EFFECT OF THIOPENTAL SODIUM ON RELATIONSHIP BETWEEN CHANGES IN THE ELECTROCORTICOGRAM AND SOME CORTICAL EVOKED RESPONSES

R. U. Ostrovskaya

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Intravenous injection of thiopental sodium in acute experiments on curarized rabbits caused changes in the spontaneous electrocorticogram together with correlated changes in transcallosal and, to a lesser degree, direct cortical responses. The changes in responses could be reproduced by intracarotid injection of the drug. In this case they developed only on the side of injection of the substance, as was demonstrated particularly clearly in experiments with bilateral recording of the responses. The results confirm that thiopental sodium has a direct cortical effect.

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Different opinions are held on the effect of barbiturates on cortical electrical activity. Most investigators consider that the cortex is less sensitive to barbiturates than the reticular formation and that all changes in cortical activity are secondary, caused by blocking of brain stem structures [8, 16]. Other workers, still few in number, claim that the cortex is just as highly sensitive to barbiturates as in the reticular formation [1, 14, 17].

Since transcallosal and direct cortical responses are potentials evoked by cortical stimulation and, at the same time, are recorded in the cortex, it appeared useful to study the effects of thiopental sodium on them and also to compare the degree of changes in these responses with each other and also with the changes in the spontaneous electroencephalogram (EEG) characteristic of barbiturates [5, 15]. Attention was directed in particular to the demonstration of a possible primary cortical effect of thiopental sodium.

EXPERIMENTAL METHOD

Details of the method were described previously [2]. Experiments were carried out on rabbits on which tracheotomy and craniotomy were performed under ether anesthesia, after which the animals were immobilized with flaxedil (remyolan) and transferred to artificial respiration. Three hours later, when the normal electrocorticogram (ECoG) was restored, recording of the potentials began. The transcallosal response (TCR) — the potential generated in the cortex during stimulation of the symmetrical point of the opposite hemisphere — and the dendritic or direct cortical response (DCR) — the potential recorded from the cortical surface alongside the stimulating electrode — were recorded in all cases, whether in different experiments or in the same experiment, simultaneously with the ECoG. The stimulation used was 1.3-1.4 times stronger than threshold for each response. Thiopental sodium was injected intravenously as a 2 % solution at the rate of 30 mg/kg body weight/min in a dose of 35 and 40 mg/kg.

EXPERIMENTAL RESULTS AND DISCUSSION

The chief characteristics of the TCR and DCR, as described previously [2], agreed with those reported in the literature [3, 4, 6, 7, 9, 13]. Thiopental sodium caused changes in these responses which showed a marked dependence on changes in the spontaneous EEG, which also were phasic in character. Since these phases followed each other very rapidly, in the course of 1-2 min during deepening of the anesthesia, it was more convenient to study them as the depth of anesthesia grew less, over a period lasting from 1 to 3 h. Deep inhibition of electrogenesis developed 10-20 sec after the end of the injection — from total absence of oscillations on the EEG to the appearance of sharp low-amplitude bursts of up to 10-15 μV

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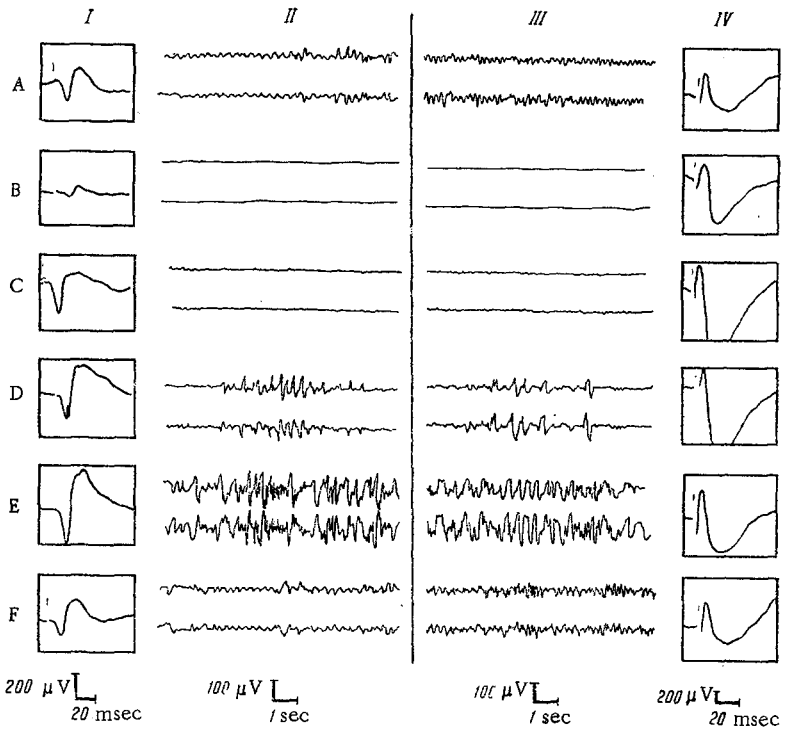

Fig. 1. On the left: comparison of phases of change in transcallosal response (I) and spontaneous ECoG (II). On the right: the same for the direct cortical response (IV) and ECoG (III). ECoG from top to bottom: right parietal, left parietal regions of cortex. A) before injection; B) 2.5 min, C) 7 min, D) 13 min, E) 40 min, F) 150 min after injection of thiopental sodium (40 mg/kg, intravenously).

