Electrophysiological and Neuropharmacological Analysis of Interaction between the Systems of Excitation and Inhibition in the Cerebral Cortex

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GABA- and cholinergic substances selectively affect different phases of the restoration cycle of primary somatosensory response in albino rats. The GABA antagonist bicuculline reduced and the deactivation inhibitor valproic acid enhanced depression of the test response when stimulated at pulse intervals of 60-125 msec. The cholinomimetic arecoline enhanced and the cholinolytic amizylum diminished facilitation of test response at intervals of 150-200 msec. The data suggest a dynamic interaction as well as a competition between GABA- and cholinergic systems in processing the sensory input.

Key words: *GABA, acetylcholine, cerebral cortex, restoration cycles of primary somatosensory response*

The interaction between systems that determine the balance between excitation and inhibition is of particular importance, since its impairment leads to various functional disorders in the central nervous system. The inhibitory GABAergic and excitatory cholinergic systems play an important role in learning and memory processes as well as in the genesis of different pathological conditions [5,11-13]. Although the participation of subcortical structures in these processes has been extensively investigated [5,8,9,11], the role of cerebral cortex, specifically of its excitability, in the control of the central nervous system function remains firmly established. In order to evaluate the total excitability of various brain structures, the method of recording the evoked potential restoration cycles is used, which provides a description of the integral excitability of structures under study. Our objective was to study the interplay of inhibitory and excitatory processes in somatosensory cortex in the rat by recording the primary response restoration cycles and to assess the contribution of GABA and cholinergic systems to this regulation.

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MATERIALS AND METHODS

Acute experiments were carried out on male albino rats weighing 200-220 g. The surgery was performed under local and ether anesthesia, then the animals were paralyzed with dithylinum (3-5 mg/kg/h, i.v.) and artificially ventilated. Potentials were recorded from the surface of the exposed part of somatosensory cortex at the focus of the maximum primary response activation evoked by stimulation of the shin skin contralateral to the exposed hemisphere. Recording and averaging of evoked potentials, as well as stimulation were performed using a B.A.S.I.S. electrophysiological complex (O.T.E. Biomedica). The stimulation consisted of pulse pairs (25-30 V, 300 msec), with the intervals between them varying from 40 to 300 msec. After application of 32 pairs of stimuli at 5-sec intervals, the results were averaged. The primary response restoration cycles were plotted in a regular manner. The amplitudes of responses to both pulses were determined, and the

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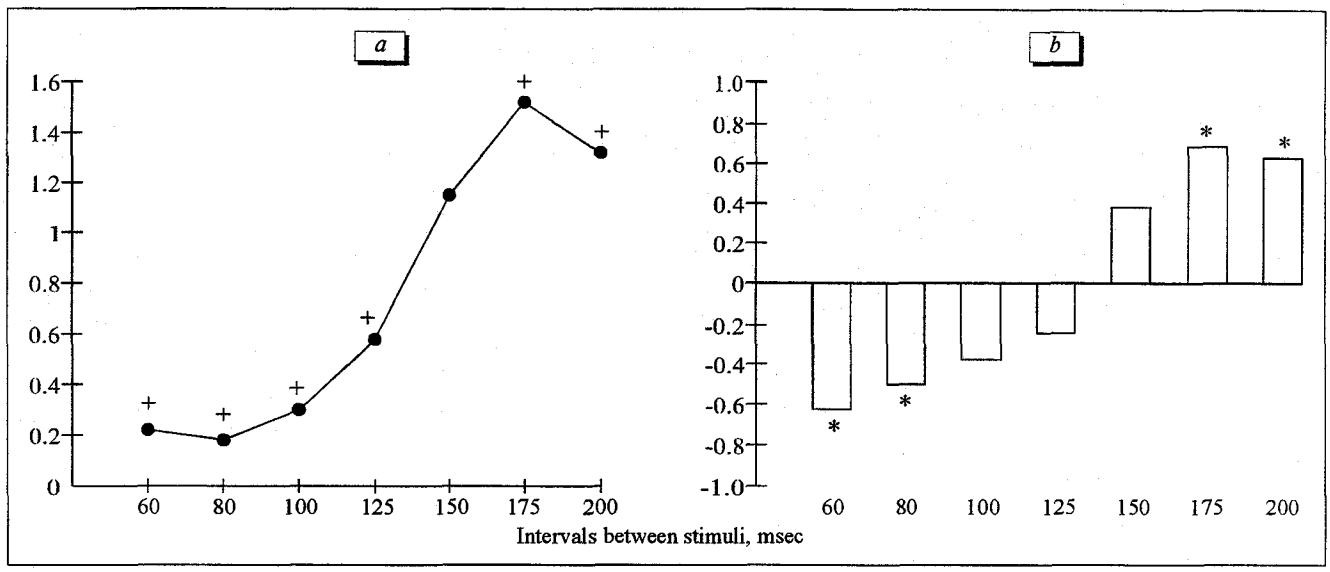

