EFFECT OF SOME DEPRIMING SUBSTANCES ON EVOKED REFLEX PYRAMIDAL RESPONSES

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In acute experiments on 30 cats the effect of narcotics (thiopental sodium, sodium hydroxybutyrate), stimulants (bemegride, caffeine), and tranquilizers (chlorpromazine, trifluoperazine) on evoked reflex pyramidal responses was investigated. The tested narcotics suppressed this response and, of the whole reflex arc involved in its realization, the intracortical connections relaying between the sensory and motor areas of the cortex were most sensitive to narcotics. The ability of stimulants to abolish this effect was discovered. Tranquilizers do not suppress reflex pyramidal or intracortical responses.

The response arising in the bulbar pyramids during peripheral stimulation can be regarded as an electrophysiological equivalent of complex reflex responses to a flow of afferent impulses in the cortex [16].

Changes in the reflex pyramidal response have been studied during the action of certain narcotics (thiopental sodium and sodium hydroxybutyrate) their antagonists (bemegride and caffeine), and tranquilizers (trifluoperazine and chlorpromazine). To analyze the results, the effect of these substances was also studied on the primary cortical response to afferent stimulation and on the intracortical response of the motor cortex to stimulation of the somatosensory area.

EXPERIMENTAL METHOD

Acute experiments were carried out on 30 adult cats. Because of the difficulty of obtaining a pyramidal response in unanesthetized animals [10], chloralose was used, but in small doses (25-30 mg/kg, intraperitoneally). In experiments in which the anesthesia was insufficiently deep, at the most traumatic moments of the operation, ether was given additionally. Access to the bulbar pyramids was obtained from the ventral aspect, through the basilar bone. At the end of the operation the cat was immobilized with flaxedil and artificial respiration applied. Responses to bipolar electrical stimulation of the contralateral forelimb were recorded with monopolar electrodes located on the bulbar pyramids 1-2 mm caudally to the pons. In cases when an antidromic pyramidal response had to be obtained to verify the state of the efferent part of the investigated reflex arc, the same area of the pyramids was stimulated by a bipolar technique; the response arising in the motor cortex was recorded. To record primary cortical responses a monopolar electrode was applied to the cortex in the region of representation of cutaneous sensation of the forelimb in area S-I (Fig. 1, scheme). To obtain the intracortical response, bipolar stimulating electrodes were applied to the surface of the cortex in area S-I, and the monopolar recording electrode in the motor cortex. Square pulses, 0.1-0.12 msec in duration and 1.3-1.5 times above the threshold voltage, generated by a Neurovar stimulator, were used. In some experiments parallel ink recording were made of the spontaneous EEG.

EXPERIMENTAL RESULTS AND DISCUSSION

The reflex pyramidal response consisted of a positive-negative wave, the amplitude of its positive component varying from 50 to 250 μV, and that of its negative component from 50 to 150 μV. The latent period of the response was 22-30 msec, the duration of the positive wave 12-20 msec, and that of the negative

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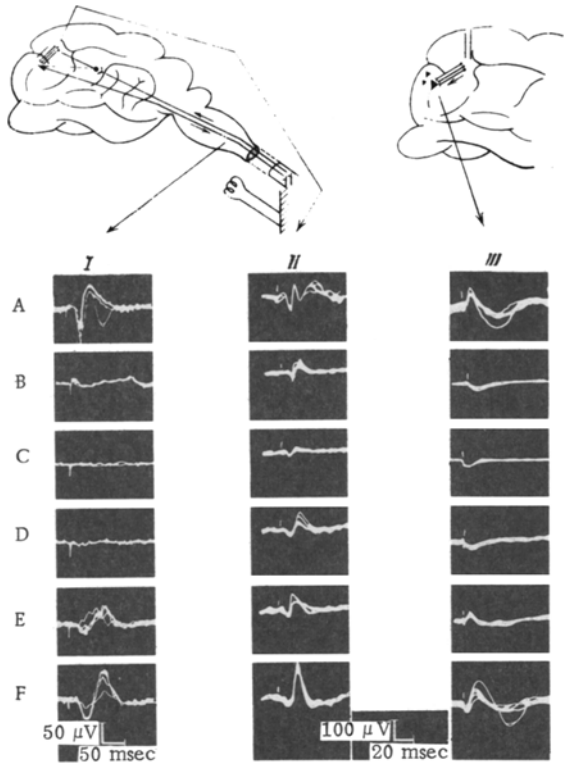