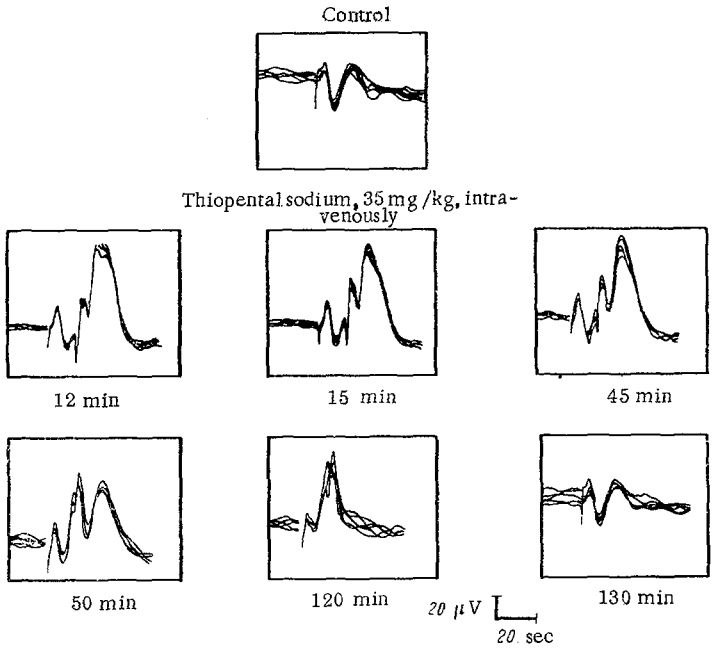

Fig. 2. Effect of thiopental sodium on transcallosal response evoked by fast supramaximal stimulation ("reduplication" of response).

against this background. After an interval of 3-4 min if the dose of thiopental sodium was 35 mg/kg, or 8-10 min if it was 40 mg/kg, the number of these oscillations began to increase, and separate bursts of

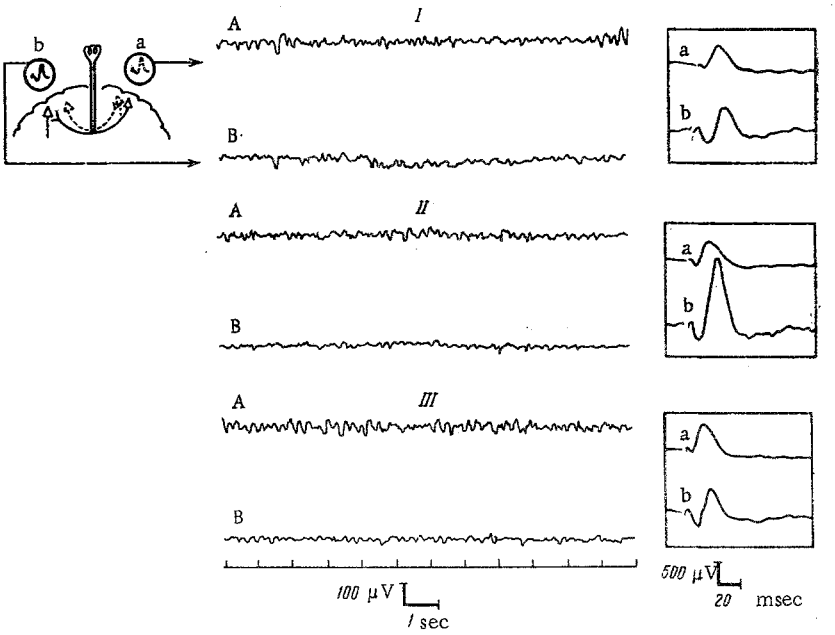

Fig. 3. Effects of intracarotid injection of thiopental sodium on transcallosal responses evoked by stimulation of the corpus callosum. On the left: diagram showing position of stimulating and recording electrodes. A) ECoG; a) TCR recorded from right parietal region. B) ECoG; b) TCR recorded from left parietal region. I) Before injection; II and III) 4 and 23 min after injection of 5 mg thiopental sodium into left internal carotid artery (0.3 ml during 30 sec).

