ANALYSIS OF THE CORTICAL ACTION OF BARBITURATES

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Electrophysiological analysis of changes in excitation of neurons of the somatic projection cortex in cats under the influence of nembutal was carried out, using as model the interzonal response arising in the second somatosensory area to stimulation of the first area. Changes in the recovery cycle of interzonal responses were observed after administration of fractional doses of the drug.

Injection of nembutal in subnarcotic doses is accompanied by blocking of late high-frequency waves and prolongation of their recovery cycle. Meanwhile the period of manifestation of increased amplitude of the test interzonal response is displaced. These results show that even in subnarcotic doses, nembutal considerably strengthens the mechanism of reciprocal inhibition in the cortex.

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Electrophysiological analysis of the action of barbiturates directly on excitation of somatosensory cortical neurons during stimulation of peripheral nerves is made difficult by the fact that barbiturates have a well-marked action on the mechanisms of stimulus conduction in nuclei of sensory projection pathways [3, 8, 13]. Changes in the level of excitation of the cortical neurons themselves can be tested only during stimulation of structures directly connected with the investigated region of the projection cortex, for example, during stimulation of the corresponding thalamic relay nuclei [2, 12]. Responses arising in one somatosensory area of the cortex to stimulation of the other somatosensory area can serve as a model for such an investigation. The mechanisms of formation of the separate components of these cortical reactions, arising through activation of direct interzonal intracortical connections [1, 6, 7], have been examined previously [10, 11].

The object of the present investigation was to analyze changes in the configuration and recovery cycle of interzonal responses of the somatosensory cortex under the action of nembutal.

EXPERIMENTAL METHOD

Acute experiments were carried out on cats immobilized with muscle relaxants and maintained on artificial respiration. All regions of incisions and of fixation of the animal in the stereotactic apparatus were infiltrated with 0.5% procaine solution. Single or paired stimuli at different time intervals were applied to the zone of representation of the fore- or hind limb in the first somatosensory area (SI) through a bipolar electrode. Evoked potentials from the cortical surface were recorded by a monopolar technique in the corresponding area of the second somatosensory area (SII).

Nembutal was injected intravenously in fractional doses (5, 10, 20, 30, 40 mg/kg body weight).

EXPERIMENTAL RESULTS

The primary response in area SII evoked in the unanesthetized, immobilized cat by local, single stimulation of the corresponding zone of representation in area SI had a complex configuration. It was due principally to two components, different in electrogenesis and superposed on each other: a positive-negative wave and a series of 4 or 5 high-frequency waves, coinciding in time with the period of develop-

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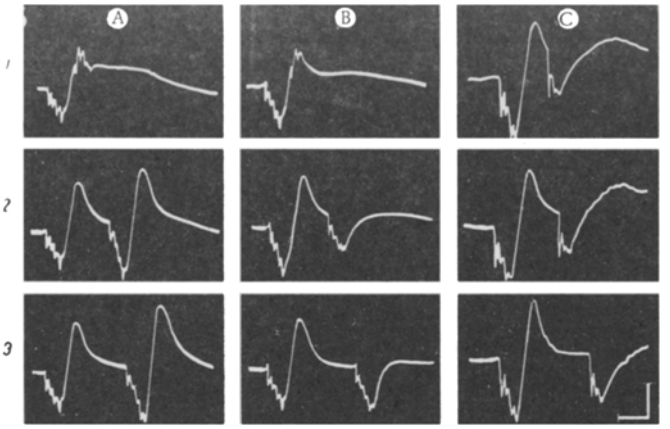

Fig. 1. Effect of nembutal on recovery cycle of high-frequency components of interzonal response. A) Before injection of nembutal; B) after injection of nembutal, 10 mg/kg; C) 20 mg/kg. Magnification in C twice that of A and B. Time calibration 10 msec; amplitude calibration 0.2 mV. 1, 2, 3) Successive increase in interval between stimuli.

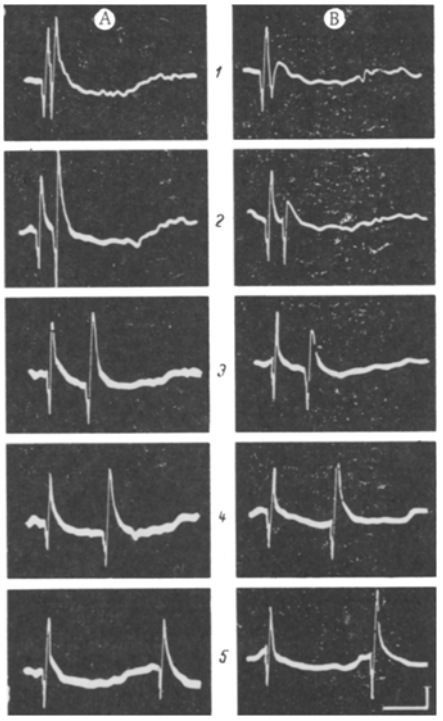

Fig. 2. Effect of nembutal on phenomenon of strengthening of test response. A) Unanesthetized animal; B) after injection of 20 mg/kg nembutal. Time calibration 50 msec; amplitude calibration 0.2 mV. 1, 2, 3, 4, 5) Successive increase in interval between stimuli.

