ANALYSIS OF PARTICIPATION OF THE HIPPOCAMPUS IN ORGANIZATION OF BEHAVIOR IN ANIMALS

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Until the present time the majority of attempts to elucidate the changes in the behavior of animals after damage to the hippocampus (HC) were based on a functional approach, consisting in finding and identifying a specific functional operation, common to all the forms of behavior which change following hippocampus damage [9]. Collectively the accepted, existing hypotheses explain the majority of the known facts regarding the influence of damage to the hippocampus on behavior, but each of them individually explains only some part of those facts. The possibility remains of combining the separate hypotheses into a general functional theory and into the neurophysiological mechanisms of the realization of the presumed functions in the hippocampus.

In the present work an attempt is made to elucidate the regarding of changes in the behavior of animals after damage to the hippocampus, taking as a basis the physiological properties of neurons and of the associations of this structure. It is shown that the participation of the hippocampus on different forms of behavior depends on the features of the transformation of signals reaching the hippocampus along the cortical input, at different levels of activity of the reticular input which are characteristic for these forms of behavior.

I. Influence of Damage to the HC on the Behavior of Animals (according to [6, 9])

1. Damage to the HC elevates the general level of motor activity.

2. Damage to the HC disturbs the organization and extinction of the orienting reflex: a shift in attention loses the connection with the novelty of the stimulus and becomes chaotic; the lawful tendency toward extinction disappears and is replaced by a tendency to perseveration.

3. Damage to the HC intensifies the effect of the disturbance of automatic conditioned reflex activity under the influence of unfamiliar stimuli.

4. If stimulus B is associated with A after the development of a conditioned reflex (CR) in response to the latter, and the complex A + B continues to be presented as the conditional signal (CS), then the formation of the CR does not take place in normal animals in response to the isolated influence of B (blocking effect), but in hippocampectomized animals the CR does form.

5. Rats with damage to the HC are trained more rapidly to respond to the same CS with two different conditioned reflexes depending upon the character of the conditioning stimuli.

6. Damage to the HC impairs the recall of the place of the receipt of a single reinforcement.

7. After damage to the HC the development of a conditioned reflex becomes significantly more difficult with low probability of reinforcement.

8. Damage to the HC disturbs the process of maze learning. This is manifested in slowing down of learning, if the HC is destroyed prior to the beginning of learning, and in the elimination of a habit acquired by the time of the destruction, if the latter occurs within the process of training. The destroyed habit is recovered as the result of additional training.

9. Animals with a damaged HC are trained more slowly to respond to the same CS with two different CRs depending upon motivational state (in conditions of food and water deprivation).

10. Damage to the HC does not affect the capacity for latent learning, which is manifested in the acceleration of learning under the influence of preliminary familiarization with the circumstances and the stimuli utilized in the absence of reinforcing stimuli.

11. Repeated presentations of the CS prior to training slows the development of the CR in response to this signal in the norm (latent inhibition), but does not affect learning in hippocampectomized animals.

12. Damage to the HC induces a disruption of spontaneous alternation, which consists of the fact that in the absence of reinforcements animals do not enter the same branch of a T- or a radial maze twice in a row.

13. In a radial maze consisting of a central area with branches radiating out from it, normally trained rats do not enter those branches in which under the conditions of the experiment there have never been lures, and do not enter repeatedly those branches in which the lure was eaten during the period of the current testing. Rats, trained before damage to the HC, after the damage relatively rapidily recover the habit of not entering those branches in which the bait has never been, but irreversibly lose the capacity to recall the branches in which the lure was eaten in the course of the given testing.

14. If two CRs in response to the same CS are reinforced, for example, with probabilities $p_1 = 0.7$ and $p_2 = 0.3$, then after training, normal animals respond with probabilities $p_1 = 1$ and $p_2 = 0$ (the contrast effect), and animals deprived of the HC, with probabilities $p_1 = 0.7$ and $p_2 = 0.3$.

15. Animals with a damaged HC more rapidly develop the habit of two-sided avoidance, which consists of crossing to zone B on signal in order to avoid a painful stimulus in zone A, and of crossing to zone A on signal in order to avoid a painful stimulus in zone B.

II. Organization of the HC (according to [2])

1. Several cell fields enter the HC: the dentate fascia (DF), and fields CA_1 and CA_3. Each field consists of two principal types of cells: excitatory neurons, sending axons to neighboring fields (the pyramidal cells, PCs), and inhibitory interneurons, whose axons end on the soma of the PCs of its field.

