INVOLVEMENT OF ADRENERGIC SYSTEMS OF THE BRAIN IN CONDITIONED REFLEX ACTIVITY

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Abstract*. Among the problems of biology and medicine, the system of regulation of adaptation processes with the help of neuropeptides is one of the most pressing. An excessive reaction to stress is a prerequisite for the occurrence of various diseases. This is due to the transformation of the adaptive response into a separate stressor event (Meyerson, 1984). Functional changes in the central nervous system under the influence of extreme environmental factors are characterized by changes in metabolism, disruption of energy processes occurring in the brain, as well as accelerated aging and cell death. Shifts in the neuropeptide regulation system lead to disruption of homeostasis and, possibly, "aging" of organs and tissues, i.e. changes in the ratio of homeostatic and behavioral reactions. In recent years, neuropeptides with anti-stress properties have attracted the attention of researchers as the most promising in terms of inhibiting age-related changes in the central nervous system.*

Keywords*: conditioned reflex activity, dopaminergic system, stress, irritation, adrenergic stimulation, catecholamines.*

Based on work on the study of adrenergic systems, it is believed that the neuronal adrenergic systems of the brain control tonic cortical activation. In accordance with these ideas, an increase in adrenergic activity was accompanied by electroencephalographic and behavioral reactions of awakening, and a drop in brain norepinephrine caused synchronization of rhythms in the cortex and a sleep-like state in animals. Similar phenomena in the central nervous system CNS of the central nervous system were observed with internal administration of adrenergic drugs. At the same time, many researchers have questioned the possibility of a direct effect of blood catecholamines on brain neurons, considering the awakening reaction to be mediated by reflex influences from angioreceptors.

Grunden, in a summary of the results of studies of intracerebral and systemic applications of catecholamines, indicates that since 1903, at least 70 studies have demonstrated opposite effects: decreased motor activity, sedation, stupor, anesthesia, analgesia. In particular, in rats such effects were observed 10-20 minutes after subcutaneous injection of adrenaline 1.5 mg/kg or intraperitoneal injection of 0.25 mg/kg. After higher doses (0.6-6.0 mg/kg), the effects became more pronounced. Intraventricular administration caused behavioral changes at doses of 0.01-0.125 mg (total dose). Back in 1914, Bass observed sleep in dogs after injecting several milligrams of adrenaline subdurally or simply into the brain tissue. The introduction of this drug into the brain cisterns of dogs caused stupor, analgesia, and sleep. In this case, hyperglycemia was observed. Norepinephrine had a similar effect. The same changes have been demonstrated in other animals and humans. It is quite clear that the doses used were very high. Essentially the effects of exposure to inappropriately strong stimuli were observed. For comparison, it may be recalled that the concentrations of norepinephrine in the cerebrospinal fluid are no more than hundredths, and in the cortex no more than tenths of a microgram per gram of tissue or fluid, and the doses used were at least 1000 micrograms. Since the mechanism of action of a drug introduced into the ventricles

of the brain may be based on its capture by the neuronal tissue of surrounding structures, in particular the caudate nucleus, it can be assumed that the data obtained can be useful to a certain extent for analyzing the mechanisms of action of the adrenoreactive system at the striatal level.

The use of intracerebral administration of adrenergic drugs was widely carried out in the works of Feldberg. He described a peculiar picture of behavior after intraventricular injections of adrenaline and norepinephrine (20-40 mcg). In the first minutes, the cats exhibited chewing movements, licking, and sometimes vomiting and defecation. Gradually, over the course of 10–20 minutes, the condition of the animals changed qualitatively: they calmed down and seemed to be in a state of mild anesthesia. After an hour, the effect of the drug weakened and completely disappeared after 3 hours.

In subsequent years, studies using intracerebral injections of the drug focused on the structures of the hypothalamus, which was explained not only by the results of determining catecholamines in the brain, but also by interest in the functioning of the hypothalamic-adrenal system as a whole.

Work carried out to study behavioral changes under peripheral influences of adrenergic and cholinergic drugs provided the opportunity to formulate a hypothesis about the mediation of reactions to biologically positive stimuli through the cholinergic system, and through the adrenergic system - reactions to biologically negative influences.

To explain facts that did not fit into the framework of this hypothesis, provisions were drawn on the possibility of antagonistic or synergistic relationships between these two systems, depending on the experimental conditions. The position was even specifically formulated that the emotionally positive and emotionally negative behavior of animals should be considered from the point of view of the functional predominance of the cholinergic or adrenergic system. The hypothesis extended not only to the peripheral part of the central nervous system, but also to the brain as a whole and was presented as a general pattern for all animal species. The place of application of the action of mediator drugs was considered to be the hypothalamus, in which the following were respectively distinguished: a) positive cholinergic system (lateral and anterior hypothalamus) and b) negative adrenergic system (posterior and medial hypothalamus). However, no significant differences in norepinephrine concentrations were detected in these 30-s. The proposed hypothesis did not stand up to experimental testing. Administration of adrenaline and norepinephrine (10-49 mcg) into the hypothalamus of cats led to the above-described picture of suppression of the general motor activity of animals. Doses of drugs less than 10 mcg were ineffective, but violations of more complex forms of unconditioned and conditioned reflex behavior were clearly detected after the use of several micrograms of drugs.

