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The Neurophysiological Validation of the Hyperpolarization Theory of Internal Inhibition

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The experiments in conscious non-immobilized rabbits showed that cessation of the reactions without reinforcement (elaboration of the internal inhibition) is accompanied by an enhanced phasic state, by alternation of activation and inhibition of neuron firing, and by the corresponding slow potential oscillation (SPO). These changes can be either localized, predominantly in the structures of conditioned stimulus, or, under enhancement of the inhibitory state, generalized in the brain structures. On the basis of our experience and published data, it is concluded that the above event results from relative enhancement of the inhibitory hyperpolarizing processes due to increase in reactivity of the inhibitory systems to stimulus, which acquires inhibitory properties during learning. Changes in the excitability and reactivity of neuron populations appearing during enhancement of the hyperpolarizing inhibition, and differing in the various brain structures, play an active role in the execution of the main function of the internal inhibition: limitation of excitation transmission to the effectors. An inhibitory mediator gamma aminobutyric acid (GABA) is of great importance in inhibiting the excitation in response to the stimulus which lost its biological significance. These experimental data and their interpretation in the light of published data give the basis for the development of the hyperpolarization theory of internal inhibition.
Keywords: psychophysiology of behavior, learning, internal inhibition, latent inhibition, gamma aminobutyric acid

En los experimentos con conejos conscientes no inmovilizados se ha mostrado que la interrupción de las reacciones tras la supresión del refuerzo, es decir, la elaboración de la inhibición interna, se ve acompañada por el incremento de fases, la alternancia de la activación y la inhibición del disparo de las neuronas, y sus correspondientes oscilaciones lentas de potencial. Estos cambios pueden ser locales, principalmente en las estructuras del estímulo condicionado o, en caso de incremento del estado de inhibición, generalizados sobre las estructuras del cerebro. Basándonos en nuestros datos y en los de la literatura actual se llega a la conclusión de que ese fenómeno está condicionado por el incremento de los procesos inhibitorios de hiperpolarización a raíz del incremento de la reactividad de los sistemas inhibitorios de la acción del estímulo, que adquiere significado inhibitorio durante el proceso de aprendizaje. La oscilación de la excitabilidad y reactividad en las poblaciones de elementos nerviosos que surge durante el incremento de la inhibición de la hiperpolarización, divergentes en distintas estructuras del cerebro, juega un papel activo en la ejecución de la función básica de la inhibición interna, la limitación de la transmisión de la excitación a los efectores. El mediador inhibidor, el ácido gama aminobutírico (GABA), juega un papel esencial en la desarrollo de la inhibición de la excitación al estímulo que ha perdido su significado biológico. Estos datos experimentales y su interpretación a la luz de los datos de la literatura dan fundamento al desarrollo de la teoría de hiperpolarización de la inhibición interna.
Palabras clave: psicofisiología del comportamiento, aprendizaje, inhibición interna, inhibición latente, ácido gamma aminobutírico

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This work has two goals: The first goal is to attract the attention of researchers to this most interesting problem in psychophysiology and psychology—the problem of internal inhibition, that is, the problems of inhibiting reactions that are inadequate to changed environmental conditions. Currently, this problem is so forgotten that there is a striking absence of papers in the literature with the keyword "internal inhibition." The second goal of my work is to report both the results of my long-term study of the neurophysiological basis of internal inhibition and certain literature data directly concerning these studies in order to provide experimental and theoretical evidence of the hyperpolarization theory of internal inhibition.

In our work, we pursued three lines of investigation: (a) studying the neurophysiological basis of internal inhibition by synchronous recording of slow potential oscillations (SPO), single-neuron activity and behavior of conscious animals during defensive conditioning and during elaboration of all types of internal inhibition, pointed out by I. P. Pavlov (main works: Shulgina, 1969, 1976, 1978, 1987); (b) analysis of neurotransmitter basis of defensive conditioned reflex and elaboration of internal inhibition by the above-mentioned technique (Shulgina, 1986; Shulgina, Petricheva, & Kuznetzova 1985; Shulgina & Okhotnikov, 1991; Shulgina & Voronina, 1997; Shulgina & Ziablitzeva, 2004); and (c) experiments on the mathematical model of a network of excitatory and inhibitory neuron-like elements in order to define the functional significance of the physiological processes observed during learning (Frolov, Medvedev, Dolina, Kuznetsova, & Shulgina 1984; Shulgina, 2002; Shulgina, Ponomarev, Murzina, & Frolov, 1985; Shulgina & Muravev, 2000).

Internal Inhibition as a Result of Learning

The learning process, as determined by I. P. Pavlov's school, includes the formation of two main forms of adaptive behavior: formation of new skills and concepts and inhibition of behavior inadequate to changed environmental conditions (Pavlov, 1973). Inhibition was shown to be either external or internal. External or unconditioned inhibition results in cessation of current activity in response to external stimuli. Internal inhibition appears as a result of learning. It is elaborated within the limits of the neuron system, which initially evokes the response to conditioned stimulus; therefore, it was called "internal." Internal inhibition appears in brain structures in response to any repeated stimuli after cessation of biologically significant reinforcement. It results in the disappearance of the peripheral (vegetative and motor, automatic and voluntary) orienting or conditioned reflex reactions initially evoked by these stimuli. Internal inhibition is not the same as fatigue, but rather has an active character. The active nature of internal inhibition results in a decrease of the intensity of the conditioned reflex in the case of association of inhibitory and activating stimuli. Moreover, reactions inhibited by repetition of a nonreinforced stimulus are transiently restored during any change in experimental conditions, including changes in the intensity or duration of the inhibitory stimulus.

The discovery by Pavlov's school of a specific inhibitory process occurring as a result of learning is a no less fundamental achievement of neurophysiology and psychology than the discovery of new forms of active behavior and their mechanisms and regularities. In particular, internal inhibition ensures precise and delicate adaptation of animals and humans to constantly changing environmental conditions. It defines the choice of the most adequate forms of behavior, inhibits and limits the excitation irradiation not only to the periphery but also to the consciousness sphere, avoiding countless numbers of reactions that do not correspond to a certain situation and are unnecessary for current activity and thinking.

Internal inhibition is of great importance to ensure correct human social behavior, establish discipline and various ethic norms, and perform many activities, from primitive everyday skills to the highest forms of creative activity. According to Pavlov's conception, human scientific activity consists of searching, selection, and fixation of hypotheses complying with reality, and of rejecting and inhibiting incorrect, mistaken conclusions (Pavlov, 1973).