Fig. 1. Primary response restoration cycle in rat somatosensory cortex (*a*) and correlation coefficients for the relationship between amplitudes of test and conditional responses (*b*). Ordinate: *a*) the ratio of amplitude of test response to conditional response, arb. units; *b*) correlation coefficients; $p<0.05$: *statistically significant coefficients of correlation; +the ratios of test and conditional responses significantly different from 1.

ratio of the second (test) to the first (conditional) response was calculated for each pulse interval and then plotted against the interval.

The following substances were used: the GABA antagonist bicuculline ("Sigma"), the inhibitor of GABA biotransformation sodium valproate (convulex, "Huhtamake"), the cholinolytic amizylum, the cholinomimetic arecoline, and Nembutal. All the substances, except convulex, were preheated to 37°C and injected intravenously. Convulex was injected intraperitoneally via a special catheter.

RESULTS

The primary response restoration cycles have two phases: depression of the test response at pulse intervals in the range 60-125 msec and facilitation of the response at intervals in the range 150-250 msec. The boundary between the two phases was considered to be the point where the ratio of the amplitudes of the responses was equal to 1. As a rule, it corresponded to the pulse intervals laying in the range 100-125 msec, irrespective shifting toward greater or smaller values for a given experiment (Fig. 1). In some cases (about 15%), there was practically no facilitation at all. Similar structure of primary response restoration cycles is typical of the other cortex regions in other species [3,4]. In order to clear up the nature of the phases of primary response restoration cycles, the correlation analysis of the relationship between the magnitude of the second (test) and the first (conditional) response was performed for each interval between the pulses (Fig. 1). As follows from the data obtained, a negative correlation between the parameters took place if the test response was depressed (for pulse intervals of 60-125 msec), the correlation the stronger the deeper the depression. So, the greater was the conditional response, the smaller was the test one. An opposite situation was observed in case of facilitation of the test response (at intervals of 150-200 msec). The greater was the conditional response, the greater was the test

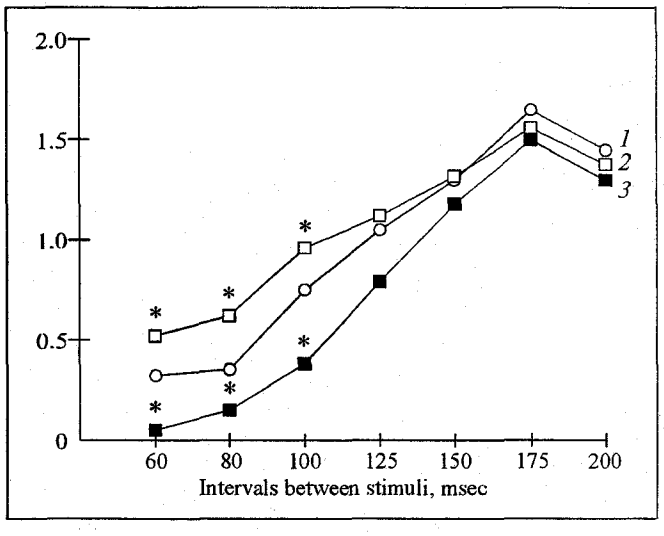

Fig. 2. Effects of bicuculline (0.1 mg/kg) and potassium valproate (300 mg/kg) on the primary response restoration cycle in rat somatosensory cortex. Control (*1*), changes induced by bicuculline (*2*) and valproate (*3*). Here and in Fig. 3: ordinate: the ratio of amplitude of test response to conditional one, arb. units. The results of one experiment are presented. Substances were injected at intervals of 90-120 min; *$p<0.05$, **$p<0.01$ compared with control.

