*Neuroscience and Behavorial Physiology, Vol. 24, No. 3, May-June, 1994*

# CORTICOHYPOTHALAMIC RELATIONSHIPS DURING THE DEVELOPMENT AND REALIZATION OF THE CONDITIONED REFLEX

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UDC 612.821+612.825+612.826

Translated from Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova, Vol. 43, No. 2, pp. 12-21, March-April, 1993.

*Received 15, 1992.*

The influence of motivational, emotiogenically positive and emotiogenically negative structures of the hypothalamus on the development and realization of conditioned reflexes was investigated in the experiments on dogs, cats, and rats. It was shown that the motivational structures primarily increase excitability of cortical neurons during the development of the conditioned connection, while the emotiogenically negative and emotiogenically positive structures increase the efficiency of synapses. A high degree of correlatedness of the averaged evoked responses to the conditional stimulus in the hypothalamus and new cortex is characteristic for the consolidated conditioned reflex. Direct stimulation of the motivational-alimentary zones of the hypothalamus reproduce food-procuring conditioned reflexes in dogs, while stimulations of the emotiogenically negative zones reproduce defense conditioned reflexes. Stimulation of the emotiogenically positive zones does not reproduce either; however, an intensification of the activity of neurons of the hypothalamus was recorded in rats during the successful accomplishment of the conditioned reaction of avoidance of an aversive stimulus. In cats which are capable of restraining a conditioned motoric reaction for the sake of obtaining a preferred food, the "motivational", long-latency functional connections between neurons of the lateral hypothalamus and the prefrontal cortex predominate. Short-latency "informational" connections predominate in the "impulsive" cats.

The role of the hypothalamus and its interaction with the new cortex in the formation of the functional system of the behavioral act have been the object of systematic investigations of K. V. Sudakov and his collaborators [9]. Since structures have been found in the hypothalamus that are associated with the actualization of needs and with the occurrence of emotions, it can be stated that the hypothalamus participates both in the earliest stages of the organization of behavior and its later stages, when the externally realized response is definitively formulated. A change in the frequency of the discharges of neurons of the hypothalamus arises after 10-20 combinations of sound and food, whereas the behavioral signs of the conditioned reflex appear only after 40-50 trials [16]. Neurons have been found in the lateral hypothalamus of monkeys which selectively react to the sight of water or a particular sort of food. After the animal is satiated by this food, the activity of the neurons decreases in response to its sight and taste, but is maintained in response to the sight and taste of other food [18]. The activity of neurons which are sensitive to the administration of glucose sharply increases in monkeys 0.8-2 sec before pressing on a lever in order to obtain food, and is suppressed during presses. Neurons which are insensitive to the administration of glucose, by contrast, intensify their activity during the performance of motoric reactions [15]. Some of the neurons which are sensitive to glucose alter their impulse activity in response to the conditional signal; the majority do so in response to reinforcement with food [10]. Alimentary motivation also prompts the predatory behavior of animals. It is not by chance that injury of the lateral hypothalamus precisely suppresses all components of the predatory behavior of rats, whether it be interest in prey, pouncing on it, or the killing and eating of mice [11].

In addition to drink and food motivations, the structures of the hypothalamus participate in the initiation of sexual behavior. Neurons of the medial preoptic zone of male rats intensify their activity when the female is pursued and mounted. This activity is not associated with movements and reflects the animal's sexual excitation [20].

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0097-0549/94/2403-0267$12.50 