Depending on the conditions of elaboration and execution of the inhibitory function, Pavlov classified several forms of internal inhibition. Extinctive inhibition occurs during the repetitive action of a conditioned stimulus without reinforcement and during extinction of the orienting reflex. Delayed inhibition ensures realization of the inactive phase of the delayed reflex. Differential inhibition inhibits the reactions to stimuli similar to the conditioned stimulus, but always acting without reinforcement. Inhibition in response to the repeated presentation of a conditioned stimulus combined with an additional stimulus without reinforcement was called "conditioned inhibition." A particular form of internal inhibition that requires consideration in the organization of educational and manufacturing processes is extinction with reinforcement, that is, the elaboration of inhibitory reactions in response to an activating stimulus in the case of prolonged monotonic presentation of activating stimulation combined with reinforcement.

Pavlov noted the essential differences in the characteristics of the inhibitory process depending on its intensity and generalization. He emphasized time and again that internal inhibition can be either localized or generalized in the brain structures. This characteristic reflects an inhibition effect on various forms of behavior. In turn, the localized process of internal inhibition emerges in the conscious state of the brain during the sustained alternation of the activating and inhibitory influences on the organism. Localized inhibition is more stable to the action of foreign stimuli. Internal inhibition becomes generalized and easily

turns into sleep during sustained repetition of inhibitory stimuli or during repeated monotonic presentation of conditioned stimuli combined with reinforcement. According to the research of Pavlov's school, generalized inhibition is eliminated more easily than "concentrated" inhibition. Thus, diversity in the conditions of vital activity, and alternation of inhibitory and reinforced stimuli provide favorable conditions for normal brain functioning.

In the last years of his life, Pavlov placed high emphasis on the physiological mechanisms of neuropsychological diseases. His school showed that almost all forms of psychological disorders arise from various forms of impaired interaction between excitation and inhibition in the central nervous system (CNS) (Pavlov, 1973).

During Pavlov's time, and for many years later, the neurophysiological mechanisms of internal inhibition were unknown. Pavlov called the matter of internal inhibition mechanisms "the damned problem" of neurophysiology. It should be noted that even at present, this important problem is not properly attended. Perhaps this can be explained by the fact that some leading neurophysiologists doubt the existence of internal inhibition itself as a specific neurophysiological process (Anokhin, 1968; Konorski, 1967; Skinner, 1959). For example, Skinner suggested that withdrawal of reinforcement only reduces excitation without elaboration of special inhibitory process. In Holliday's opinion, Skinner's ideas have drawn the attention of researchers of higher nervous activity away from the problem of internal inhibition (Holliday, 1973). Observing the first stage of food reflex extinction, Anokhin reached the conclusion that, under such conditions, a new functional system appears (Anokhin, 1968). Activation of this system is more intensive compared to activation of the basic system determining food behavior. This new system manifests in motor excitation of animals in the absence of food and inhibits food behavior. The subsequent stage of inhibition of food reactions, when motor excitation disappears and reaction to the conditioned stimulus is not restored, was called "economical inhibition" by Anokhin. The neurophysiological mechanisms of economical inhibition as well as the mechanisms of inhibition of defensive reactions were not examined, as Anokhin considered that these reactions simply disappear without reinforcement due to their biological insignificance. However, as proved by Pavlov's school, inhibition, particularly elaborated at the stage of absence of peripheral reactions to inhibitory stimulus, is of an active nature. The patterns of elaboration and realization of internal inhibition compared to those of food conditioned reflexes and defensive conditioned reflexes were found to be identical as well (Pavlov, 1973). In recent years, the term internal inhibition is rarely used in literature. Psychologists and psychophysiologists (e.g., Freud's followers or the founders of such trends in psychotherapy as neurolinguistic programming) use the following terms: forgetting, repression, substitution, suppression, erasing. Almost all these concepts are based on the inhibition process studied in detail both by Pavlov's school and by followers of general neurophysiology. The use of available data on inhibitory processes by psychologists and psychophysiologists could essentially improve our understanding of brain function and various forms of psychopathology. It is noteworthy that the term "habituation" most often used in neurophysiology is a broader and less definite concept than internal inhibition. It includes both learning to eliminate the inadequate reactions and weakening of response (e.g., during presentation of stimuli with short intersignal intervals). In recent years, another term, in essence similar to the concept of internal inhibition, is commonly used in psychiatry and in the works on biological models of schizophrenia. It is the term "latent inhibition." Latent inhibition occurs in response to repeated stimuli prior to learning and results in hampering subsequent formation of new behavior to this stimulus (Lubow, 1989). The weakening of latent inhibition versus the normal state (i.e., the inability to ignore biologically insignificant events) is one of the main symptoms of schizophrenia (Lubow & Gewirtz, 1995; Vaitl et al., 2002.). There is data that show that damage of corresponding regions of hippocampus results in habituation weakening (internal inhibition, according to Pavlov) (Finamore, Seybold, Noble, & Port, 2001) and in latent inhibition weakening (Solomon & Moore, 1975). The hampering of conditioning to stimulus when learning follows extinction of the orienting reflex to this stimulus was established long ago by researchers of the Pavlovian school (Narbutovich & Podkopaev, 1936). Yet this is only part of the broad sphere of studies on problems of inhibition of behavior that do not correspond to environmental conditions.

Various forms of epilepsy are also obviously the result of impaired interaction between excitation and inhibition in the brain structures. "Convulsive" discharges occur in the epileptogenic zone under conditions that favor synchronization of oscillations of the membrane potential and the action potentials of neighboring neurons involving inhibitory interneurons (Avoli, 1996; Babb, Pretorius, Kupfer, & Crandall, 1989**;** Enomoto & Ajmon-Marsan, 1959; Frolov et al., 1984; Jefferys & Whittington, 1996; Lusher, 2002; Vein, Levin, & Tarasov, 2003).

Simultaneous Record of Single-Neuron Action Potentials, Slow Potential Oscillations (SPO), and Behavior as an Informative Method for the Study of Neurophysiological Mechanisms of Internal Inhibition

Changes in Summary Slow Potential Oscillations in the Neocortex and in Other Brain Structures during Learning

In spite of variety of available experimental material on this issue, one main regularity of summary SPO dynamics

during active and inhibitory conditioning can be distinguished. Most experiments performed in very different subjects, including humans, revealed an increase in the amplitude of both background and evoked potential oscillation during repeated presentation of nonreinforced stimuli, and also revealed a decrease in this amplitude during activating reinforcement and, subsequently, in response to conditioned stimulus acquiring signal significance (Christian, 1960; Clemente, 1968; Gastaut et al., 1957; Gluck & Rowland, 1959; Hernandez-Peon, 1960; Kogan, 1961; Kratin, 1967; Rougel-Buser & Buser, 1973; Shulgina, 1969, 1976, 1978, 1986, 1987). Reduction in the similarity of slow oscillations and their frequency and phase mismatch in the various structures of the CNS are observed during elaboration of internal inhibition (Livanov & Shulgina, 1983). Thus, the study of summary SPO showed clear differences in their parameters during active functioning compared to those during the inhibition of excitation irradiation to the periphery.