Fig. 1. Comparative action of thiopental sodium and bemegride on reflex pyramidal response (I), response of somatosensory cortex (II), and intracortical response (III). A) Before administration of drugs; B) 3 min after intravenous injection of sodium thiopental, 10 mg/kg; C) 3 min after additional injection of thiopental sodium, 20 mg/kg; D) 6 min after intravenous injection of bemegride, 10 mg/kg; E) 10 min after same injection; F) 3 min after additional injection of bemegride, 10 mg/kg. Above – schemes showing location of stimulating and recording electrodes: on the left, for recording reflex pyramidal response and specific response in somatomsensory cortex; on the right, for intracortical response.

wave from 20-40 msec. This response was diminished 1-2 min after injection of thiopental sodium (starting with a dose of 10 mg/kg), and after 3 min it was completely suppressed (Fig. 1). Recovery of the response took place after 30 min, and in some experiments this was preceded by a transient increase in amplitude over the initial level. Similar results were obtained also by administration of sodium hydroxybutyrate, starting with a dose of 200 mg/kg (Fig. 2, III).

Comparison of the dynamics of changes in the reflex pyramidal response with the primary response in area S-I showed that the primary response was affected to a lesser degree by both narcotics: in doses causing complete suppression of the reflex pyramidal response, thiopental sodium and sodium hydroxybutyrate merely diminished the amplitude of the primary response (Fig. 1B). Its suppression required a further injection of sodium thiopental (Fig. 1C) or sodium hydroxybutyrate. In an attempt to weaken the depression of the responses by means of analeptics, earlier restoration of the primary response was obtained. For instance, to abolish the effect of thiopental sodium on the pyramidal response, larger doses of bemegride were necessary than to restore the primary response (Fig. 1, D-F). The same results were obtained in the case of abolition of depression produced by sodium hydroxybutyrate by means of caffeine.

The reflex pyramidal response recorded from axons of the first descending cortical neuron is known to be the result of spread of the impulse along a complex path whose afferent part passes from the receptor through the spinal cord or medulla to the thalamus, and then to the area of cortical representation; the efferent part consists of the pyramidal tract, commencing in the motor cortex [7, 9, 13]. This reflex arc can be closed through direct connections between the thalamus and motor cortex [14] and through intracortical connections. The presence of cortico-cortical connections between the sensory and motor areas of the cortex, performing associative functions [1, 4, 8], have been demonstrated anatomically, and fibers of cortical layers III-IV have been shown to be responsible [11, 12, 15]. Sencer [17] and Narikashvili et al. [3, 4] discovered these connections by electrophysiological methods.

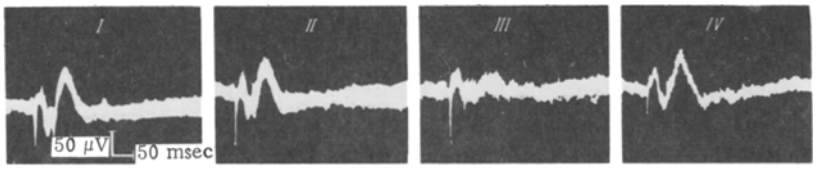

Fig. 2. Changes in reflex pyramidal response under the influence of sodium hydroxybutyrate and caffeine. I) Control; II) 15 min after intravenous injection of sodium hydroxybutyrate in dose of 50 mg/kg; III) 15 min after intravenous injection of sodium hydroxybutyrate, 200 mg/kg; IV) 10 min after intravenous injection of caffeine in dose of 12 mg/kg.