ment of the positive part of the positive-negative wave. These waves reflect the discharge of a particular group of cortical neurons of which direct projection fibers from SI terminate.

In the recovery cycle during application of paired stimuli to the cortex, in the period of development of the facilitatory response the positive-negative wave of the test response was blocked, but the high-frequency waves persisted (Fig. 1A, 1). With intervals of 30-40 msec the amplitude of the slow components of the test response not only was completely restored, but it actually exceeded the amplitude of the first response slightly. The phenomenon of strengthening of the test response was observed up to intervals of about 100 msec between stimuli. The increase reached a maximum when the intervals were 30-50 msec in duration (Fig. 2A).

After intravenous injection of nembutal into the animal in doses of 5-10 mg/kg, the late wave of the interzonal response was inconstant in its appearance, and was appreciably reduced in amplitude or even completely blocked (Fig. 1B). The amplitude of the positive-negative wave was practically unchanged by these doses of nembutal. Only the first two waves were preserved in the test response in the period of development of the facilitatory response, and the third wave did not recover until an interval of 20 msec, and the fourth when the interval was about 30 msec (Fig. 1A, 2, 3). With about the same length of interval, the amplitude of the positive wave of the slow component of this response recovered, but complete recovery of the test response was not observed with intervals less than 50-70 msec. This was followed by a phase of strengthening of the test response, although not to the same degree as in the unanesthetized animal.

Following injection of nembutal in doses of 20-40 mg/kg, the amplitude of the primary component of the

interzonal response was considerably reduced (Fig. 1C), and the number of fast waves was usually reduced to three. The third wave of the test response did not appear before 40-60 msec. The amplitude of the test response to injection of nembutal in doses greater than 20 mg/kg did not recover completely in under 100 msec, although the phenomenon of increased amplitude, exhibited with intervals of 120-240 msec between stimuli, could still be retained. With doses of nembutal exceeding 30 mg/kg, the phenomenon of strengthening of the test response was not observed.

It can be concluded from these results that injection of nembutal, even in subnarcotic doses (5-10 mg/kg), causes blocking of the late high-frequency waves accompanying the development of the positive wave of the interzonal response. Since these waves are produced by discharges of a homogeneous group of neurons, highly synchronized in frequency, on which direct intracortical interzonal connections terminate, there is reason to suppose that their blocking is associated with an increase in the postsynaptic inhibitory potential arising immediately after the discharge in the cortical pyramidal neurons [4, 5]. Further supporting evidence is given by the preservation of high-frequency waves in the test response in the unanesthetized animals with short intervals between stimuli, and their blocking after administration of barbiturates.

It is interesting to note that nembutal has a similar action on relay neurons of the thalamic nucleus relaying to the somatosensory cortex. This may point indirectly to a definite similarity in physiological properties between cortical neurons receiving direct projections from other structures and relay neurons of nuclei of the sensory tracts. If this approach is used, cells of this type can be regarded as the cortical component of the relay pathway from which excitation irradiates throughout the systems of intracortical connections.

Nembutal also produced definite changes in the character of manifestation of the increase in interzonal test response. The increase in amplitude of the test response has been thoroughly investigated in the case of responses of the projection cortex produced by stimulation of thalamic relay nuclei [5, 9]. The increase in amplitude of the test response is associated with an increase in amplitude of secondary excitatory postsynaptic potentials. The marked similarity in configuration of the interzonal and thalamo-cortical responses and also the similarity in character of changes in these biochemical responses following administration of barbiturates [12], indicate that the same mechanisms lie at the basis of their generation. It can be postulated that strengthening of the inhibitory phase after administration of nembutal prolongs the period of recovery of excitability of the neuron systems generating secondary excitatory postsynaptic potentials on pyramidal neurons of the projection cortex.

By its direct effect on activity of the cortical neurons, nembutal, even in subnarcotic doses, thus increases the phase of inhibition after stimulation and considerably prolongs the period of recovery of their excitability.

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