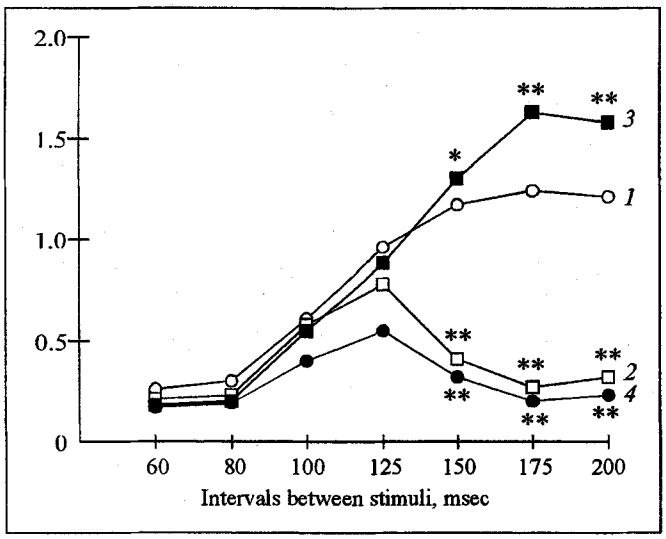

Fig. 3. Effects of amizylum (1 mg/kg), arecoline (1.5 mg/kg) and Nembutal (40 mg/kg) on the primary response restoration cycle in rat somatosensory cortex. Control (*1*), changes induced by amizylum (*2*), arecoline (*3*) and Nembutal (*4*).

one. This indicates that the magnitude of test response is strictly determined by the conditional one in both phases of the primary response restoration cycles.

Both GABA- and cholinergic substances selectively affected certain phases of the restoration cycle. GABAergic agents modified the depression phase of the test response. Thus, bicuculline injected in preconvulsive doses (0.05-0.1 mg/kg) reduced the depression of test response, while the GABA deactivation inhibitor potassium valproate (200-300 mg/kg) enhanced it (the changes in area measured between the corresponding curve and the abscissa on the plot were 42.7±10.4 and -29.3±6.1%, respectively; $p<0.05$, Fig. 2), the facilitation phase being slightly changed (-4.9±2.7 and -10.2±3.7%). In addition, mutual antagonism between these substances was revealed.

By contrast, cholinergic substances affected the facilitation phase of the test response. The cholinolytic amizylum (1 mg/kg) inverted, while the cholinomimetic arecoline (1.5 mg/kg) enhanced facilitation of test response (changes in the area for this phase were -84.7±15.4 and 51.5±9.3%, respectively; $p<0.01$). The depression of test response changed by -15.2± 5.4 and -9.6±4.7%, respectively (Fig. 3). In addition, the mutual antagonism between these substances was revealed. It is of interest that Nembutal (40 mg/kg, Fig. 3) produced similar effect as amizylum; however, its effect could not be abolished by arecoline.

The present data concerning the test response inhibition at pulse intervals in the range 60-125 msec as well as its facilitation at larger intervals (150-250 msec) point to systems in the cerebral cortex that control its excitability while processing the sensory input. The strong dependence of the test response amplitude on the conditional one, provided either depression or facilitation is essentially high, points to active recurrent interaction between the systems. Meanwhile, the lack of such a relationship during transition from depression to facilitation as well as the variability of the boundaries between these phases in different species and under different experimental conditions suggest a dynamic interaction and, probably, a competition between the inhibitory and excitatory systems. The fact that the depression phase of test response is affected predominantly by GABAergic agents implies that cortical recurrent inhibition is GABAergic in nature. This is consistent with the data obtained by different methods for other species and various cortex regions [6,7,14]. Test response facilitation in the primary response restoration cycles may be bound to activation of the thalamocortical system of recurrent excitation [4]. Our results and the data concerning the effect of amizylum on the visual cortex primary response restoration cycles in the rabbit [3] indicate that cholinergic structures are involved in its functioning. The fact that Nembutal produces a similar effect as amizylum, predominantly acting upon the reticular formation [1,2,10] implies that this structure is involved in the genesis of the test responses facilitation phase. The absence of this phase or its weak manifestation in the primary response restoration cycles in some animals points to changes in reticular influences on the cortex and the thalamus, which in turn may be revealed in their behavior.

From our results it can be concluded that the test response depression in the primary somatosensory cortex response restoration cycles is of GABAergic nature and the facilitation is of cholinergic nature. It can be suggested that a dynamic interaction, as well as competition, takes place between the GABA- and cholinergic systems of recurrent inhibition and excitation. The developed method of correlation and regression analysis of evoked potential restoration cycles may be useful in pharmacological or physiological research, particularly in humans.

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