EFFECT OF SUBSTANCES MODIFYING γ-AMINOBUTYRIC ACID METABOLISM ON RECOVERY CYCLES OF THE INTERZONAL RESPONSE OF THE CAT MOTOR CORTEX

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The effect of thiosemicarbazide (TSC), depakin and bicuculline on recovery cycles of the interzonal response of the motor cortex was investigated in unanesthetized, curarized cats. Substances modifying the metabolism of γ-aminobutyric acid (GABA) selectively influence the facilitation of this response (with intervals of 20-100 msec between stimuli). After injection of TSC, which lowers the GABA content in the brain, and of bicuculline, which specifically blocks GABA-ergic synapses, facilitation is increased, but after injection of depakin, which increases the GABA concentration, and after intraventricular injection of GABA facilitation is reduced. Caffeine and bemegride increase the amplitude of both conditioning and test responses but have no selective action on facilitation of the test response. Benactyzine and arecoline, substances exciting cholingergic structures, likewise had no selective effect on the recovery cycles. It is suggested that the facilitation described above is the result of interaction between systems of recurrent excitation and inhibition. GABA plays an important role in the regulation of this interaction.

KEY WORDS: γ-aminobutyric acid (GABA); interzonal cortical response; GABA-ergic brain structures; cholinergic brain structures.

Connections between the sensory and motor cortex [7, 10], along with thalamocortical connections, are essential for the performance of complex motor responses [16]. The neurochemical nature of the corresponding synaptic structures and, in particular, their sensitivity to γ-aminobutyric acid (GABA), can be conveniently studied by analysis of the recovery cycles of the interzonal cortical response. The use of GABA in such investigations is beset by a number of technical difficulties. A more promising approach is by the use of methods such as inhibiting activity of glutamic acid decarboxylase, causing a decrease in the GABA concentration, for example by thiosemicarbazide (TSC), inhibiting the activity of GABA transaminase, leading to its accumulation, for example by depakin [14] and, finally, blocking GABA-ergic receptors by their specific blocking agent bicuculline.

The object of this investigation was to study changes in the excitability of interzonal connections in the sensomotor cortex during changes in the concentration of endogenous GABA and blocking of GABA-ergic receptors.

EXPERIMENTAL METHOD

Experiments were carried out on cats weighing 2.5-3 kg. Under ether or halothane anesthesia, tracheotomy was carried out, cannulas were introduced into the femoral vein, and the skull was trephined. The anesthetic was then stopped, the animals were immobilized with gallamine (3-5 mg/kg), and artificial respiration applied; the experiment began 2.5-3 h later. The cortex was stimulated through bipolar silver ball electrodes applied in the region of the fossa lateralis (area S1 of the sensory cortex). Pairs of square

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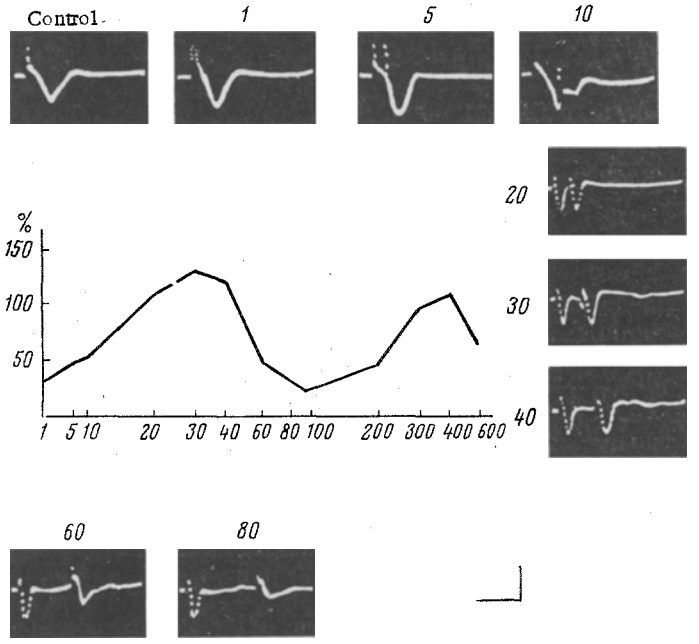

Fig. 1. Recovery cycle of interzonal response of cat motor cortex. Records for each interval up to 80 msec (indicated by numbers) shown alongside graph. Calibration: amplitude 600 μV; time: for top row of records 20 msec, for the rest 60 msec. Abscissa, intervals between conditioning and test stimuli on logarithmic scale; ordinate, ratio between amplitude of test response and amplitude of conditioning response (in %).

dc pulses (100 msec, 14-18 V) were led to the electrodes from the output of a two-channel "Physiovar" stimulator through radiofrequency attachments. The following intervals between conditioning and test stimuli were used: 1, 5, 10, 20, 30, 40, 60, 80, 100, 200, 300, 400, 600, and 800 msec. The silver ball recording electrode was located on the lateral border of the precruciate gyrus and the Ag–AgCl wick reference electrode was applied to the bones of the frontal sinus. The potentials were amplified by an "Alvar" XVI TR electroencephalograph, from which they were led to a type S 1-19B oscilloscope (for visual monitoring) and to a "Neiron-1" instrument. For further processing the total amplitude of the responses (from the maximum of the positive wave to the maximum of the negative) was measured and the ratio between the amplitudes of the test and conditioning responses calculated for the interval.

Solutions of the substances were prepared immediately before injection: the depakin was injected intraperitoneally (in the course of 5-10 min to avoid hemodynamic effects) and the other substances intravenously.