2. The cell fields of the HC are linked with one another and with the cortical fields of the entorhinal cortex (EC) by a system of topographically organized excitatory connections, the main ones of which form the following sequence: $EC-DF-CA_3-CA_1-EC$. The excitatory fibers end on the dendrites of the PCs.

3. Along with the topographically organized cortical connections there are several systems of connections with a diffuse organization, whose influences are uniformly distributed within the limits of each cell field of the HC. The most well studied among these is the cholinergic pathway, originating in the rostral portion of the reticular formation (RF) and reaching the HC after switching at the neurons of the medial septal nucleus (the RF input). The fibers of the RF input terminate in the DF and CA_3 in two ways: directly on the PCs in the region of their proximal dendrites, and on the inhibitory interneurons of both fields.

III. Plastic Properties of the Associations (according to [3, 4])

1. Low-frequency electrical stimulation of the pre-synaptic fibers (0.1-1 Hz) elicits depression of the synaptic efficiency of the excitatory associations of the HC; under the same conditions the efficiency of the inhibitory associations in the main does not change. After the stimulation is terminated synaptic efficiency gradually recovers. With repeated stimulation the magnitude of the depression and the duration of the recovery period increase.

2. In the process of stimulation at a frequency exceeding several hertz, a frequency potentiation of the excitatory post-synaptic potentials (EPSPs) and of the impulse responses of the PCs, and in parallel, a frequency depression of the inhibitory PSPs (IPSPs), take place. The potentiation in the system of cortico-hippocampal associations (EC-DF, $DF-CA_3$) is especially well pronounced, and is maintained for a long time after the termination of the stimulation (prolonged potentiation, PP). With repeated stimulations the magnitude and duration of the PP effect increase. The magnitude of the potentiation decreases under the influence of low-frequency (less than 1 Hz) pre-synaptic stimulation, but after the termination of the stimulation it gradually recovers almost to the initial level.
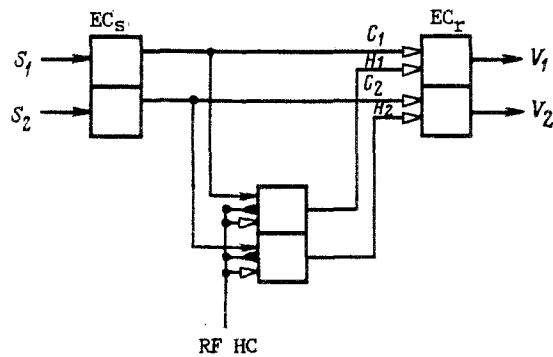
Fig. 1. Schema of the model. Each square corresponds to a group of functionally homogeneous neurons. Arrows indicate excitatory associations; circles indicate inhibitory associations. Constant associations are depicted by black symbols; variable, by light. Explanation in text (Pt. V, 1).

Data on the possibility of PP of the endings of the RF input and on the changes in the IPSPs in the period corresponding to the development of the PP of the EPSPs are relatively few, and apparently ambiguous.

IV. Activity of the RF and the Neurons of the Hippocampus during Different Kinds of Behavior

1. The influences of the RF on the HC are converted in the medial septal nucleus into a uniform sequence of impulse packets which generate the theta rhythm of the HC. The regularity and the frequency of the theta rhythm are in direct dependence upon the level of activity of the RF and are indices of the latter during different forms of behavior. Irregular activity with elements of low-frequency theta rhythm (4-5 Hz) is characteristic for the inactive state of wakefulness and for automatic behavior. Learned behavior under conditions of choice is accompanied by regular theta rhythm. The highest theta (7-9 Hz) is observed during search and investigatory behavior [2, 5, 6, 8].

2. The excitation of inhibitory interneurons of the HC correlates with the appearance of the theta rhythm. A high level of activity of PCs is observed during superficial sleep. The reaction of waking and passive wakefulness are characterized by a minimal level of PC activity. A shift to investigatory activity is accompanied by an increased frequency of PC activity relative to the level of passive wakefulness [8].

3. The only reliably established, specific correlate of PC activity was found to be the location of the animal in the experimental chamber. It was established that reactions of the "place cells" are determined by complexes of stimuli located both outside and inside of the experimental chamber, and are governed by afferentation arriving along the cortical input [7].