The interpretation of SPO genesis in the active brain and in the inhibitory state of the brain is a matter of some difficulty. Upon analyzing the possible mechanisms of internal inhibition, Pavlov supposed that it resulted from cessation of activity of the corresponding neurons (Pavlov, 1973). For a long time, this idea was regarded as a matter of course by many other researchers of internal inhibition. However, the increase in the amplitude of potential oscillation during elaboration of various forms of internal inhibition does not agree with the concept of cessation of neuron activity after reinforcement withdrawal.

The second difficulty in the interpretation of neurophysiological meaning of changes in the SPO during learning consists of the uncertain location of the electrical source due to the ability of slow oscillation of physical propagation through the volume conductor. Parameters of potential oscillations, recorded from certain brain structures, are determined not only by degree of their native activity but also by their location with respect to another more powerful biopotential generator. Recording of single-neuron activity is used to gain understanding of the processes occurring during learning.

Changes in the Quantitative Structure and Intensity of Neuron Reactions during Elaboration of Internal Inhibition

In most works on this trend, the reactions to stimuli without reinforcement were not specially studied, but instead were only compared to responses to the activating conditioned stimulus. Analysis of the dynamics of neuron action potentials showed low intensity or an opposite sign of reactions to the stimuli without reinforcement compared to those to activating reinforced stimuli (Albrecht, Davidova, & Gabriel, 1990; Farley & Alkon, 1985; Freeman & Nicholson, 1999; Fuster & Alexander, 1971; Horn, 1967; Jasper, Ricci, & Doane, 1960; Kubota, Wolske, Poremba, Kang, & Gabriel, 1974; Kubota, Yamamoto, & Suzuki, 1996; Morrell, 1960; Powel, Watson, & Buchman, 1990; Rabinovich, 1975; Repa et al., 2001,.; Shulgina, 1969, 1976, 1978; Storozhuk, Sanzharovsky, & Busel, 1998; Tshizhenkova, 1998; Watanabe, 1986). Some works demonstrated the presence of neurons with a more intensive response to the inhibitory stimulus than to the positive stimulus. These neurons are predominantly found in the conditioned stimulus analyzer. During delayed defensive conditioning, the cortex neuron activation peak is gradually shifted to the moment of reinforcement. When describing the dynamics of neuron reactions to positive and inhibitory stimuli, most authors do not report any specificity in neuron activity during elaboration of internal inhibition, including latent inhibition (Best & Best, 1976). The revelation of this specificity probably requires simultaneous recording of changes in neuron activity and SPO.

Phase Activity, Alternation of Activation and Inhibition of Neuron Firing as a Result of Alternation of Depolarization and Hyperpolarization of the Neuron Soma

The answer to the question of whether or not inhibitory hyperpolarizing processes participate in elaboration of internal inhibition is the cardinal problem of behavioral neurophysiology. Attempts to resolve this problem theoretically face certain difficulties. First of all, it is necessary to match the data on the duration of inhibitory postsynaptic potentials (IPSP), ranging from milliseconds to tens of milliseconds, with the data on the duration of the internal inhibition process, ranging from several seconds to several minutes. The memory of the inhibitory significance of stimuli lasts for years. Another difficulty in the study of this problem is of a methodological nature. Examination of the inhibitory processes in neurophysiological experiments is usually performed with intracellular recording techniques in narcotized or immobilized animals (i.e., under conditions that exclude the possibility of learning), thus excluding the direct use of the obtained data to explain behavior inhibition processes. Experimental analysis of the role of inhibitory processes, previously known in neurophysiology, in elaboration and realization of internal inhibition requires indexes of brain activity that could provide unambiguous interpretation of the interaction of activating and inhibitory processes during learning of conscious nonimmobilized animals. In this regard, simultaneous recording of SPO, background and evoked potentials, and action potentials of brain neurons was found to be very productive. Flashes of light presented as the conditioned stimulus were found to be the most informative method. The neurophysiological studies demonstrated that presentation of either short diffused light of sufficient intensity or of electrical stimulation of

projection paths evokes phase reactions and the alternation of activation and inhibition of neuron firing at all levels of the visual analyzer from the retina to the neocortex (Baumgarten, 1955; Grüsser & Grützner, 1958; Guselnikov & Supin, 1968; Kondratjeva & Polansky, 1968; Li, Ortiz-Galvin, Chou, & Howard, 1960; Shulgina, 1969, 1976, 1987; Watanabe, Konishi, & Creutzfeldt, 1966). It was shown that the inhibitory pause in these reactions coincides with the hyperpolarization of the neuron soma IPSP types. The compliance of the late surface-negative and deep-positive components of evoked potentials (EP) in the visual neocortex with the inhibitory pause in the reactions of a considerable part of the neuron population in this area in response to flashes of light was found as well. Then, the synchronism of IPSP recorded intracellularly and the inhibitory pause in late EP components in neuron firing was revealed. Hence, clear compliance of phase reactions of neurons of the visual cortex and late EP components in response to flashes of light with the alternation of depolarization and hyperpolarization of cells was revealed. At the same time, the inhibitory pauses in neuron firing were synchronous to the increase in the level of neuron soma polarization.

The essential feature of the late EP components in the visual analyzer in response to flashes of light is the similarity of their genesis and that of the background slow oscillations in the electroencephalogram (EEG). Such a similarity was suggested long ago (Bishop & Clare, 1952). Experiments using intracellular recording revealed the compliance of background oscillation of single-neuron membrane potential depolarization and hyperpolarization with the alternation of activation and inhibition of neurons firing and with slow EEG waves both in the visual and sensorimotor cortex in animals and humans (Andersen & Anderssson, 1968; Creutzfeldt & Ito, 1968; Creutzfeldt, Watanabe, & Lux, 1966; Jasper & Stefanis, 1965, Morell, 1967; Steriade, 1999, 2001) Statistical analysis also showed that the firing of a considerable part of the neurons in the visual and sensorimotor cortex depended on slow EEG oscillation (Shulgina, 1987). In turn, this dependence was observed in the neurons of the visual field in which alternations of activation and inhibitory pauses in reactions to light flashes coincided with late EP components, which confirmed the concept of the identical genesis of the EEG and the late EP components. Both processes are caused by the alternating of the relative prevalence of depolarization and hyperpolarization of a considerable part of the neurons in the recorded area of the brain cortex. Thus, the results of the study on the genesis of the phase activity of neocortex neurons and of corresponding summary background and evoked SPO allow us to use the dynamics of these indexes of brain activity to study the interaction of inhibitory and activating processes in learning of conscious nonimmobilized animals, using extracellular recording of biopotentials.