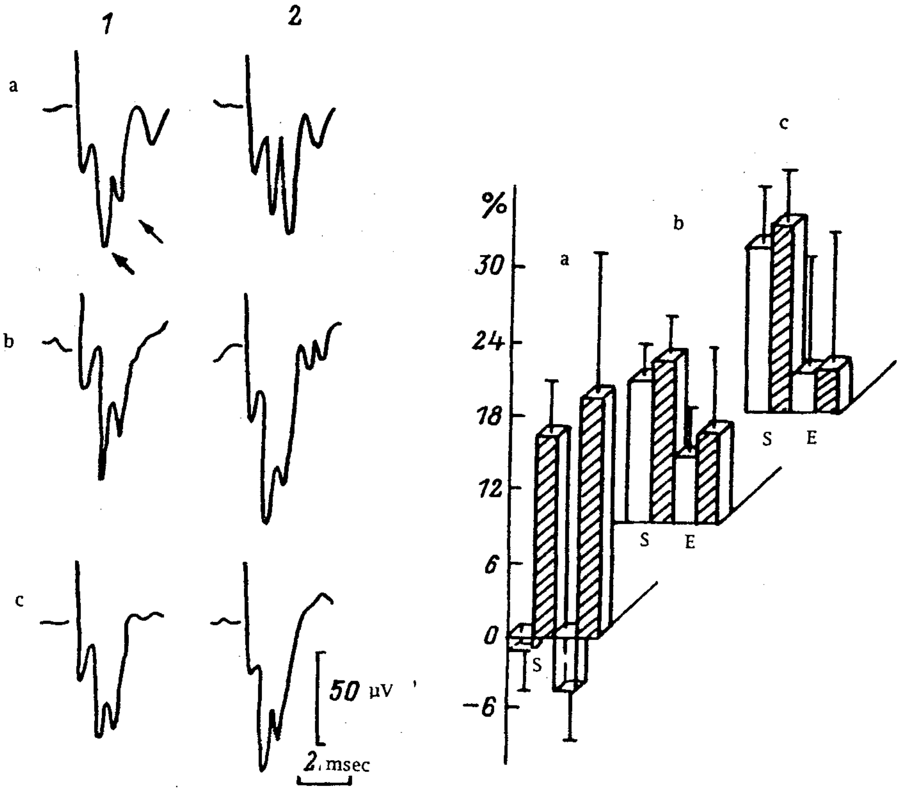


Fig. 1. Change in the response of the pyramidal tract in three experimental situations (a–c) which simulate the development of a conditioned reflex. On the left, examples of individual responses recorded in the same experiment, before (1) and during (2) presentation of the combinations. a) Decrease in the amplitude of direct component (thick arrow) and increase in the amplitude of monosynaptic component (thin arrow) of the pyramidal tract response during the combination of stimulations of two points of the sensorimotor cortex; b) increase in both components of the response during the combined action of direct cortical stimulations and the additional stimulation of the lateral hypothalamus; c) the same changes in a model of instrumental conditioned reflex with reinforcing stimulation of the lateral hypothalamus. Between a and b, as well as b and c, an extinction procedure was used (the presentation of individual conditional stimuli without combinations). On the right, summary data with respect to experiments involving an increase in the synaptic component of the pyramidal tract response. White columns correspond to relative (the control before the combinations taken as 100%) changes in the amplitude of direct; hatched columns, changes in the amplitude of the synaptic component of the pyramidal tract response during the combinations (C) and during extinction (E).

If the lateral hypothalamus and preoptic area are associated with the metabolic and reproductive needs and the positive emotions arising when they are satisfied, then it is the medial hypothalamus and the periaqueductal gray substance which serve as the substrate of the negative emotions. Stimulation of these structures elicits defense reactions in rats, on the basis of which it is possible to develop an instrumental conditioned reflex. It is interesting that in man stimulation of the gray substance induces panic, while stimulation of the medial hypothalamus induces a sense of alarm [19]. Structures which modulate defense reactions are localized in the anterior medial hypothalamus of rats, while those modulating the attack reactions of aggressive behavior are localized in the posterior hypothalamus [17]. A lesion of the ventromedial hypothalamus provokes outbursts of rage in patients [12].

Thus, the structures of the hypothalamus are involved in the formation of both motivational and emotional states. The difficulty in differentiating them resides in the fact that, arising in connection with the satisfaction, or, conversely, with the non-satisfaction of vital and more complex (zoosocial, investigatory, etc.) needs, the emotions themselves secondarily possess a motivational force, since animals strive to minimize (attenuate, interrupt, prevent) negative emotions and maximize (intensify, prolong, repeat) positive emotions [7]. We propose to give below a review of experimental data obtained recently by colleagues of our laboratory.

V. A. Markevich, together with L. L. Voronin [1], had previously developed a conditional pyramidal response by means of the combination of a single bipolar electrical stimulation of the cortex with a train of three to five stimuli, at a frequency of 100 Hz. Both pairs of electrodes were located in immediate proximity to one another in the sensorimotor cortex of the rat in the zone of the representation of its forepaw. This combination was accompanied by stimulation of that point of the lateral hypothalamus which, in preliminary experiments, induced the self-stimulation reaction. The re-