V. Neuronal Model of the Hippocampus

1. Working Schema. In this article we have assumed a schema (Fig. 1) in which the HC, represented by a single cell field of PCs, is included in parallel with the cortical circuit. The associations are topographically organized (Pt. II, 2) such that each element of the receiver cortical field (EC_r) receives direct (C) and transhippocampal (H) associations only from the specific element of the source cortical field (EC_s) corresponding to it.

The RF exerts a diffuse, uniformly distributed influence, which has a dual character on the HC: a stable, inhibitory influence directed to the soma of the PCs, and an excitatory influence, directed to the dendrites and increasing under the influence of frequency potentiation (Pt. II, 1, 3; III).

Several supplementary assumptions are assumed for specificity.

a. The excitation of the neurons of the EC_r by a complex of external stimuli directs the animal's attention to these stimuli. In accordance with the example of [1] let us con-
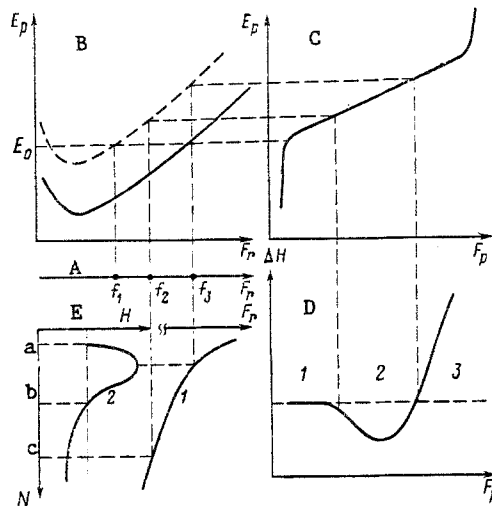
Fig. 2. Functional characteristics of the model.
A) Activity of the RF (F_r, along the abscissa)
during different kinds of behavior: $F_r < f_1$,
automatic behavior; $f_2 < F_r < F_3$, behavior under
conditions of choice; $F_r > f_3$, investigatory be-
havior. B) Solid line indicates the dependence
of the magnitude of the PSP of the PCs (E_p along
the ordinate) on the level of the activity of
the RF input (F_r along the abscissa); broken line,
the same under conditions of constantly acting
cortical input. C) The transformation of the
magnitude of the PSPs of the PCs (E_p along the
ordinate) into the frequency of impulse activity
(F_p along the abscissa). D) The dependence of
the change in the efficiency of the synaptic en-
dings of the PCs (ΔH along the ordinate) on the
level of pre-synaptic impulse activity (F_p along
the abscissa). E) The dependence of the magni-
tude of the RF input into the HC (F_r along the
abscissa, curve 1) and the efficiency of the
synaptic endings of the PCs (H along the absccissa,
curve 2) on the ordinal number of the presentations
of a new stimulus (N along the ordinate). a-c)
See text.

sider that the choice of orientation to one of the two complexes of stimuli, S_1 and S_2, found simultaneously in the animal's visual field, is determined by the relationship $p_i = \dfrac{V_i}{V_1 + V_2}$, where V_i is the magnitude of the reaction of the neurons of the EC_r responding to S_i, and p_i is the probability of the focusing reaction to stimulus S_i; $i = 1.2$ (see Fig. 1).

b. In the learning period the efficiency of the C-associations with respect to specific stimuli increases irreversibly under the influence of the reinforcement of reactions elicited by these stimuli. These changes underlie the long-lasting maintenance of acquired habits which takes place without the participation of the HC [2].

c. The reduction in the reactivity of the neurons of the EC_r, induced by the destruction of the HC, is compensated for by a non-selective increase in their excitability (not shown in Fig. 1) from the side of the RF (compare Pt. I, 1), or as the result of the sprouting of the cortical endings at the site of the destroyed hippocampal neurons.

2. Functional Characteristics of the Model. In accordance with the data of Pt. IV, 1 on the horizontal axis in Fig. 2, A are marked the ranges of the values which the activity of the RF assumes (F_r) with different kinds of behavior: during superficial sleep, $F_r \approx 0$; with automatic behavior, $0 < F_r < f_1$; behavior under conditions of choice, $f_2 < F_r < f_3$; in the process of investigatory behavior, $F_r > f_3$.

