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Synaptic Reactions of the "Nociceptive" Neurons in the Cat Cortex up on Stimulation of the Periaqueductal Gray and Application of Some Pharmacological Agents

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Mini Review

The problems of extracellular and intracellular signaling and its participation in control of the living systems are recognized to be one of the major directions in modern fundamental sciences, which are also used in clinical medicine for treatment and correction of the certain CNS disorders. The activity of cortical neurons that are related to the system of nociception, similarly to the activity of neurons of other cerebral nociceptive/antinociceptive structures, is subjected to modulatory influences coming from a few brain centers.

The etiology of a number of mental diseases is based on disorders in the functioning of extra thalamic brainstem-cortical neurochemical systems. It is known that electrical stimulation of the periaqueductal (central) gray (PAG) results in significant modifications of the reactions evoked in spinal, medullary [1], and thalamic [2] neurons by nociceptive stimulation. At the same time, the effects of PAG stimulation on synaptic processes in cortical neurons, which are closely related to the system of nociception, remain at present relatively poorly examined.

Injections of microdoses of opiate alkaloids and opioid peptides into the CNS induces clear analgesic effects [3]. Such experimental facts confirm the statement on the special relation of the PAG to the cerebral antonociceptive system, whose functions are realized with the involvement of opioid receptors. At the same time, information of the effects exerted by the opioidergic cerebral systems on various neuronal populations in the cerebral cortex remains fragmentary [4]. At present, there is no doubt that epileptic and epileptiform activities of cortical neurons are determined by their hyperactivation and disorders of the processes of central inhibition. Models of epilepsy induced in experimental animals by electrical stimulation of different brain structures and by the action of epileptogenic substances and examined using microelectrode techniques allow researchers to study the activity of single neuronal units in the course of development, formation, and cessation of epileptiform activity [5].

Research of the relations between disorders of central inhibition and hyperactivity of cortical neurons opens up certain possibilities to detect specific changes developing during epileptogenesis and helps to interpret peculiarities of the pharmacology of synaptic transmission, organization, and functioning of cortical units, structural and functional bases of generation of epileptiform EEG phenomena, and a few other important aspects of neurophysiology of the cortex.

Methods

Acute experiments were carried out on cats. Surgical interventions (tracheostomy), catheterization of the femoral vein, pneumothorax, and trepanation of the skull above the pericruciate cortical area were performed under inhalation (ether) anesthesia; after this, α-chloralose or arduan (40mg/kg) was injected under permanent control of the efficiency of anesthesia. Deep formations of the brain were stimulated via constantan bipolar electrodes with an interpolar distance of 0.5mm. The electrodes were introduced according to the coordinates of the stereotaxic atlas in the regions corresponding to localization of the PAG and Ventro Posteromedial nucleus (VPM) of the thalamus. Rectangular current pulses were used for electrical stimulation of the cerebral structures.

Openings were made in the upper fangs of the experimental animal using a dental burr; thin wire electrodes isolated except for their tips were introduced through these openings for stimulation of the dental pulp. The activity of cortical neurons was recorded intracellularly using standard techniques. Microelectrodes filled with potassium citrate solution (2.0M) were used. The electrodes were inserted in the somatosensory area of the cortex under visual control. Cortical neurons were identified as units belonging to the first group ("purely nociceptive"), in the case where synaptic potentials developed in these neurons exclusively after stimulation of the dental pulp afferents with intensity not lower than to 2PT. The use of weaker

stimuli did not evoke in such neurons any postsynaptic responses. Neurons of the second group (convergent units) were evoked at stimulations of both the dental pulp and thalamic VPM. Changes of such synaptic effects in neurons of the two above-mentioned groups after systemic introduction of 0.3mg/kg morphine were examined. Intracortical ionophoretic application of strychnine solution (1%) was performed through one of the barrels of two-barrel assembled glass microelectrodes (distance between tips of the recording and application electrodes 50-60μm, constant electric current up to 200nA). Leakage of strychnine from the application microelectrode within inter stimulation periods and its subsequent diffusion were prevented by opposite-direction locking current (5nA). For surface applications on the cortex, solutions of strychnine citrate (1%) diluted in 3ml of physiological saline was used. Solutions of these substance were applied through a thin polyethylene tube inserted in the trepanation opening and connected to a micro syringe. Electrical signals recorded from the nerve cells were DC-amplified and recorded by a magneto recorder for subsequent reproduction and analysis. Localization of the electrode tips was verified histologically on frontal brain slices. Numerical results were treated statistically using standard techniques, the Student's t-test in particular. Intergroup differences were considered significant in the cases with $P \leq 0.05$.

Result and Discussion

We examined the effects of electrical stimulation of the periaqueductal gray (PAG) and systemic morphine injections on postsynaptic processes in neurons of the cat somatosensory cortex, which were activated by nociceptive influences. Single stimulation of the ipsilateral PAG locus evoked in nociceptive neurons a reaction looking like a complex of EPSP-action potential (AP)-IPSP. Such reactions were similar, to a certain extent, to the responses evoked by stimulation of the dental pulp (A1). Stimulation of the PAG resulted in long-lasting suppression of synaptic reactions induced by stimulation of dental pulp nociceptors. There was certain parallelism within the conditioning effects of PAG stimulation and effects of systemic introduction of morphine. Ionophoretic application of strychnine on such pyramidal cortical neurons did not evoke paroxysmal depolarization shifts (PDSh) of the membrane potential in such neurons. At the same time, surface application of this agent on the cortex (which influenced extensive populations of cortical neurons) resulted in the development of considerable PDShs [6]. This observation confirms the synaptic nature of the above shifts. Applications of strychnine using both techniques resulted in the blockade of, first of all, early IPSP components in pyramidal neurons but did not affect significantly late components of these potentials; this is indicative of different geneses of the above components. It is supposed that the early IPSP component is generated due to activation of axo-somatic inhibitory synapses, while the late component of such reactions is related to activation of inhibitory synapses localized in the dendrites. Results of our studies of modulation of the postsynaptic responses in neurons of the somatosensory cortex activated by stimulation of nociceptors showed that processing of nociceptive information at the level of "upper" CNS structures is realized with the involvement of not only the opioidergic system, but also of the dopaminergic, serotonergic, and cholinergic systems [7]. It seems likely that synaptic mediators provide not only transmission of the nerve signals but also regulation of the biochemical processes in target cells, with the involvement of intracellular messengers, such as cAMP and cGMP. Upon the action of painful stimulations, the decrease in the amplitude or complete suppression of IPSPs in nociceptive neurons, as well as partial decrease in the IPSP amplitudes in convergence neurons, is probably related to the development of analgesia, while complete suppression of IPSPs in convergence neurons is probably associated with the development of a seizure-like state in the cortex. It seems likely that such modulation is based on changes realized within both pre- and post-synaptic intracortical mechanisms.

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