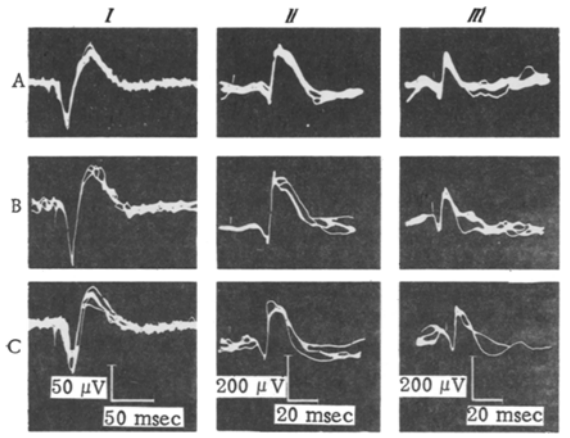

Fig. 3. Effect of trifluoperazine on reflex pyramidal (I), primary (II), and intracortical (III) responses. A) Before injection of drugs; B) 30 min, and C) 60 min after intravenous injection of trifluoperazine, 5 mg/kg.

Remembering the earlier inhibition of the reflex pyramidal response compared with the primary response, and also the fact that the antidromic pyramidal response was not suppressed at that moment, it was postulated that this effect could be due to the predominant influence of these drugs on pathways of transmission of impulses between the sensory and motor areas of the cortex. To clarify this position, experiments were carried out to study the evoked intracortical response arising in the motor cortex during stimulation of somatosensory area I. This response was characterized by a latent period of 2-4 msec and a duration of 20-30 msec. It was formed of a positive-negative wave (the amplitude of the positive wave varied). If the sweep of scanning was increased, 3 or 4 spike-like waves were observed on the positive wave, similar to those found by Rabin [6] when studying responses arising in area S-II during stimulation of area S-I.

The present experiments showed that sodium thiopental, in a dose of 10-15 mg/kg, depressed the intracortical response, and did so to a greater degree than the primary response, while bemegride abolished depression of the intracortical response later than that of the primary (Fig. 1). Similar results were obtained after injection of sodium hydroxybutyrate and subsequent abolition of depression of the responses with caffeine. It is important to emphasize that the intracortical response differed from the direct cortical ("dendritic") response: as parallel recordings of both responses showed, it occurred in response to stronger stimulation, it had a longer latent period (that of the direct cortical response was less than 1 msec), and, as already mentioned, spikes were present on the positive wave of the intracortical response. The intracortical response differed from the "dendritic" also in its sensitivity to narcotics: depression of the "dendritic" response was observed after injection of thiopental sodium in doses twice or three times higher than the doses required to suppress the intracortical response. After blocking of respiration, the intracortical response disappeared sooner than the "dendritic" and the first of these was suppressed before the spontaneous EEG-activity disappeared, while the second was suppressed only after complete disappearance of the spontaneous activity. The dendritic response is considered to be monosynaptic, while the intracortical response is evidently conducted through additional synapses.

So far as the tranquilizers trifluoperazine and chlorpromazine are concerned, these substances, in the dose range studied (3-7 mg/kg), depressed neither reflex pyramidal nor primary nor intracortical responses (Fig. 3). The only exceptions were individual tests in which chlorpromazine, when injected rapidly, produced a temporary (5-6 min) decrease in amplitude of the responses, associated with lowering of the arterial pressure.

The results of these experiments suggest that intracortical relay mechanisms are highly sensitive to thiopental sodium and to sodium hydroxybutyrate, and that the observed changes in the reflex pyramidal response are largely due to their effect on these structures. Conversely, the investigated tranquilizers do not depress synaptic transmission from the sensory cortex to the motor area and do not inhibit the reflex pyramidal response.

As the writers have shown previously, another evoked response, formed entirely in the cortex (the transcallosal), is also sensitive to narcotics [2, 5]. Differences in the direction of the changes – an increase in amplitude of the transcallosal response and depression of the pyramidal response – are evidently due to the fact that the first was recorded in curarized animals and the second in animals anesthetized with chloralose. In one case the bioelectrical activity was normal in the original state, while in the other there was a definite degree of depression (after chloralose in a dose of 25-30 mg/kg, when, judging from the EEG, the depth of depression was moderate). For this reason even small doses of barbiturates and sodium hydroxbutyrate, against the background of chloralose, do not increase the amplitude of the potentials, as is characteristic of a moderate depth of depression, but produce the characteristic inhibition of deep depression. This hypothesis was confirmed by experiments in which the transcallosal response was investigated in cats

anesthetized with chloralose; in these animals barbiturates and sodium hydroxybutyrate, in small doses, were found to inhibit the response. These findings confirm that the character of premedication for anesthesia can determine the direction of the effect of pharmacological agents on the brain biopotentials.

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