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The dependence of the magnitude of the post-synaptic potential (PSP) of the PCs on the level of the RF input is depicted in Fig. 2, B. The insignificant activation from the side of the RF elicits primary inhibition of the PCs as the result of the more efficient placement of the inhibitory synapses on the soma. With increase in the activity of the RF a frequency potentiation of the EPSPs occurs without change or in combination with depression of the IPSPs which makes for a total increase in the excitability of the PCs. Such a dependence corresponds to the data on the changes in the activity of the PCs during different types of behavior (Pt. IV, 2). Let us assume for simplicity that the magnitude of the signals in the cortical input is constant, and that the cortical PSPs are linearly added to the PCs with the PSPs of the RF input. Under these conditions the action of the cortical input is equivalent to the parallel transposition of the characteristic shown in Fig. 2, B, along the vertical axis (broken line).

The transformation of the magnitude of the PSPs into the frequency of impulse activity of the PCs, arbitrarily chosen to be linear, is shown in Fig. 2, C.

The dependence of the change in the efficiency of the synaptic endings of the PCs of the H-associations on the frequency of their impulse activity is depicted in Fig. 2, D in accordance with Pt. III. The various segments of the characteristic correspond (1) to maintenance of a constant magnitude of efficiency, (2) to post-activational depression, and (3) to prolonged potentiation.

3. Transformation of the Cortical Signal in the HC as a Function of the State of the RF Input. Influence on the Organization of Behavior. If the general condition of the characteristics of the individual links in the model is known (Fig. 2, A-D), then it is still necessary to establish the mutual disposition of the individual characteristics relative to common axes, in order to determine the qualitative features of the transformation of the cortical signals in the HC during different forms of activity. The main claim of the present work consists of the fact that for the successful explanation of the diverse data regarding the participation of the HC in the organization of behavior, the individual characteristics of the model must be correlated with one another, as has been done in Fig. 2.

Let us, under these conditions, examine the features of the transformation of the cortical signals in the HC during different forms of behavior and given different states of the RF input. Reinforced automatic behavior ($F_r < f_1$) is characterized by the blocking of the passage of any signals through the HC (Fig. 2, A, B, C), in combination with the strengthening of the efficiency of the C-associations (and of the responses of the neurons of the EC_r) with respect to CS (Pl. 1 b). In keeping with (Pt. 1 a, this decreases the probability of the switching of attention to unfamiliar stimuli. After destruction of the HC a general increase in the reactivity (excitability) of the neurons of the EC_r (Pt. 1 c) increases the effect of unfamiliar stimuli (Pt. I, 3, 4, 5).

Under conditions of choice-related behavior ($f_2 < F_r < f_3$), the activity of the cortical input, for example, that is elicited by the complex of stimuli at work during entry into one of the branches of a radial maze, is linearly transformed in the HC (Fig. 2, A, B, C), and elicits that impulse activity of the PCs, under the influence of which a decrease in the efficiency of the corresponding H-associations takes place (Fig. 2, D). The latter circumstance must lead to a decrease in the reaction of the neurons in the EC_r, and to a decrease in the probability of orientation to that group of stimuli, which is manifested in the tendency to ignore the given branch in the following choice (Pt. I, 12, 13).

Investigatory behavior under conditions of the indeterminacy elicited by the action of new stimuli, by unexpected reinforcement, etc., develops at that level of the activity of the RF ($F_r > f_3$) at which the passage of the cortical signal through the HC induces the prolonged potentiation of the endings of the PCs corresponding to it (Fig. 2, A-D). The prolonged potentiation of the associations to which, for example, the complex of signals is directed from the site of reinforcement, increases the probability of the orientation to the given complex of signals in the following testing. Depending upon the predominating tendency to approach or avoidance of the stimuli attracting the attention of the animal (with positive or negative reinforcement), the cited mechanism increases or decreases the probability of approaching the site of reinforcement during subsequent testing (Pt. I, 6, 7, 8, 15).