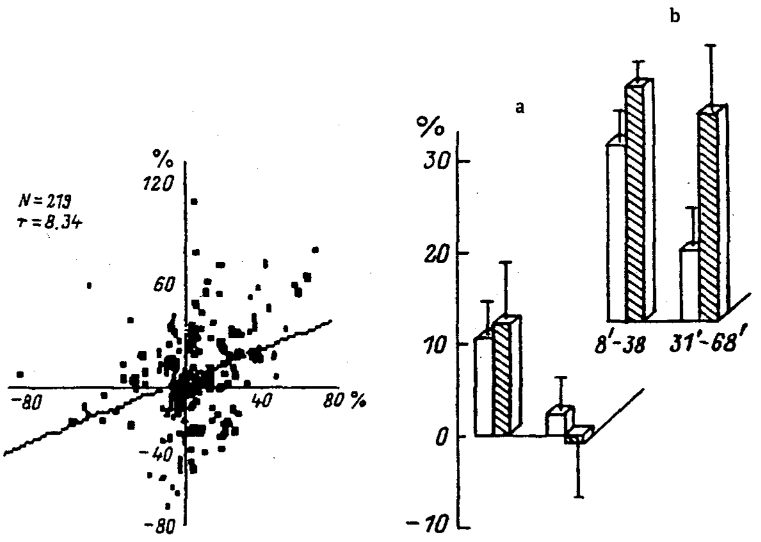


Fig. 2. Posttetanic changes in the pyramidal tract response. On the left, graph of the positive linear correlational association between the changes (across all experiments) of the direct (along the abscissa) and monosynaptic (along the ordinate) components of the response. N, number of measurements of the means (of 11-33 presentations of test stimuli) of the magnitude of the responses of the pyramidal tract; r, the coefficient of correlation. On the right, histograms of the changes in the pyramidal tract responses recorded in the first (0-30′) and second (31′-60′) 60-minute period of the entire time analyzed, in the case of tetanic stimulation of the cortex (a) and in combined tetanization of the cortex and lateral hypothalamus (b). Remaining designations the same as in Fig. 1 (as described by R. G. Kozhedub).

cording of the response of the pyramidal tract was carried out at the level of the medulla oblongata. The process of combining all three stimuli led to an increase in the synaptic components of the response with relative stability of the direct component. These changes were not observed in the control experiments, in which stimulation of the hypothalamus preceded the cortical stimuli, or when cortical stimulations were combined without the additional stimulation of the emotiogenic zones of the hypothalamus. Thus, participation of the emotiogenic zones of the brain has proven to be essential for the development even of a comparatively simple analog of the conditioned reflex.

By contrast with the experiments of V. A. Markovich and L. L. Voronin, R. G. Kozhedub [4] used the stimulation of those structures of the hypothalamus of the rabbit, the activation of which was accompanied by pronounced signs of food-procuring behavior: sniffing, search for and eating of food even following satiation. She demonstrated the role of the lateral hypothalamus in the elementary mechanisms of cortical plasticity in models of an analog of the conditioned reflex and prolonged potentiation. In experiments simulating the development of a conditioned reflex, the pyramidal tract response which permits the simultaneous analysis of change in cellular excitability with respect to its direct component, and of synaptic efficiency with respect to the monosynaptic component, was recorded in three experimental situations: 1) with a combination of direct stimulations of two points of the sensorimotor cortex; 2) with the combined action of direct stimulations and the electrostimulation of the lateral hypothalamus; and 3) with stimulation of the lateral hypothalamus in response to the appearance of a pyramidal tract response which was increased as compared with the control level (a model of the instrumental conditioned reflex). Comparison of the changes in the responses of the pyramidal tract (Fig. 1a, b, and c) with respect to the single responses represented on oscillograms, and with respect to average data obtained in experiments involving the enhancement of synaptic efficiency, shows that stimulation of the lateral hypothalamus leads to a significantly more substantial increase in the cellular excitability of cortical neurons.

