EFFECT OF SODIUM HYDROXYBUTYRATE ON TRANSCALLOSAL AND DENDRITIC POTENTIALS

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Because sodium hydroxybutyrate has a narcotic action and is used for anesthesia during surgical operations [7], its effect on the cerebral cortex is of great interest. Electrophysiological methods usually used to study this effect consist of recording the corticogram or the evoked potentials arising during stimulation of peripheral nerves. However, these methods reflect the state not only of the cortex, but also of subcortical structures.

One method of direct electrophysiological investigation of the cortex sometimes used is recording the transcallosal and dendritic potentials. It was therefore considered that this method was suitable for the study of the effect of sodium hydroxybutyrate.

EXPERIMENTAL METHOD

The effect of sodium hydroxybutyrate on transcallosal and dendritic potentials (responses) was investigated in 54 acute experiments on rabbits prepared by the method described by V. M. Vinogradova [1]. Tracheotomy was performed and the scalp and parietal bones were removed under ether anesthesia, after which the animal was immobilized with flaxedil (3 mg/kg intravenously) and maintained on artificial respiration. The dura was opened 2.5-3 h later, and electrodes applied to the surface of the cortex (Fig. 1). The cortex was stimulated with bipolar silver electrodes; the potentials were recorded by a monopolar technique, the indifferent electrode being fixed to the soft tissues of the head. Rectangular pulses, 0.08-0.1 msec in duration for the dendritic and 0.2-0.3 msec for the transcallosal response were generated by a "Neurovar" stimulator. The response was recorded photographically from the tube of a "San'esokki" 2-channel oscillograph, and the electrocorticogram and electrocardiogram on an "Alvar" electroencephalograph. Sodium hydroxybutyrate was injected intravenously in 20% solution in doses of between 300 and 1500 mg/kg. For application to the cortex a 1% solution (pH 7.2) at a temperature of 36° was used, more circles of filter paper 1 mm in diameter being soaked in it; these were applied to the surface of the cortex in the region of the recording electrodes.

EXPERIMENTAL RESULTS AND DISCUSSION

The transcallosal response (TCR) is a biphasic wave consisting of an initial positive deflection with a latent period of 5-6 msec and duration of up to 10-12 msec, followed by a negative wave 15-30 msec in duration. If stimuli of increasing magnitude are used (starting from subthreshold values), a negative wave appears first, and as the strength of the stimulus increases it is preceded by a positive, and with a further increase in strength of stimulation late positivity appears (up to 40 msec). With the experimental conditions used (treatment of wound surfaces with procaine, maintenance of a temperature of 35-36° in the room, application of warm mineral oil to the cortex) the evoked responses were stable despite the fact that, in contrast to the experiments of other investigators, the investigation was carried out on unanesthetized animals, remembering that substances of narcotic type have an action on the cortex.

Starting with a dose of 400-500 mg/kg, sodium hydroxybutyrate caused a marked increase in amplitude of the TCR; usually this applied to both its components. The degree of increase varied, but in most cases it amounted to 130-140% compared to the initial level for a dose of 500 mg/kg, 200-300% for a dose of 750 mg/kg, and 250-300% when the maximal dose used (1500 mg/kg) was given. The duration of both components increased by from 30-40 to 200%. In some experiments the shape of the response became more

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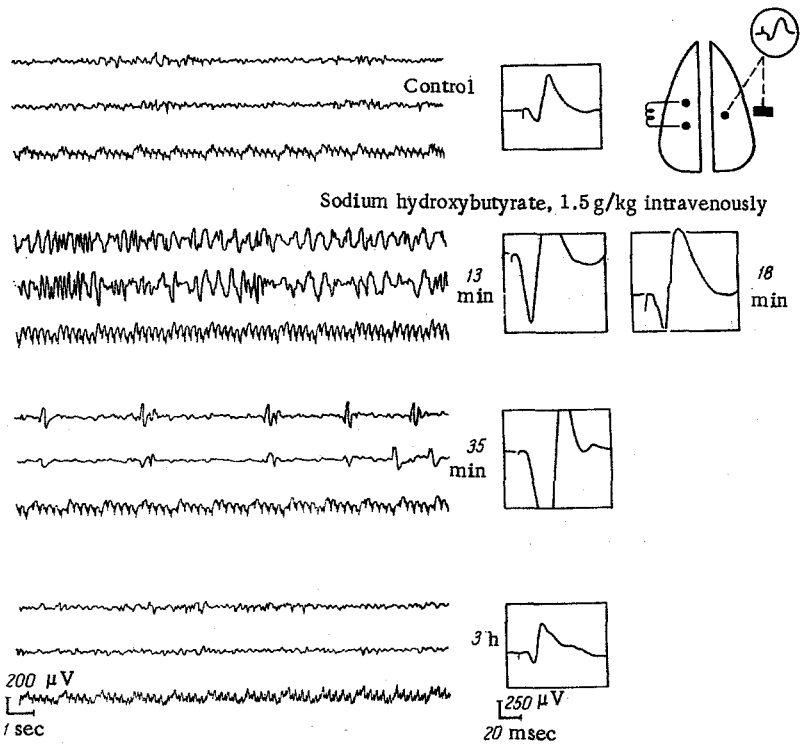

Fig. 1. Effect of sodium hydroxybutyrate on the spontaneous electrocorticogram and transcallosal response. Leads: EEG of sensorimotor and parietal regions of cortex, ECG. Stimulus 10 V, 0.3 msec. A diagram showing the position of the electrodes to obtain the TCR is shown above on the right; stimulating electrodes applied to the left parietal region, recording electrode to the right; the thick line represents the indifferent electrode.