With repeated presentations of a new stimulus, the efficiency of the H-associations corresponding to it change as shown in Fig. 2, E, 2 (provided that the magnitude of the RF input to HC decreases in accordance with curve 1). The segment a-b corresponds to the phase
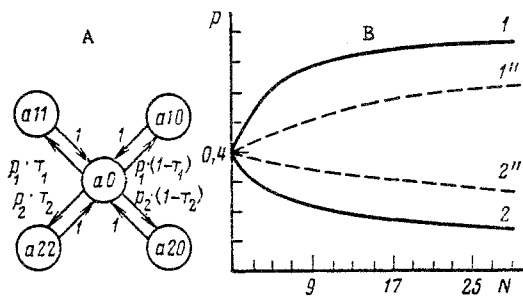
Fig. 3. Schema of states (A) during learning
in a T-maze (circles) and possible shifts be-
tween individual states (arrows); beside each
arrow are indicated the probabilities of the
corresponding shifts. B) Changes in the prob-
ability of frequently reinforced (1, 1") and
infrequently reinforced reactions (2, 2") in
the learning process for a model with the HC
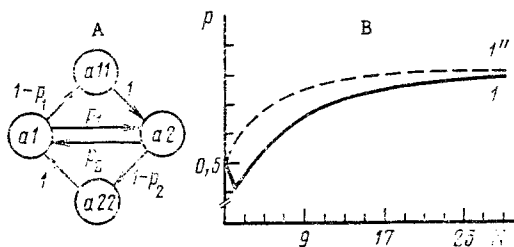(solid lines) and without the HC (broken lines).
Explanation in the text.

Fig. 4. Schema of states (A, circles) during
learning of two-sided avoidance and possible
shifts between individual states (arrows). B)
Changes in the probability of avoidance upon the
CS in the learning process. Other designations
as in Fig. 3.

of selective attention and of facilitation of the CR (Pt. I, 2, 7, 8), and b-c, to extinction
and latent inhibition (Pt. I, 2, 11). The manifestation of this hippocampal mechanism in be-
havior depends also on the conditions of the experiment. If, for example, in the period of
familiarization with a new maze an animal has free access to all of its sections, the effi-
ciency of all of the primed associations increases simultaneously and, in accordance with
Pt. 1, a, none of the stimuli obtain preferred status during subsequent choices (Pt. I, 10).
If the distribution of excitation in the RF input is not uniform (as was assumed above), but
depends, for example, on the type of motivation, then with different types of motivation, dif-
ferent neurons of the HC are active. Among all the potentiated associations, only the asso-
ciations of the neurons active at the given moment (for which $E_p > E_0$, Fig. 2, B) exert an
influence on the neurons of the EC_r. Therefore, with a choice of reaction (in the sense of
Pt. 1, a) under conditions of a specific motivation, those associations are taken into account
which were potentiated against the background of this same motivation. Such a mechanism ex-
plains the participation of the HC in the taking stock of the motivational context of the
developed CR (Pt. I, 9).

4. Participation of the HC in the Formation of the Contrast Effect (Pt. I, 14). A
schema of behavior in the T-maze under conditions of random reinforcement is shown in Fig.
3. An animal can, from the starting chamber (a0), shift at the CS to one arm of the maze or
another with probabilities of p_1 and p_2, and obtain reinforcement with probabilities of t_1
and t_2. Having oriented reinforcement (al1, a22), or having become convinced of its absence
(al0, a20), the animal returns to the starting chamber, after which the cycle repeats. By
a computer statistical modeling method [1], the model set forth in Pt. 1-3 (Fig. 1, 2) was
tested according to this schema of behavior, and the sequence of probabilities p_1 and p_2 were
obtained. In brief, the computation procedure consisted in the following. The reactions in

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the EC_s and the HC (Fig. 1) were assumed constant, equal to unity. Having chosen, according to the formula cited in Pt. 1, a, arbitrary initial values of the probability of the reactions of the associations, the probabilities p_1 and p_2 of the reactions in the first testing were calculated. Using a random number generator, one of the two reactions was chosen in accordance with the probabilities p_1 and p_2, and in accordance with the probabilities t_1 and t_2, the presence or absence of reinforcement. Depending upon the result obtained (a11, a10,...) the association of the model were changed according to the rules adopted (see below). Given the new values of the associations, the probabilities p_1 and p_2 were calculated for the next testing, after which the cycle repeated. During the testing of the model it was assumed that the efficiency of the C-associations increased after each reinforcement (Pt. 1, b), and that the efficiency of the H-associations increased with reinforcement (a11, a22) and decreased in its absence (a10, a20; Pt. 3). Under these conditions, qualitative agreement with the actual data was achieved in a wide range of initial values and parameters of the model.

The averaged learning curves for reinforcement probabilities $t_1 = 0.7$ and $t_2 = 0.3$ are shown in Fig. 3, B. Each curve here and in Fig. 4 is the result of the averaging of 200 individual sequences of probabilities p_1 or p_2. The participation of the HC is expressed in a distinct contrast effect: the probabilities of the reactions reinforced with various frequencies change more rapidly and diverge more sharply.