EXPERIMENTAL RESULTS AND DISCUSSION

Normally the following components could be distinguished in the recovery cycle of the interzonal response of the motor cortex: a phase of early depression of the test response (with intervals of 1-10 msec between conditioning and test stimuli); next, an increase in amplitude (facilitation) of the test response (intervals of 20-100 msec) usually reaching a maximum with an interval of 40 msec, but not observed in all animals; finally, phases of late depression and late facilitation of the test response, less marked than the corresponding early phases (Fig. 1). Restoration of the amplitude of the test response was observed after 800-1000 msec. These results agreed with those of analysis of the recovery cycle of the interzonal response arising in area S1 during stimulation of S2 [1]. No changes were observed in the cycle when it was recorded for several hours.

TSC in subconvulsive doses (5-10 mg/kg) increased the amplitude of both responses; however, the amplitude of the test response (for intervals of 20-100 msec between stimuli) was increased considerably more (Fig. 2, I). The effect of TSC began to appear 80-90 min after its injection, it reached a maximum after 110-120 min, and was maintained for 2-3 h, in conformity with the dynamics of the behavioral effect of this substance [3].

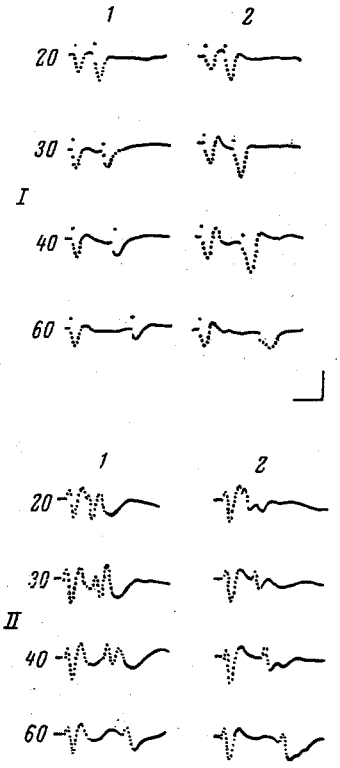

Fig. 2. Effect of thiosemicarbazide, 5 mg/kg (I) and depakin, 300 mg/kg (II), on recovery cycle of interzonal response of motor cortex: 1) control, 2) maximal effect (120 min for TSC, 30 min for depakin). Numbers on left of records denote intervals between stimuli (in msec). Calibration: amplitude 500 μV, time 30 msec.

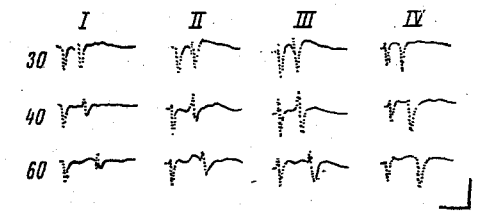

Fig. 3. Effect of caffeine, bemegride, and bicuculline on recovery cycle of cortical interzonal response: I) control; II) caffeine, 40 mg/kg, 10 min after injection; III) bemegride, 2 mg/kg, 10 min after injection; IV) bicuculline, 0.05 mg/kg, 15 min after injection; 30, 40, 50) intervals between stimuli (in msec). Calibration: amplitude 600 μV, time 60 msec.

Bicuculline, in subconvulsive doses (0.07-0.15 mg/kg), also increased the amplitude of both responses, but in this case also the amplitude of the test response changed more (Fig. 3, IV). The effect of bicuculline developed in the course of 1-5 min. After injection of this substance in doses evoking seizure discharges on the EEG, the increased facilitation of the test response remained even after their disappearance.

Since both TSC and bicuculline had an activating action in small doses, but a convulsant action in large doses, the next step was to compare them with other substances with excitatory and convulsive action. By contrast with bicuculline and TSC, caffeine (20-40 mg) and bemegride (0.5-2 mg/kg), although they increase the amplitude of both responses, did not induce a selective increase in the test response (Fig. 3, II, III).

The action of depakin on the recovery cycle was opposite to that of TSC and bicuculline, but also relatively selective. In a dose of 200-300 mg/kg and with intervals of 20-100 msec between stimuli it reduced the amplitude of the test response (Fig. 2, II) or suppressed it completely (especially in intervals of 20-40 msec). In some experiments the amplitude of the conditioning response increased. The effect began to appear 20 min after the injection, it reached a maximum after 30-40 min, and it was maintained for 1-1.5 h, in agreement with the dynamics of GABA accumulation under the influence of depakin [14]. Selective inhibition of the test response also was observed after injection of GABA (20 mg) into the lateral ventricle.

Acetylcholine exerts an excitatory effect on cortical neurons and it was thus important to compare these results with the effects of a cholinolytic (benactyzine) and a cholinomimetic (arecoline). Their effects differed essentially from those of substances controlling GABA metabolism. Arecoline (0.3 mg/kg) caused activation of the EEG, against the background of which equal weakening of both responses was observed ("occlusion"). Benactyzine (1 mg/kg) caused synchronization of the EEG without altering the recovery cycle of the interzonal response, but if injected after arecoline it abolished the "occlusion" effect and returned both responses to their original amplitude.

An increase in amplitude of the test response in the recovery cycle of the primary response of the visual cortex has been shown to be accompanied by increased unit activity [6, 12, 13]. This may be determined by the activity of the recurrent excitation system [2]. The presence of such a system has also been accepted in the sensomotor cortex [5]. On the other hand, the presence of a system for recurrent inhibition, the mediator of which is GABA [8, 9, 11], has also been established in the cortex [4, 15]. This system evidently controls the work of the excitatory neurons. By lowering the GABA concentration or blocking its receptors, it may evidently lead to predominance of the activity of the excitatory system, whereas by increasing the GABA concentration it leads to functional predominance of the inhibitory system.

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