Enhancement of Phase Activity of Neurons and SPO during Elaboration of Internal Inhibition as a Reflection of Enhancement of Inhibitory Hyperpolarizing Processes (Results of Author's own Experiments)

In several series of experiments, we analyzed changes in behavior and in simultaneously recorded SWP, and in the activity of the neurons of the visual and sensorimotor neocortex and dorsal hippocampus during defensive conditioning and elaboration and realization of all forms of Pavlovian internal inhibition (Shulgina, 1969, 1976, 1978, 1986, 1987; Shulgina, Balashova, & Okhotnikov, 1991; Shulgina & Okhotnikov, 1991). The experiments were performed in conscious nonimmobilized rabbits with paws fastened to the bedframe. Glass electrodes filled with 0.9% NaCl were placed in the brain via a micromanipulator fixed to the rabbit's head over a hole of 3 mm in diameter.

To amplify and record the activity of the neurons and summary slow potentials, breathing, and the myogram of the hind paws, on which the electrocutaneous shock was applied, the following devices were used: biopotential amplifiers BPA1 or BPA2, the Universal electrophysiological device UEF1-03 (constructed by the Central Construction Bureau of Universal Devices of the Russian Academy of Sciences), and an 8-channel ink-writer (USCH8-03). Rhythmic light flashes with a frequency rate of 1 per second were used as the conditioned stimulus. Isochronous electrocutaneous shock on the hind paw (ECSh) was the unconditional stimulus. The conditional stimulus-unconditional stimulus interval was the same in each series of experiments and, in different series, was either 1, 2, or 4 seconds. A continuous light served as a conditional inhibitor (CI). On its background, flashes of the same frequencies as the conditional stimulus were switched on, but without reinforcement. The CI was used in turn with combinations of light flashes with ECSh. Peristimuli histograms were drawn up when analyzing the experimental results. Differences were estimated according to Wilkokson's criteria (Bolshev & Smirnov, 1965). The mean amplitudes of both late negative and late positive EP components, as well as the probabilities of motor reactions to inhibitory and activating conditioned stimuli, were calculated. A detailed description of the results of the statistical analysis is provided in the related publications. On the whole, in the various series of experiments, the activity of more than 400 neurons in neocortex and hippocampus was recorded. Neuron activity was recorded predominantly in the deep layers of the cortex; it was seemingly the activity of pyramidal neurons. In the experiments using recording of bioelectrical activity in conscious nonimmobilized rabbits during defensive and inhibitory conditioning, we failed to determine precisely the type of recorded neurons. This will be the objective of future experiments.

The analysis of the obtained material showed that elaboration of all investigated forms of internal inhibition is

accompanied by similar changes in bioelectrical indexes of brain activity, resulting in enhancement of the phase activity of neocortex neurons; that is, alternation of activation and inhibition of their action potentials and increase in the amplitude of the corresponding background and evoked SPO. The first presentation of flashes of light prior to defensive conditioning usually resulted in orienting movements. Subsequently, the inhibitory pauses in the responses of visual cortex neurons to flashes of light decreased, as did the amplitude of EEG and of the corresponding late EP components, compared with the responses to subsequent presentations of flashes of light. During repeated presentation of stimuli, the orienting reflex disappeared, and the amplitude of EEG, EP, and the inhibitory pauses in neuron responses to flashes of light increased. Combined presentation of light flashes with pain reinforcement reduced the duration of inhibitory pauses and decreased the SPO amplitude. After several presentations of these paired stimuli (light flashes and ECSh), the effect of reinforcement was substituted by the effect of the flashes of light, which evoked movements in the rabbits (i.e., the light flashes became the signal of defensive conditioned reaction).

During elaboration of extinctive inhibition, when the flashes of light were presented without reinforcement, disappearance of the conditioned motor reactions was accompanied by enhancement of phase activity and alternation of neuron firing activation and inhibition in response to the inhibitory stimuli. The amplitude of late negative-positive EP components, complying with inhibitory pauses and with postinhibitory activation, was increased (see Figure 1). Enhancement of the inhibitory state was accompanied by SPO generalization and by the appearance of irregular phase activity of neurons, not only in the visual cortex but in other brain structures as well. Such changes in the responses of