An analysis of the contribution of the lateral hypothalamus to cortical plasticity during prolonged potentiation (Fig. 2) not only confirmed the influence of this structure on the degree of participation of membrane mechanisms, but in fact revealed the role of motivation in the maintenance of plastic synaptic manifestations arising in the cortex. The correlation analysis used in the study made it possible to demonstrate the presence of a positive linear association between posttetanic changes in cellular excitability and in synaptic efficiency; this points to an interaction between these elementary mechanisms of plasticity. It can be seen on the graph that different changes in the amplitudes of both the P and N component can be observed in different experiments, changes pointing to the variability of the manifestation of cortical plasticity, which consists both in prolonged potentiation as well as in prolonged depression. It can be seen from the histograms in Fig. 2 that the changes in the amplitudes of the direct and monosynaptic components of the pyramidal tract response, given combined activation of the cortex and the lateral hypothalamus (Fig. 2b), in the first 30 min following tetanization, exceeded the corresponding values with stimulation of the cortex alone (Fig. 2a). In the same

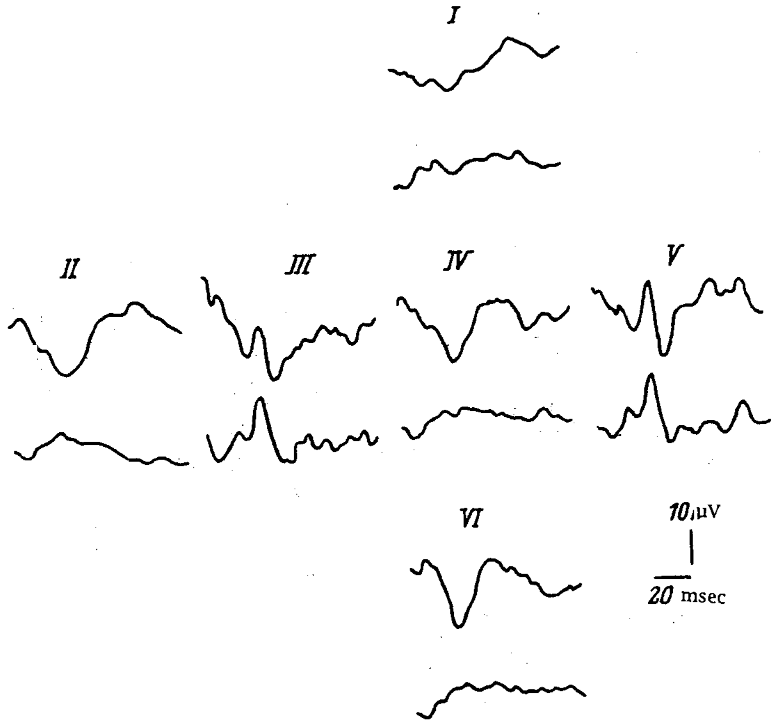


Fig. 3. Interrelationship of the averaged evoked potentials in response to an acoustic conditional signal (clicks) in the auditory cortex (a) and lateral hypothalamus (b) of the cat during the development, extinction, and differentiation of food-procuring reflexes (as described by G. L. Vantsyan). I) Alimentary satiation; II) before the development of the instrumental food-procuring conditioned reflex (IFR); III) IFR (4 Hz); IV) extinguished IFR; V) restored IFR; VI) differentiation (2 Hz).

succeeding time interval, the average amplitude of the monosynaptic component during additional stimulation of the lateral hypothalamus was increased still more substantially, whereas in the case of cortical stimulation alone, it was comparable with its control value. These data can be regarded as proof that motivational stimulation of the lateral hypothalamus accelerates the development of a conditioned reflex through the mechanism of an increase in cell excitability, thereby promoting the manifestation of the basic mechanism of the conditioned reflex, namely, intensification of the synaptic efficiency of excitatory connections. Taking note of data that indicate that, when it reaches a certain level, the increase in cellular excitability creates a dominant state, one cannot fail to take note of the similarity of these data with the behavioral situation, in which the creation, and then the removal of the dominant, accelerated the development of the conditioned reflex, to the point of the formation of a connection following a single combination [6].

Taking into account the currently available information, R. G. Kozhedub proposes the following sequence of events in the organization of the memory trace: the activation of the cell triggers (evidently through the NMDA receptors) enzymatic processes that are targeted to a common intracellular substrate, which provides for the interaction between the elementary mechanisms of plasticity. The positive linear correlational association identified by R. G. Kozhedub between the changes in cellular excitability and synaptic efficiency point to this. The formation of extracellular messengers which diffuse into the extracellular milieu takes place during the intracellular chemical modifications; this provides for a retrograde connection of the postsynapse with the presynapse. The following complex of biochemical transformations in the presynaptic region leads in the final analysis to a long-lasting enhancement of synaptic efficiency through increased secretion of the mediator.