5. Influence of the HC on the Development of Two-Sided Avoidance (Pt. I, 15). The schema of behavior is depicted in Fig. 4, A. An animal in compartment 1 (a1) or 2 (a2) at the CS crosses with probability p_1 (p_2) to the other compartment, or with probability $1 - p_1$ ($1 - p_2$) remains in place and receives a jolt of current (a11, a22) after which it crosses to the other compartment. Testing of the model according to this schema was carried out with the same rules of changing the associations as in Pt. 4. Fig. 4, B shows that the functioning of the HC (1) slows learning.

CONCLUSIONS

POSSIBILITIES OF CHECKING THE MODEL

From the positions of the present study, the principal functions of the HC are the selective singling out or suppression of specific complexes of stimuli (apparently, somehow or other representing the animal's position in the surrounding space [7]) on the basis of the mechanism of "working" memory which, depending upon the conditions of functioning, provides for multidirectional changes in the efficiency of the hippocampal associations.

Several avenues for the experimental checking of the correctness of the principal assumptions of the model may be noted.

1. From the results of the study it follows that the duration of the changes in the probability of a choice in a maze (see Pt. I, 6, 12, 13) depends on the duration of the changes in the efficiency of the associations of the HC (after potentiation and depression). This claim may be checked by comparing the constant times of the return of the corresponding values (the probability of choice and the efficiency of the associations) to the initial level.

2. It follows from the principal claims of the study that with near-threshold (for the obtaining of potentiation) stimulation of the cortical input, the HC may elicit post-activational changes which are opposite by sign, i.e., the potentiation or depression of responses, depending on whether the magnitude of the RF input at the time of the stimulation is at a higher or lower level.

3. From the results of the study it also follows that the probability of a choice in a maze in the next trial of the same branch which was chosen in a preceding trial depends on the frequency of the theta rhythm at the time of the preceding trial. An increase in the probability should be expected if the stay in the given branch in the preceding trial was accompanied by high frequency theta rhythm, and a decrease in the probability should be expected at a low frequency of theta rhythm and with non-regular activity.

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CORTICAL UNIT ACTIVITY IN CATS DURING CONDITIONED INHIBITION

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An important aspect of the physiology of higher nervous activity is the problem of internal inhibition. Views about its mechanisms were for a long time based on extensive experimental data on changes in animal behavior, but they give no information about the processes taking place in nervous structures.

The introduction of microelectrode techniques enabled the behavioral expression of internal inhibition to be compared with neuronal responses in different parts of the brain. Papers were published describing competent neurophysiological analyses of the formation and recall of various types of conditioned reflexes (CR) and of internal inhibition [1, 2, 4, 7-9, 14]. However, if the characteristics of neuronal spike responses in diffeent brain structures during the development of simpler forms of internal inhibition, namely extinction and differentiation, are sufficiently well known [3, 9, 10], there have been only isolated studies aimed at the neurophysiological analysis of one of the most complex forms of inhibition, namely conditioned inhibition (CI) [14, 15]. In one of these studies responses of motor cortical neurons were investigated during presentation of conditioned inhibitory stimuli to fully trained animals, so that it is impossible to judge the time course of development of inhibition during the formation of a negative CR.

Since in the initial period of investigation in Pavlov's school CI was regarded as a manifestation of external inhibition because of the presence of an irrelevant stimulus in the conditioned inhibitory combination, it was considered worthwhile to compare the character of neuronal responses during CI formation and during external inhibition of CR, which we ourselves had studied under similar experimental conditions previously [6].

The aim of this investigation was to study responses of somatosensory cortical neurons in the cat brain during CI formation.

METHODS

Chronic experiments were performed on four conscious cats (males weighing 2.5-3.5 kg). On the first days the animal, suspended in a hammock, was accustomed to the experimental situation. Placing the paw on a support in response to touching its dorsal surface was accompanied by food reinforcement. After the appearance of spontaneous placing of the paw on the support, the conditioned stimulus (sound) was introduced. At the end of formation of a conditioned reflex response of placing the paw to an acoustic stimulus, the animal was anesthetized with pentobarbital for the operation of trephining the skull above the projection zone of area 3, and removal of the dura. A plug into which a plastic cylinder, containing a channel for insertion of the microelectrode during the experiment, was screwed, was fixed in the burr-hole with quick-hardening plastic. Unit activity was recorded extracellularly