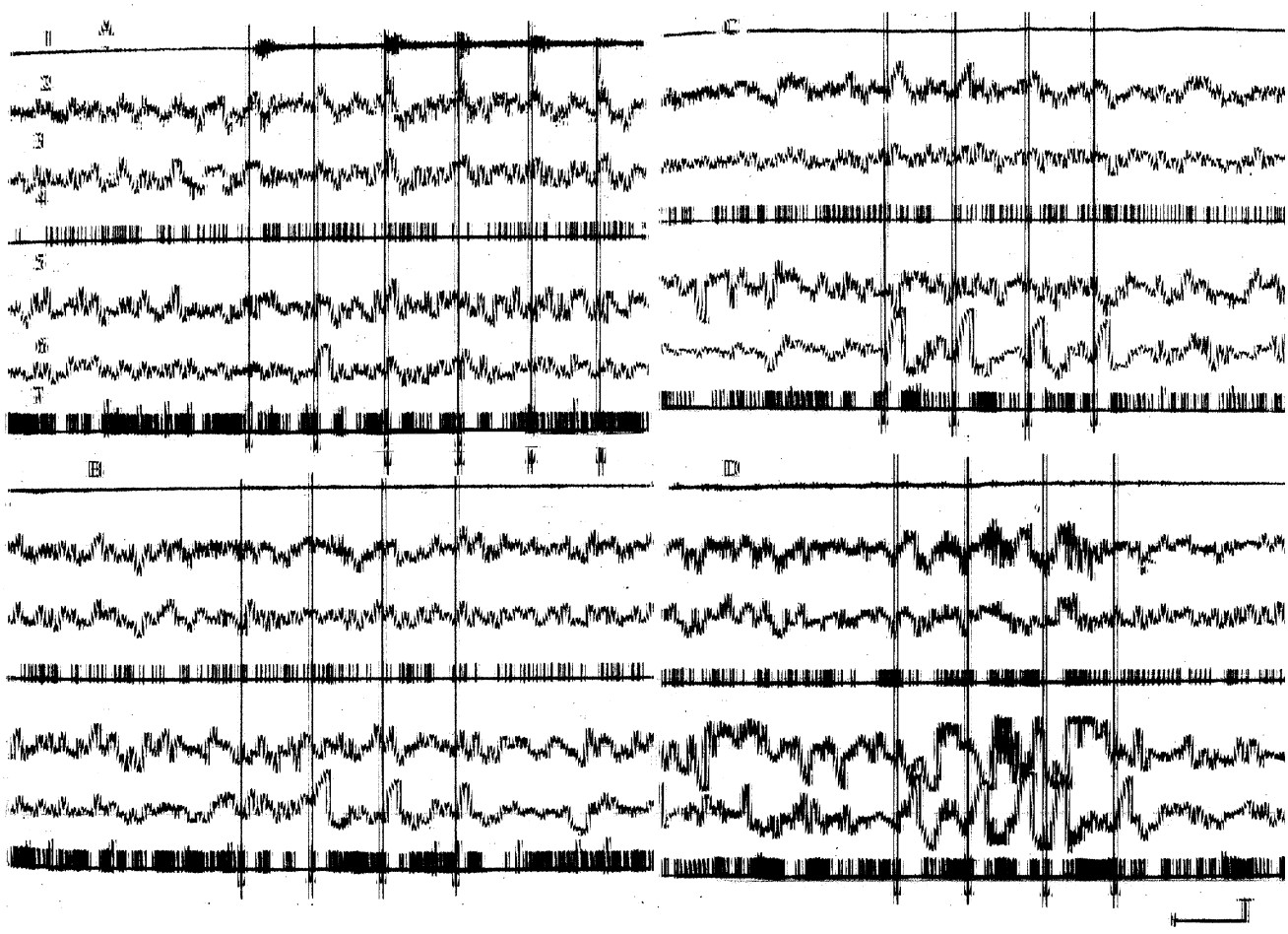

Figure 1. Changes of biopotentials during elaboration of the extinctive inhibition.
A = responses to pairing of light flashes (upper arrows) with ECSh (lower arrows); B = the 1st use of light flashes without reinforcement; C = the 14th use of light flashes without reinforcement; D = the 39th use of the light flashes without reinforcement.
1 = myogram of the hind paw; 2 = record of the SPO of the dorsal hippocampus; 3 = SPO of the sensorimotor cortex area; 4 and 5 = records of spike activity and SPO in the sensorimotor area using the same microelectrode; 6 = SPO of the visual cortex area; 7 = record of spike activity in the visual cortex area using the same microelectrode. In all records, the activity of the same neurons is shown. Negativity is upward. Calibration: 250 mkV, 1 second.

visual cortex neurons and late EP components to flashes of light were observed during the development of delayed reflex inhibition; and differential and conditioned inhibition (see examples in Figures 2, 3). In view of the above-mentioned literature data, these changes result in the relative enhancement of inhibitory hyperpolarizing processes.

The two forms of this phenomenon are observed at various stages of elaboration of internal inhibition. At the early stage of extinction development, during inhibitory conditioning, differentiation or inhibition of delayed reflex—that is, in conditions of a relatively high level of functional state—local enhancement of inhibitory processes could be seen in the projection structures of the conditioned stimulus. During further intensification of the inhibitory state, group discharges of neurons separated by inhibitory pauses and the corresponding SPO became more generalized. This phenomenon reflected enhancement of inhibitory processes not only in the structures of the conditioned stimulus but in other brain structures as well, and not only in response to the conditioned stimulus but also in background bioelectrical activity. The usual pattern of late EP components at the stage of generalization of the background SPO and the irregular group discharge activity of neurons could be disturbed. They became similar to high-amplitude background SPO (see the example in Figure 1, D).

Comparing the results obtained to the above-mentioned literature data, we may conclude that enhancement of the phase activity of neurons and the corresponding high-amplitude background and evoked SPO during elaboration of internal inhibition reflects relative enhancement of inhibitory hyperpolarizing processes in the corresponding brain structures.

Participation of the GABAergic Neurotransmitter System in Elaboration of Internal Inhibition (Results of Author's own Experiments)

As well known, gamma-aminobutyric acid (GABA) appears to be the most probable hyperpolarizing inhibitory transmitter in the brain cortex (Tebecis, 1974). Hence, in order to study the neurotransmitter mechanisms of internal inhibition, experiments about the influence of GABA on cortical neuron activity during learning are needed. At present, a Phenibut-phenyl derivative of GABA (hydrochloride of the gamma-