As the experiments of G. L. Vanetsyan have shown, the development of an instrumental food-procuring conditioned reflex in cats in response to a series of clicks (4 Hz), leads to highly correlated relationships of the averaged evoked potentials in the lateral hypothalamus and the auditory cortex ($A_1$); the coefficient of correlation reaches 0.7 for $p < 0.01$ (Fig. 3). Satiation of the cat, acute discontinuous extinction of the instrumental food-procuring reflex, and the development of differentiation (clicks with a frequency of 2 Hz) were accompanied by a decline in the correlatedness of the averaged evoked potentials, which increased again as the conditioned reflex was restored.

If up until this point we have been discussing the participation of the motivational and emotiogenic structures of the hypothalamus during the development of the conditioned reflex, now we will consider data relating to the capacity of these structures to initiate previously developed conditioned reactions.

E. K. Davydova and G. A. Grigoryan developed classical [2] and instrumental [3] motoric alimentary and defense condi-

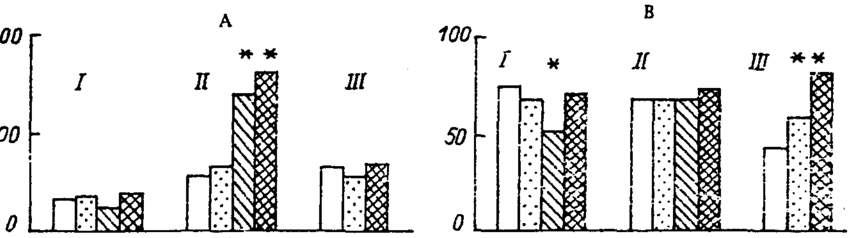


Fig. 4. Changes in the impulse activity of the motivational (A) and emotiogenically positive (B) neurons of the lateral hypothalamus of rats during the accomplishment of classical (I) instrumental conditioned elimination reactions (II) and avoidance reactions (III) in per cents of their activity outside of the experimental situation. White columns, over the course of 5 sec before the presentation of a conditional signal (light); dotted columns, during the action of the light; ordinary hatching, with the combined action of light and stimulation of the tegmentum; double hatching, the first 5 sec following the action of light or light and current (as described by N. G. Mikhailova, M. I. Zaichenko, and Yu. V. Raigorodskii).

tioned reflexes in dogs. In the first instance, the passive raising of one of the forepaws was combined with the instillation of milk or a solution of acid into the mouth; in the second, the dog itself had to raise the paw in response to the conditional signal (tone), in order to receive the milk or to prevent the instillation of the acid. Following the consolidation of the conditioned reflexes, stimulation of the motivational-alimentary structures ("hunger centers") of the lateral hypothalamus by means of an electrical current (50 Hz, impulse duration 1 msec. amplitude 15-20 V, duration of stimulation 1-2 sec) was carried; stimulation of the emotiogenically positive structures, inducing the reaction of self-stimulation of structures of the lateral hypothalamus (200 Hz, 0.5 msec, 15-25 V, 0.5 sec); and of the emotiogenically negative structures, inducing the reaction of avoidance of the structures of the lateral hypothalamus, medial hypothalamus, and central gray substance (50 Hz, 15-20 V, up to 5-7 sec).

The results of the experiments (in per cents of the total number of trials) are presented in Table 1. It can be seen that stimulation of the motivational-alimentary structures of the lateral hypothalamus reproduced the alimentary motoric conditioned reflexes, while not influencing the defense reflexes. Such stimulation led to a decrease in the threshold of the motoric reaction, which served as the signal in the development of the classical alimentary conditioned reflex (judging on the basis of the intensity of the stimulation of the cortical representation of the corresponding paw). Stimulation of the emotiogenically negative zones of the lateral hypothalamus induced only an instrumental defense reflex; further, the authors were unable to obtain it when stimulating the medial hypothalamus and the central gray substance. Finally, stimulation of the emotiogenically positive structures of the lateral hypothalamus did not reproduce either food-procuring or defense reactions. Evidently, activation of the emotiogenically positive structures during natural behavior suggests the successful completion of adaptive actions and cannot play the role of a motivating factor, with the exception of cases in which similar activation takes on a self-targeted character, as occurs in the case of self-stimulation.