This pattern in relation to the effects of large and small doses was manifested in reactions to the administration of both adrenergic and cholinergic drugs. Thus, a complex pattern of behavior (hissing, defecation, motor agitation, erection, salivation, vomiting) was observed after the injection of 8 mcg of carbocholine into the hypothalamus. Similar reactions have been produced by administration of similar doses of carbocholine to many other brain structures and appear to be nonspecific.

A thorough study of behavior during chemical stimulation of the hypothalamus was carried out in the well-known work of Grossman. The administration of crystalline carbocholine (1-5 μg) into the lateral compartment in saturated rats caused a significant increase in fluid consumption. Typically, rats began drinking 10–120 s after administration of carbocholine and continued

drinking without interruption for 15–20 min. Thirst induced by stimulation decreased gradually over the course of an hour. It has been shown that when water is freely available, the cessation of the drinking response can be caused by feedback from receptors in the mouth and stomach (similar to natural thirst). Control administration of sodium chloride did not change drinking reactions. Doses of carbocholine less than 1 mcg were ineffective. Intraperitoneal injections of atropine (50 mg/kg) one hour before stimulation completely blocked the effect of carbocholine.

An increase in fluid intake in rats was observed with cholinergic stimulation of the dorsomedial hippocampus, septum, cingulate cortex, anterior thalamic nuclei and fornix.

Stimulation of other structures: the posterior hippocampus, ventromedial hypothalamus, paraventricular nuclei of the thalamus, frontal cortex and caudate nucleus did not affect fluid intake. Further analysis of the effects of chemical stimulation of the lateral hypothalamus showed that the administration of carbocholine changed not only drinking reactions. Motor and sexual reactions, body temperature, blood sugar, urine secretion and its concentration changed. All this indicated the participation of cholinergic neurons of the hypothalamus in the regulation of diverse autonomic and behavioral reactions.

The injection of crystalline adrenaline and norepinephrine into the lateral hypothalamus caused a food reaction in rats after 5-10 minutes. Characteristically, no changes in fluid consumption were observed. There was a dose-response relationship between 1 and 5 μg. The use of higher doses led to a decrease in the activity of animals and an increase in the latent period of reactions to sensory stimuli.

Adrenergic substances caused food consumption in saturated animals, but inhibited the drinking response in rats deprived of fluid. According to Grossman, this phenomenon is similar to the reciprocal inhibition of the food reaction during thirst. During the period of increased food consumption, weight gain increased. In rats with a developed food-procuring reaction, adrenergic stimulation caused a significant increase in these reactions, which confirmed a change in the level of motivation.

The norepinephrine-induced food reaction was blocked by intraperitoneal administration of ethoxybutamoxane (0.25-1.0 μg/kg), a central adrenoblocker, but was not suppressed by the use of a peripheral adrenoblocker, dibenzyline, which proved the central genesis of this reaction. On the other hand, dibenzyline had a clear inhibitory effect on food motivation both when administered systemically and when administered into the hypothalamus, which proved the participation of both central and vascular adrenergic receptors in the regulation of food motivation. With systemic administration of the adrenergic blocker, side effects were observed - hypoactivity, decreased response to external stimuli. However, even high doses of the drug did not completely stop the adrenergic food reaction, i.e., not only adrenergic, but also other mediator systems apparently take part in the regulation of eating behavior at the level of the hypothalamus.

The reaction caused by adrenergic stimulation was slightly reduced by intraperitoneal administration of atropine (50 mg/kg). These doses caused extreme hyperactivity, restlessness, agitation, and the observed reduction may have been due to these side effects. The use of lower doses of atropine (10 and 25 mg/kg), which did not produce side effects, confirmed this position, since at these doses the food reaction did not decrease.

When interpreting the results of adrenergic stimulation of the hypothalamus as a consequence of activation of the hunger center, one has to take into account the complexity of this part of homeostasis. Most likely, stimulation of the hypothalamus leads to a general increase in

the activation thresholds of many functional systems of the hypothalamus and the perception of heterogeneous impulses from extero- and interoreceptors.

In experiments using adrenergic stimulation of the hypothalamus, other parameters indirectly related to food motivation were also recorded: blood sugar levels and oxygen consumption indicators. If the systemic administration of norepinephrine caused hyperglycemia and an increase in oxygen consumption, then intrahypothalamic injections of this substance increased the thresholds for turning on the mechanisms of intensification of metabolism and a compensatory increase in body temperature when the body cools. In general, various indicators of the level of metabolic processes changed in the same direction: the introduction of catecholamines into the hypothalamus increased the thresholds for the activation of individual homeostasis mechanisms in response to afferent flows from various interoreceptors. The intimate mechanism of action of adrenergic substances when administered systemically is associated with the excitation of both hypothalamic neurons and the activation of alpha and beta receptors of the vascular system.