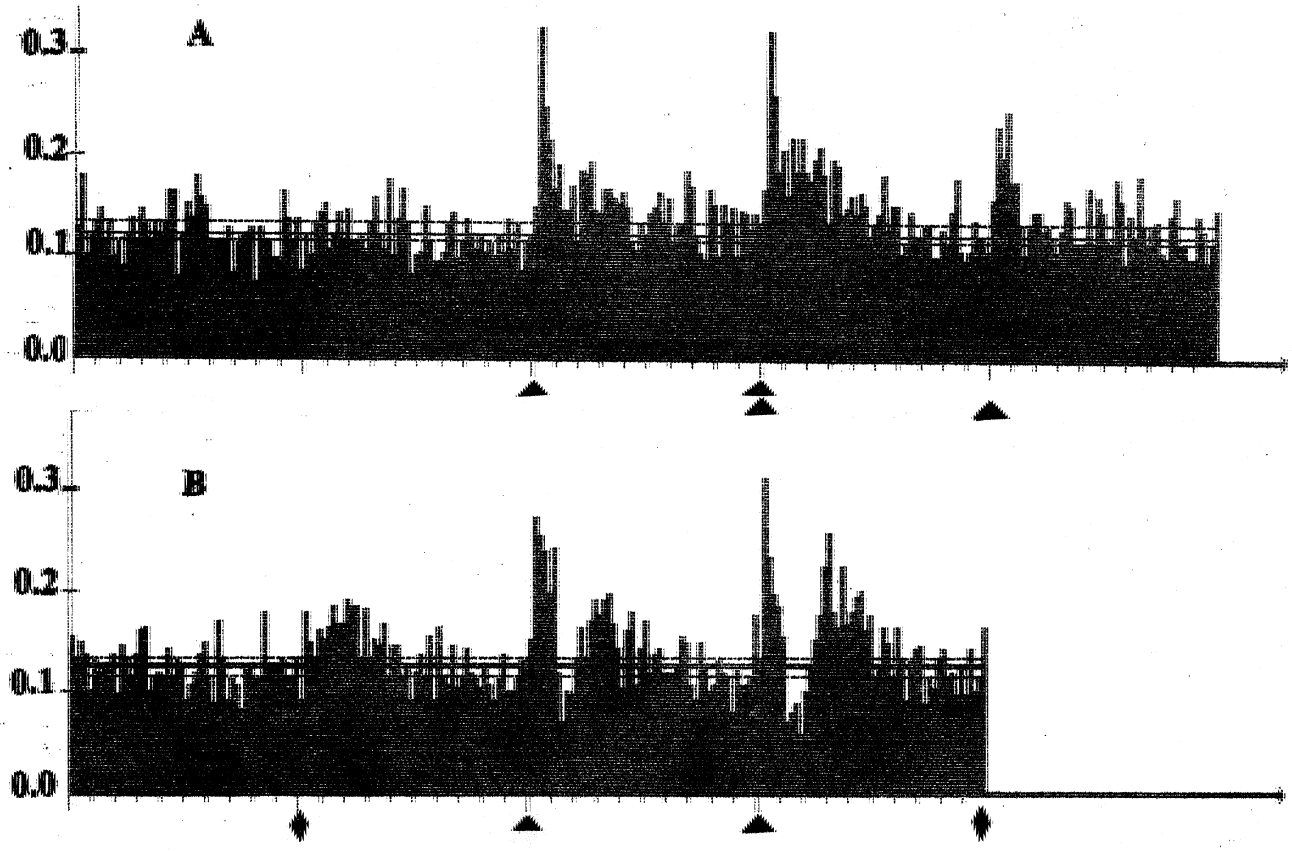

Figure 2. Peristimuli histograms of the averaged activity of 94 visual area neurons. A = responses to the combination of light flashes (upper arrows) and ECSh (lower arrows); B = responses to flashes (arrows) against the background of continuous light—conditional inhibitor (rhombus). The ordinate shows the average number of spikes per 20 ms, the abscissa shows time with 20 ms spacing.

amino-beta-phenilbutiric acid), which easily crosses the blood-brain barrier (Perekalin & Zobatcheva, 1959), is widely used in treatment of neuropsychological diseases. Phenibut is a nootropic drug that is used in Russia in the treatment of mental diseases, including children's hyperactivity and ambulatory therapy of schizophrenia after in-patient treatment.

In experiments on conscious nonimmobilized rabbits, we studied the influence of phenibut on behavior and on bioelectrical activity of the brain cortex during defensive conditioning in response to flashes of light and during inhibitory conditioning (the same flashes as for defensive conditioning but presented on a background of permanent light without reinforcement) (Shulgina, 1986; Shulgina, Petricheva, & Kuznetzova, 1985; Shulgina & Ziablitzeva, 2004). The action potentials, of the neurons of the visual cortex, SPO of visual and sensorimotor areas of neocortex and hippocampus, breathing, and the motions of the hind paw, to which the pain reinforcement (EPSh) was applied, were recorded prior and within 3-4 hours after percutaneous administration of phenibut, at the dose of 40 mg/kg in 3 ml of a 0.9% NaCl solution.

Firstly, after phenibut administration, an increase in the amplitude of late components of evoked responses and the corresponding alternation of activation and inhibition of the neurons of the visual cortex to flashes of light were observed, particularly in reaction to nonreinforced flashes presented on the background of light—inhibitory conditioning (IC). Then, a stable prevalence of high-amplitude potential oscillations and the corresponding irregular group discharges of neurons separated by inhibitory pauses in all leads (from visual and sensorimotor cortex and from hippocampus) appeared both in response to flashes of light and during intersignal intervals. Reinforcement presentation, similarly to the situation prior to phenibut administration, resulted in a decrease of slow oscillation amplitude and in the reduced duration of inhibitory pauses in neuron firing (see Figure 3). After phenibut administration, the rabbits showed a clear enhancement of the distinction between reinforced and inhibitory flashes of light due to increased response probability to the activating stimuli, and to the reduced number of motions in response to inhibitory stimuli. The results obtained confirm the supposition that enhancement of the phase activity of neurons in the brain cortex and the corresponding SPO during elaboration of internal inhibition reflects enhancement of inhibitory hyperpolarizing processes. The GABAergic neurotransmitter system is of great importance to this process. This statement is in accordance with the fact that rats with a deficiency of lateral (internal) inhibition, used as a biological model of schizophrenia, show a reduction in the number of inhibitory interneurons of prefrontal cortex and hippocampus (Japha & Koch, 1999). There are data on disorders of GABA synthesis in the cortex in schizophrenia which allow us to recommend medications regulating GABA metabolism for the treatment of this disease (Costa et al., 2004).

It is known that schizophrenic patients also have a deficiency of "prepulse" inhibition. This form of inhibition ensures suppression of the startle reflex to sound during the presentation of a foreign stimulus, provided that this stimulus is presented approximately 100 msec before the sound. This type of inhibition is probably similar to the Pavlovian external inhibition. Available data report that latent and "prepulse" inhibitions are performed through different neuronal substrates (Coutureau, Gosselin, & Di Seala, 2000; Ellenbroek, Budde, & Cools, 1996; Finamore et al., 2001; Murphy, Di Iorio, & Feldon, 2001). However, discussion of the neurophysiological mechanisms of external inhibition and "freezing," which is the consequence of fear, is beyond the goals of our work.

It should be emphasized that analysis of the neurotransmitter mechanisms of internal inhibition is a complex problem. The inhibition of reactions that are inadequate to environmental conditions is realized through complex systemic processes. These processes seemingly include both an increase in the self-activity of the general and local inhibitory systems and in the activity of structures which activate these inhibitory systems. Different forms of plasticity of GABAergic and glycinergic synapses are reported for different areas of the brain (Gaiarsia, Caillard, & Ben-Ari, 2002). Evidence that different patterns of internal inhibition are carried out not only through the GABAergic but also through the cholinergic neurotransmitter system of the brain is available in the literature (Mukhin, 1984). It is shown that latent inhibition depends on the state of the N-Methyl-D-Aspartate (NMDA)-receptors in some areas of the limbic system (Santini, Muller, & Quirk, 2001).

The information about the essential role of GABAergic neurotransmitter system in the realization of internal inhibition provides the neurophysiological basis for use of GABA and its derivatives in the treatment of schizophrenia, children's hyperactivity, and other neuropsychological diseases associated with weakening of internal inhibition. It is known that GABA agonists have an anxiolytic effect, whereas GABA receptor (sub A) antagonists increase feelings of fear (Dalvi & Rodgers, 1996; Mosolov, 2002).

