simulators, while increasing the time during which the rats stayed in the illuminated sector, had no effect on the motor activity of the experimental animals (Table 1). The facts adduced show that the neuronal matrix of anxiety, formed on the basis of negative zoosocial emotional-stress reactions, engages not the DA- or glutamate-, but the adrenergic, 5-OT, and GABA-ergic transmitter components of the LC. This conclusion accords with the data obtained recently with the use of different methodological approaches which indicate that in rodents, on the LC level, the neuronal matrix of anxiety formed as a result of an acute presentation of a stress stimulus engages the functionally important GABA-ergic and adrenergic transmitter mechanisms [5, 13]. Indeed, the selective occlusion of one of them, achieved in our experiments by the microinjection into the LC of an adrenoblocker, phentolamine hydrochloride, is probably accompanied by the switching over of the functionally important DA- or 5-OT- and

glutamate-ergic synaptic inflow into the neuronal matrix, which provides for an anxiolytic effect in the model [3] where only the motivation of fear dominates (Table 1).

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MICROBIOLOGY AND IMMUNOLOGY

Neutrophil Chemiluminescence in Active Cytomegaloviral Infection

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Cytomegaloviral (CMV) infection is one of the most common viral infections occurring in the antenatal and postnatal period. The infection is diagnosed in 0.4-2.3% of all newborns [3,5], although the incidence differs in various populations. Harmless for the mother, in the fetus CMV infection may cause developmental defects and other grave complications which most frequently manifest themselves after birth in symptoms of central nervous system involvement, namely delayed mental development, microcephaly, blindness, deafness, epilepsy, muscular weakness, etc. [2,11]. The results of numerous studies on the course and outcome of CMV infection in pregnant women indicate a possible contribution of the relationships between CMV and the host immunity system to the pathogenesis of cytomegaly. An abundance of paper devoted to this problem have not yet got to

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