high-amplitude pointed waves began to appear between them; and this was followed by the establishment of a stable, slow, high-amplitude activity. This period of synchronization was usually followed by a phase of fast, desynchronized rhythms. The time taken for restoration of the original ECoG varied from 50 to 100 min when the dose of thiopental sodium was 35 mg/kg, and from 90 to 180 min when it was 40 mg/kg. The period of maximal depth of depression corresponded to a gradual decrease in amplitude of the responses. Total suppression of the responses developed if no oscillations were present on the EEG for 3-4 min. In the process of deepening of depression, the TCR appeared 30-60 sec sooner than the DCR (Fig. 1B). The positive component of the DCR disappeared first, followed by the negative. When separate low-amplitude oscillations appeared on the EEG against the background of "zones of silence" the responses began to increase (Fig. 1C) and they remained increased in the phase of synchronization (Fig. 1E). However, the dynamics of changes in the TCR and DCR showed differences in this period also. Both components of the TCR (Fig. 1, I, D, E) were considerably increased in amplitude (to 200-300 % of their initial level) and duration (up to 140-200 %). The degree of these changes was to some extent parallel with the degree of EEG synchronization. In some experiments, especially when fast, strong stimulation was used, the shape of the components of the TCR was changed, and they became reduplicated through the appearance of supplementary waves (Fig. 2). As regards the DCR, only the amplitude and duration of the positive component underwent significant changes; they usually increased by at least 2-3 times (Fig. 1, I, IV, C, D). Conversely, the negative component of the DCR did not exhibit such marked changes (Fig. 1, IV, E); its amplitude usually increased to 140-150 %, and only occasionally to 200 %, while its duration and shape remained unchanged. Whereas the degree of changes in the TCR correlated with the degree of EEG synchronization, no such correlation was present in the case of the DCR.

The fact that the negative component of the DCR disappeared after the rest in the period of deep depression, and also increased by a smaller degree in the period of synchronization suggests that is relatively less sensitive to barbiturates than both components of the TCR and the late, positive component of the DCR. Similar relationships were discovered previously when sodium hydroxybutyrate was studied [2], with the difference that under the influence of the latter substance the depth of EEG depression did not reach a maximum accompanied by depression of all responses. No data are available which could be used to compare the sensitivity of these responses to other substances. It will be noted that the relative stabil-

ity of the negative component of the DCR is also manifested in anoxia. In Chang's [7] experiments, it disappeared during inhalation of pure nitrogen later than the positive component of this same response. By using simultaneous recording of the TCR and DCR and studying the dynamics of their changes after blocking respiration (experiments on curarized rabbits), we found that suppression of the negative component of the DCR developed 30-60 sec later than that of the TCR. The reasons for these differences is not clear. It may be supposed that they are connected with differences in the synaptic organization of these responses. The negative component of the DCR reflects a monosynaptic process [4]; the transcallosal response, even if it is monosynaptic [12],* it is in any event associated with conduction along longer pathways, as reflected by its much greater latent period. This may perhaps determine the differences in sensitivity of the various responses to pharmacological intervention. In particular, microelectrode investigations have shown that cortical neurons responding to peripheral stimulation with a shorter latent period are less sensitive to barbiturates than neurons with a long latent period [17]. The fact that responses were preserved at the beginning of deep depression of the EEG may perhaps be explained on the assumption that during blocking of the synapses on the cell body produced by barbiturates, synapses on dendrite endings preserve or actually increase their activity [10], and the depression extends to the dendrites only when it becomes deeper.

The positive and negative components of the TCR reflect transmission of excitation from the callosal fibers to cell bodies in the deep layers and to dendrites of the surface layer respectively; the negative component of the DCR arises through transsynaptic excitation of apical dendrites of the pyramidal cells, terminating in the first layer of the cortex, while its positive component reflects secondary excitation of the deep layers [3]. It may be postulated that the changes described in the TCR and DCR reflect changes in conduction at these levels. However, the possibility is not ruled out that they are not the result of a direct action on cortical transmission, but the result of removal of afferent influences of the brain stem, since barbiturates block the reticular formation. To solve this problem, experiments were carried out in which thiopental sodium was injected into the internal carotid artery. In this way the effect of the drug on the caudal portions of the brain stem, supplied by the vertebral artery, was excluded. The transcallosal response was investigated because its changes following systemic injection of the drug were correlated with the degree of EEG synchronization and were more marked. In these experiments transcallosal responses were evoked not by stimulation of the cortex, but by stimulation of the corpus callosum, and responses appeared in both hemispheres. Thiopental sodium, when injected by the intracarotid route, caused changes in the responses (an increase in amplitude and duration in a dose of 5 mg, suppression in a dose of 10-15 mg, only on the side ipsilateral to injection, the response on the opposite side remaining similar to the control (Fig. 3). The unilateral nature of these changes, and a control investigation with methylene blue showed that, provided the velocity and volume of injection were kept at a certain level (0.3 ml in 30 sec), the substance did not enter other vessels forming the circle of Willis, i.e., they could not act on the caudal structures of the reticular formation. So far as its rostral portions are concerned, the substance could enter them when injected into the internal carotid artery. However, we do not consider that this could be the cause of the observed changes in the TCR. It is known that synchronization of the EEG is characteristic of blocking of the rostral portions of the reticular formation by barbiturates [11]. In the present experiments thiopental sodium, when injected into the internal carotid artery, caused EEG synchronization, but it was very short in duration and in some experiments it was in fact absent, yet nevertheless the increase in TCR developed in this case also (Fig. 3). The results described above suggest that changes in the TCR produced by thiopental sodium are observed under conditions excluding any effect via the reticular formation, and this must indicate that they are of a primary cortical character.

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*Some workers are doubtful about this, suggesting that production of the TCR involves additional relays between the deep and superficial layers of the cortex.

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