Neurophysiological Mechanisms of the Organization of Inhibitory Hyperpolarizing Processes in the CNS

The increase in the level of cell polarization can be passive, due to reduced excitatory influence, and active, due to the activation of inhibitory synapses and the development of inhibitory postsynaptic potential (IPSP), according to contemporary conceptions. IPSP can appear in neurons as a result of direct afferent influence and via recurrent collateral axons of firing neurons, which realize recurrent and latent inhibition (Andersen & Andersson, 1968; Avoli, Hwa, Louvel, Kurcewicz, Pumain, & Lacaille, 1997; Babb et al., 1989; Benardo, 1997; Clemente, 1968; Eccls, 1964, 1969; Fisher & Levin, 1989; Freund & Gulyas, 1997; Gaiarsia et al., 2002; Guselnikow & Supin, 1968; Koys & Tepper, 1999; Micheva & Beaulieu, 1997; Shulgina, 1987; Steriade, 1999, 2001; Vein, Levin, & Tarasov, 2003; Zappone & Sloviter, 2001). It is

assumed that both direct and recurrent inhibition are realized via switching from excitatory to inhibitory influence through the inhibitory interneurons. Cells of similar characteristics to the inhibitory Renshow cells of the spinal cord are reported by different authors to be found in various areas of the brain. These cells are mostly studied in the cerebellum, olfactory bulb, thalamic nuclei, and hippocampus. On the basis of several indexes, it is considered that inhibitory synapses are located predominantly on the neuron soma. Regardless of the concrete way that interaction of depolarizing and hyperpolarizing processes is organized in the neural structures, it is of great importance for our further argumentation that this interaction can be realized in very diverse formations, and it appears not only due to external inhibitory influence but also as a result of mutual influence of elements in localized brain structures, that is, in the thalamic nuclei after cutting their neural connections with the neocortex (Andersen & Andersson, 1968). It was shown as well that, in spite of the main possibility of the development of slow bioelectrical oscillation in localized brain structures—particularly due to the recurrent inhibition system—in natural conditions, these oscillations occur as a result of close interaction between certain structures. Thalamocortical connections are of great importance in the organization of background and evoked bioelectrical activity of the neocortex (Andersen & Andersson, 1968; Shumilina, 1968; Steriade, 1999).

Currently, a number of facts indicate that the inhibitory state is mediated by activation of either local mechanisms of inhibition or special systems of interrelated brain structures. These systems include the orbital surface of the frontal lobe, the basal area of the forebrain, including Hess' hypnogenic zone, the medial thalamic nuclei, caudate nucleus, and caudal part of the medulla oblongata. It was shown that stimulation of the structures of this inhibitory system results in the

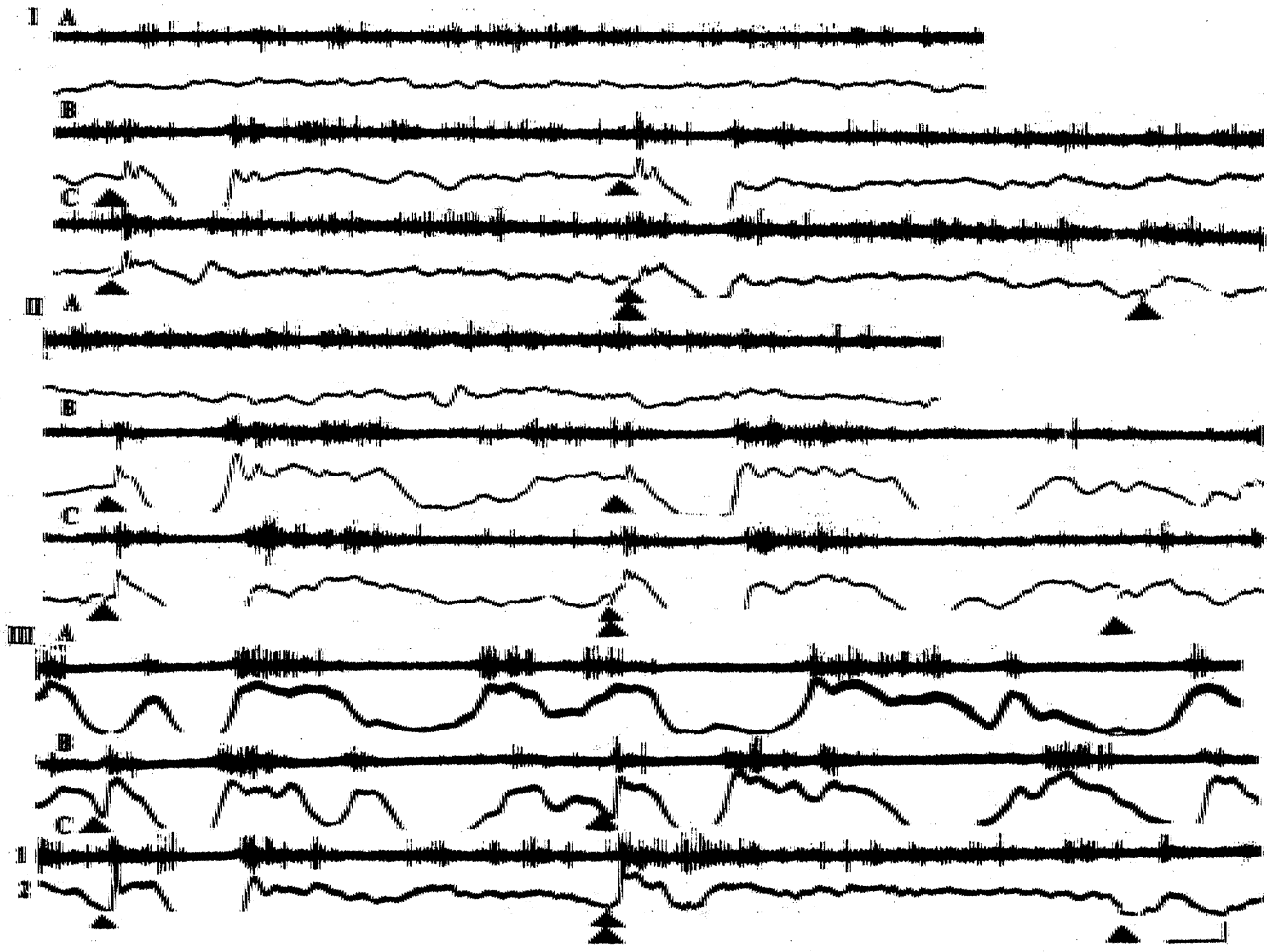

Figure 3. The effect of phenybut on the SPO and the activity of several neurons recorded simultaneously with one microelectrode. I = before the injection of phenybut; II = 30 min after the injection; III = 1.5 hours after the injection. 1 = recording of spike activity; 2 = recording of SPO using the same microelectrode. Upper arrows show switching on light flashes; lower arrows show switching on ECSh. A = background activity; B = responses to flashes against the background of the continuous light—conditional inhibitor; C = responses to combination of flashes and ECSh. Negativity is upward. Calibration: 250 mkV, 100 ms.