According to Myers, with adrenergic stimulation of the hypothalamus, its descending influences on the peripheral mechanisms of metabolism and thermoregulation are blocked. Apparently, the significance of peripheral adrenergic receptors is much broader. Experiments with desympathization showed that a decrease in the secretion of adrenaline in the peripheral part of the sympathetic nervous system led to a significant deterioration in defensive conditioned reactions, while insufficiently strengthened connections were disrupted to a greater extent and more difficult tasks were solved worse. It is assumed that activation of the peripheral part of the sympathetic nervous system can be considered as secondary negative reinforcement.

The second proposed area of application of adrenergic drugs when administered systemically is the reticular formation of the brainstem. The injection of adrenaline into both the reticular formation of the brain stem and the vascular system led to an awakening reaction in the cortex. Systemic administration of aminazine had the opposite effect, although the point of application of its action remains controversial - primary effects on the cortex [29], blockade of adrenoreactive structures of the brain stem, or blockade of vascular receptors [22].

Interesting facts were obtained in the work of I.P.Anokhina [6] when recording EEG and observing changes in the behavior of rabbits against the background of intracerebral injections of adrenergic drugs into the reticular formation of the midbrain. Upon injection of a 0.05-0.1% solution of adrenaline (0.05-0.1 ml) in the sensorimotor and occipital areas of the cortex, a clear desynchronization was recorded, and low amplitude activity appeared with a frequency of 20-50 Hz.

A clear synchronized rhythm was observed in the contralateral region of the reticular formation and the medial thalamus

4-7 Hz. The described character of brain biocurrents was recorded within 15-40 minutes after the administration of adrenaline. Simultaneously with changes in electrical activity, a slight decrease in heart rate and increased and deepening of breathing were observed. The rabbits were becoming restless.

When, against the background of the action of adrenaline, a 0.5-0.25% solution of aminazine was introduced into the reticular formation of the same volume, changes in electrical activity developed gradually and reached a maximum after 5-15 minutes. In the sensorimotor and occipital areas, slow high-amplitude activity was recorded, against the background of which characteristic spindles periodically appeared, consisting of frequent (20-25 Gd) high-amplitude

waves. A detailed diagram of the catecholaminergic system with a description of possible ways of exerting influences is presented in the work of Crowe and Arbuthnott with a functional division into the ventral and dorsal subsystems. According to this scheme, the locus caeruleus receives connections from visceral afferents, and in particular from taste receptors. From the locus caeruleus, noradrenergic fibers are sent to almost all parts of the brain, especially to the cerebral cortex, cerebellum and hippocampus (possibly through the hypothalamus). From the ventral part of the mesencephalic part of the brain, a path begins that passes through the lateral hypothalamus to the formations of the striatum and some nuclei of the amygdala.

There are some differences in the effects of self-stimulation when electrodes are localized in the ventral bundle (dopaminergic system) and in the dorsal bundle (noradrenergic system). In the first case, there is a pronounced increase in directed activity, characteristic of the central release of dopamine and manifested in the reactions of sniffing, lapping, and chewing. In the second case, such behavior is not observed.

In contrast to the effects of adrenergic stimulation of the hypothalamus, injections of norepinephrine into the caudate nucleus (1-5 μg) did not change the latent period of the avoidance reaction, but suppressed spontaneous motor activity, increased the latent period and reduced the number of food-procuring reactions. Administration of dopamine into the same structure led to an increase in motor activity and increased the latent period of motor reflexes. The use of the drug haloperidol as a dopamine antagonist caused a sharp drop in muscle tone.

If the activation of the dopaminergic system is associated with the action of unconditioned stimuli, then the activation of the adrenergic system is associated with the mechanism of conditioned reflex action. Structurally, this can be explained by functional differences in the reticular and neostriatal levels of the adrenergic system of the brain.

Work on the mechanisms of participation of the adrenergic systems of the brain in conditioned reflex activity has demonstrated its functional heterogeneity. If the ascending adrenergic systems of the brain stem have the ability to exert a tonic effect on the cerebral cortex, then the adrenergic structures of the hypothalamus are closely related to increasing the activation thresholds of many functional systems and the perception of heterogeneous impulses from extero- and interoreceptors. It is assumed that activation of the peripheral part of the sympathetic nervous system can be considered as secondary negative reinforcement.

The striatal level, being predominantly adrenoreactive rather than adrenergic, can be a link of negative feedback to the activating systems of the brain stem.

The data obtained highlight significant functional differences between the dopaminergic systems of the striatum and the adrenergic structures of the hypothalamus and the reticular formation of the brainstem.

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