The question of the participation of the emotiogenically positive structures of the lateral preoptic area and of the lateral hypothalamus, just like that of the emotiogenically negative zones of the ventromedial hypothalamus, in the effectuation of various forms of the defense conditioned reflexes in rats was investigated by N. G. Mikhailova, M. I. Zaichenko, and Yu. V. Raigorodskii. The reflex was developed by combining a light flash with emotionally negative stimulation of the dorsomedial tegementum. The passage of the rat to the safe section of the chamber during the action of the current was regarded as an elimination reaction, while a run into the light, which prevented stimulation of the tegementum, was regarded as an avoidance reaction. Motivational neurons were distinguished in the lateral hypothalamus which decreased the frequency of impulse activity following feeding of the deprived animal, and positively reinforcing neurons, the activity of which, on the contrary, increased immediately after feeding.

Changes in the frequency of the impulse activity of the neurons in percents of the usual level, recorded outside of the experimental chamber, are shown in Fig. 4. Each column in the figure corresponds to a time segment equal to 5 sec before the turning on the conditional signal, during the action of the light and the stimulation of the tegementum, and during the after-effect. The inhibition of the impulse activity of the positively reinforcing neurons, which is significantly manifested during the combined action of the light and current, takes place in the situation of the classical conditioned reflex. The activation of neurons of the motivational group in the ventromedial hypothalamus is observed simultaneously. An increase in the frequency of impulses of the motivational neurons of the lateral hypothalamus in the presence of the combined action of light and current, as well as during the after-effect, is characteristic for the instrumental defense elimination reflex. Neurons of the ventromedial hypothalamus tonically increase their impulse activity from the time the rat is placed into the experimental chamber. With regard to the instrumental avoidance reflex, when the animal entirely ceases to be subjected to the action of the current, intensification of the impulse activity of the positively reinforcing neurons of the lateral hypothalamus during the period of the action of the light, and especially following the performance of the adaptive reaction, are most typical for it. The neurons of the ventromedial hypothalamus are tonically activated at all stages of the effectuation of the conditioned defense reflex.

Summarizing the results of this investigation, the inference can be drawn that the activation of the emotiogenically

TABLE 1. Reproduction of Conditioned Motoric Reaction During the Activation of Motivatiogenic and Emotiogenic Structures of the Lateral Hypothalamus in Dogs by Means of Its Electrostimulation (Based on E. K. Davydova and G. A. Grigoryan))

| Conditioned reflexes | Structures stimulated | | |
|---|---|---|---|
| | motivational "hunger center", % | emotiogenically negative zones, % | emotiogenically positive zones |
| | Alimentary | | |
| Classical | 83 | — | — |
| Instrumental | 91 | — | — |
| | Defense | | |
| Classical | 7 | — | — |
| Instrumental | — | 73 | — |

negative structures of the ventromedial hypothalamus and of the motivational neurons of the lateral hypothalamus serves as a motivation in all forms of defense conditioned reflexes. With regard to the emotiogenically positive neurons of the lateral hypothalamus, they participate only in the effectuation of the conditioned avoidance reaction, in which the adaptive actions of the rat exclude "punishing" intracerebral stimulation of the tegementum.

The functional connections of the lateral nucleus of the hypothalamus with the dorsomedial region of the prefrontal cortex have turned out to correlate with the individual features of the conditioned reflex activity of cats. G. Kh. Merzhanova, A. I. Berg, and Yu. L. Martinson developed an alimentary conditioned reflex to light, in which the value of the reinforcement depended on the time of delay in pedal pressing: a rapid motoric reaction with a latent period of 1-2 sec was reinforced by the meat and rusk mixture, while a reaction that was delayed 8-10 sec, was reinforced with meat [5]. Of three experimental cats, one proved to be "impulsive", while two revealed the capacity for "self-control" [14], i.e., they restrained their reaction in order to obtain the preferred meat. Multineuronal activity was recorded in the lateral hypothalamus and the prefrontal cortex with subsequent selection of the spikes by the amplitude window discrimination. The activity of the neurons, coupled with prolonged time delays that depends on the degree of hunger, was called "motivational" connections by the authors, while the functioning of cells with short time intervals (up to 30 msec), which does not depend on food deprivation, was called "informational" connections.

The curves of the distribution of the number of hypothalamofrontal interregional interactions in the relation to their time delays in the cats of the two types during the accomplishment of preferred and alternative reactions are shown in Fig. 5. It can be seen that in the cats which were capable of "self-control" (A), the "motivational" connections from the lateral hypothalamus predominate significantly ($p < 0.001$), whereas there are significantly more connections of the "informational" character in the impulsive cat (B). These data confirm the hypothesis we advanced previously [8] to the fact that the individual features of the interaction of the hypothalamus with the anterior divisions of the new cortex underlie an indicator such as "strength of the nervous system" (using the terminology of I. P. Pavlov).