development of an inhibitory state in animals, reflected in the inhibition of various patterns of behavioral responses, and in the increase in high-amplitude SPO, either in the stimulation rhythm or rhythm independent. Stimulation of neural structures of the inhibitory system results in the decreased activity of neurons of the reticular formation (RF) (Siegel & Wang, 1974). In this connection, enhancement of inhibition during the development of high-amplitude SPO may be the consequence of the weakening of the activating influence of the RF. However, it was also shown that stimulation of the brain inhibitory systems results in the enhancement of neuron hyperpolarization in various brain structures, either monosynaptically or via small number of switches (Clemente, 1968). There is also data that neocortical excitability is regulated by tonic GABAergic modulation via extrasynaptic receptors on the neuron soma and on the neuron dendrites (Semyanov, Walker, & Kullmann, 2003). Participation of various brain structures in the realization of concrete behavioral patterns (active and passive) can be very specific. At present time, various methods are employed to analyze this problem (Fendt, 1998; Jones & Gonzalez-Lima, 2001; Oswald, Yee, Rawlins, Bannerman, Good, & Honey, 2002). The presence of an inhibitory substrate in almost all brain structures seemingly ensures the possibility of elaboration of internal inhibition, even in decorticated animals (Kotani, Kawahara, & Kirino, 2002; Yeo, Hardiman, Moore, & Russel, 1983).

The relative enhancement of inhibitory hyperpolarizing processes during elaboration of internal inhibition revealed by us indicates an increase in the reactivity of the brain's inhibitory systems to inhibitory stimuli during learning. The irreversibility of these changes is proved by the fact of the long-term memory of inhibitory significance of nonreinforced stimuli and by indexes of brain functioning, such as behavior and bioelectrical activity.

The Functional Role of Relative Enhancement of Hyperpolarization during Elaboration of Internal Inhibition

The functional role of enhancement of inhibitory hyperpolarizing processes seemingly consists of limitation of excitation (in response to an inhibitory stimulus) transmission to the effectors. As shown by our experiments on the model of network of excitatory and inhibitory neuron-like elements, sharp excitability changes, alternation of excitation and inhibition of neurons restricts the excitation from spreading in response to the stimulus, which causes the activation of local and general inhibitory systems. The presence of the phases of reduced excitability and reactivity at successive points of excitation "switches" stops its further transmission. (Shulgina & Muravev, 2000; Shulgina, 2002). Furthermore, as described above, the specific feature of the background and evoked SPO during elaboration of internal inhibition is their difference in amplitude and frequency within various brain structures. This phenomenon was observed in experiments with the use of microelectrodes and multipolar biopotential recording techniques (John & Morgades, 1969; Livanov & Shulgina, 1983). As mentioned above, the substrate for inhibitory hyperpolarization processes (realization of direct, recurrent, and lateral inhibition through the "switching" of excitatory influences via inhibitory interneurons) is available practically in all the studied brain structures. Therefore, enhancement of inhibition in these structures results in the development of high-amplitude SPO which differ in frequency and in phase shift. On account of differences in frequencies and phase shift of SPO in neuron populations, limitation of excitation transmission occurs at the points of excitation "switch." This limitation eliminates the main condition of excitation irradiation to the periphery—convergence of excitations from many sources. Reduction of the number of these sources results in the rapid attenuation of the excitation wave that arises in the structures receiving the inhibitory conditioned stimulus. Hence, enhancement of inhibitory hyperpolarizing processes in response to a stimulus that has lost its biological significance limits excitation transmission both on cell and on systemic levels.

Conclusion

In conclusion, our concept of the possibility of the development of the hyperpolarization theory of internal inhibition can be said to have found confirmation in a number of works by other authors. As mentioned above, an increase in the amplitude of background and evoked SPO during elaboration of internal inhibition was observed by many authors in various subjects in experiments with the use of various techniques, including the study of voluntary activity in humans. Some authors, on the basis of their experiments using EEG and behavior recordings, also concluded that hyperpolarizing inhibition is of great importance in the genesis of internal inhibition (Clemente, 1968; Rougel-Buser & Buser, 1973). The enhancement of inhibitory processes resulting in an increase of the irregular phase activity of neurons in the neocortex and basal structures was also observed by other authors during either elaboration of inhibition of defensive reflexes (Varukha & Gulyakova, 1980) or inhibition of food search activity (Sudakov & Zhuravlev, 1981). Hence, our experimental data showed that during elaboration of internal inhibition, the neurons of the corresponding brain structures do not cease their activity, as suggested by Pavlov (Pavlov, 1973), but turn to a new phase functioning mode. This fact eliminates the contradiction between the duration of IPSP (milliseconds) and internal inhibition (seconds, minutes, or hours, in the case of sleep). Long-term changes in the reactivity of inhibitory systems, stored for many years, are probably determined by histochemical changes in the effectiveness of the corresponding synapses. Our experiments with the

use of a mathematical model of neural network learning on the basis of changes in the effectiveness of excitative and inhibitory synapses yielded satisfactory evidence of this hypothesis (Shulgina, Ponomarev, et al., 1985).

Many authors observed enhancement of SPO and the neuron phase activity in the phase of slow-wave sleep (Arduini, Berlucchi, & Strata, 1963; Ewarts, 1963; Huttenlocher, 1961; Steriade, 1999, 2001). This phenomenon seemingly reflects enhancement of inhibitory hyperpolarizing processes as well. These data provided particular experimental validation of Pavlov's suggestion that sleep and internal inhibition have identical genesis (Pavlov, 1973). As known, the organization of neuron phase activity with the participation of recurrent and lateral inhibition is characterized by its propagation to the neighboring neurons. This property probably underlies the phenomenon of irradiation of internal inhibition.

In the view of hyperpolarization theory of internal inhibition, the data from the Pavlovian school on the specific role of bromides in the regulation of inhibitory processes in the cortex become understandable. Bromine ions are among the elements that produce an increase in membrane potential during the action of an inhibitory transmitter. Administration of bromides results in enhancement of the phase activity of neocortical neurons (Khapazhev, 1978).

Development of the hyperpolarization theory of internal inhibition opens up extensive prospects for the purposeful analysis of the following topics: (a) the neurophysiological basis of local and generalized mechanisms of elaboration and realization of internal inhibition; (b) the study involving various inhibitory and activating neurotransmitter systems in this process; (c) development of the necessary techniques to analyze the histochemical changes that ensure long-term memory of the inhibitory significance of changes in either the external or internal environment of living organisms; and (d) applying this knowledge to the determination of the genesis and treatment of neuropsychological diseases.

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