## CONCLUSION

Assessing the entire aggregate of the above-described experimental facts, we have reached the conclusion that the ascending influences of the hypothalamus to the cerebral cortex have essential importance for the formation and realization of conditioned reflex activity. Thus, the direct stimulation of the motivational and emotiogenic structures of the lateral hypothalamus ensure the occurrence of a temporary neural connection between the combinations of two stimuli addressed to the sensorimotor cortex that precede this stimulation. At the same time, the motivational structures primarily increase the cellular excitability of cortical neurons, while the emotiogenic structures have the same effect on the efficiency of the synapses. As a result, a well-consolidated alimentary conditioned motoric reflex to a series of clicks is characterized by the closest functional connections between the lateral hypothalamus and the auditory cortex; this is suggested by the high degree of correlation of the averaged evoked responses to the clicks in these two brain formations.

On the other hand, stimulation of the hypothalamus with an electrical current is capable of eliciting a previously formed conditioned reflex; further, events observed in the process are least similar to the nonspecific "energizing influence of the subcortex on the cortex". Thus, stimulation of alimentary motivational structures of the lateral hypothalamus induces only a food-procuring conditioned reflex, while stimulation of the emotiogenically negative structures elicits only a defense conditioned reflex. With regard to the emotiogenically positive structures, their activation does not reproduce either alimentary or defense reactions. The fact of the matter is that the occurrence of emotionally positive states signalizes the successful completion of a behavioral act, the satisfaction of the corresponding need.

Nevertheless, under the conditions of natural behavior, and not in the case of artificial stimulation of the "pleasure centers" by an electrical current, the emotiogenically positive elements participate in the realization of defense conditioned reactions, if these reactions have the character of avoidance which prevents the action of a noxious factor. This is suggested by the intensification of the impulse activity of the positively reinforcing neurons of the lateral hypothalamus during the action of the conditional signal and immediately following the performance of the adaptive reaction.

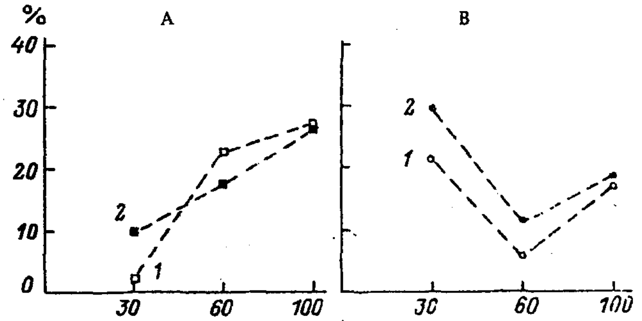


Fig. 5. Curves of the distribution of the number of hypothalamo-frontal interneuronal interactions according to their time delays in cats with various types of behavior during the accomplishment of preferred and alternative reflexes. A) In cats capable of prolonging the reaction; B) in cats of the "impulsive" type. Along the abscissa: time of the interneuronal interactions, msec; along the ordinate: number of connections (all of the connections identified for each form of behavior taken as 100%). 1) During the performance of briefly postponed; 2) prolonged postponed reflexes (as described by G. Kh. Merzhanova, A. I. Berg, and Yu. L. Martinson).

The character of the functional connections of the hypothalamus with the structures of the new cortex differ in animals with individual behavioral characteristics. It has been demonstrated that in cats which are capable of delaying conditioned motoric reactions for the sake of obtaining a preferred food, the "motivational" long-latency connections between the neurons of the lateral hypothalamus and the prefrontal cortex predominate. The predominance of short-latency "informational" connections is characteristic for the "impulsive" cats which react 1-2 sec following the conditional signal.

It can be stated in conclusion that the interactions of the hypothalamus with the new cortex would be sufficient for the acquisition of skills and the organization of behavior in the presence of a pronounced dominance of any one need (hunger, thirst, sex), and in a milieu in which all signals possess high probability of their reinforcement by food, water, a sexual partner, etc. In real conditions, on the other hand, the animal constantly runs up against the competition of simultaneously actualized needs and signals, the probability of the reinforcement of which is highly problematical, although it is inadmissible to ignore it, especially in the case of a potential threat. That is why, in addition to the hypothalamus and the new cortex, evolution has created at a minimum two other structures which are responsible for the taking behavioral decisions. We have in mind the nuclei of the amygdaloid complex and the hippocampus [8].

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