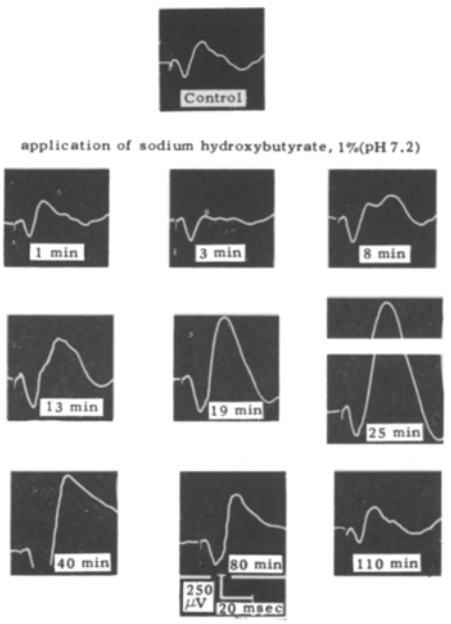

Fig. 2. Changes in transcallosal response after application of 1% solution of sodium hydroxybutyrate.

complex on account of the appearance of supplementary waves (most frequently negative), as the result of which the response appeared "split." It follows from the results of these experiments that sodium hydroxybutyrate, if injected intravenously, causes substantial changes in the TCR (Fig. 1).

Changes of a similar character in the TCR appeared after local application of a 1% solution of sodium hydroxybutyrate to the cortex: the amplitude of the response at the maximum of the action (25-40 min) amounted to 300-350% of the initial value, and the duration of both components of the TCR increased (Fig. 2). It should be mentioned that these changes did not develop immediately after application, but only 5-7 min later. Their appearance was preceded by a distinctive phase during which depression of the negative wave was observed, giving the response a distorted shape. When more concentrated solutions (2-5%) were applied, at first the negative, and later the positive wave was depressed. If this initial phase was excluded, the changes in the TCR under the influence of sodium hydroxybutyrate when applied to the cortex or given intravenously were unidirectional in character. This applied also to changes in the spontaneous electrocorticogram: the increase in amplitude and slowing of the dominant rhythm of the EEG previously found after injection of sodium hydroxybutyrate [8], and also obtained in the authors' experiments of a similar type, could also be reproduced when

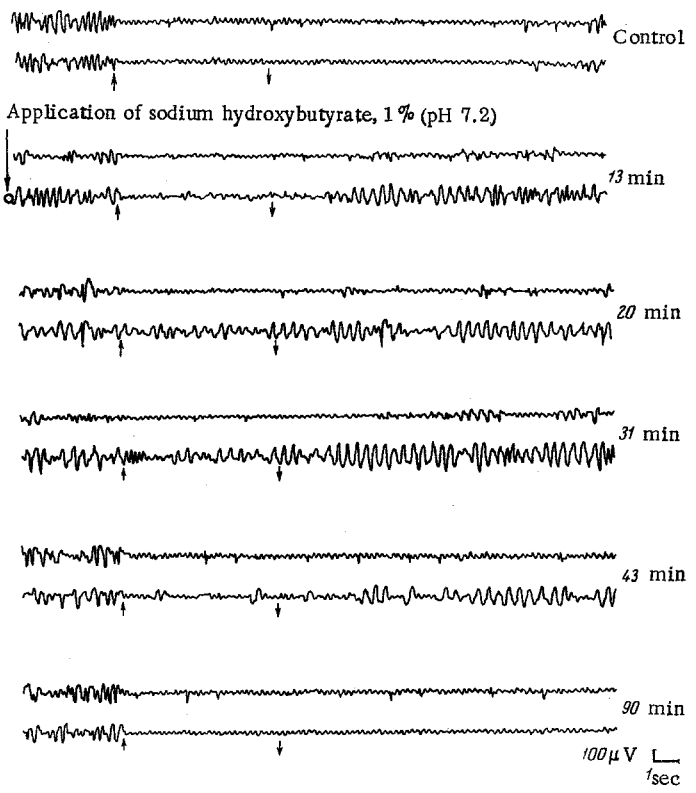

Fig. 3. Dynamics of arousal reaction following local application of hydroxybutyrate to the cortex. In each pair of curves the upper is recorded from a region not treated with sodium hydroxybutyrate, and the lower from an area to which the preparation has been applied. ↑)Beginning, ↓)end of action of acoustic stimulus evoking EEG-arousal reaction.

the compound was applied to the cortex. The marked and prolonged synchronization of the EEG was accompanied by blocking of the arousal reaction, following a definite pattern: the depth of the block increased until the 25th-30th minute, and the reaction was restored after 80-90 min (Fig. 3). In adjacent areas of the cortex not treated with sodium hydroxybutyrate, the background rhythm and arousal reaction persisted unchanged throughout.

The next series of experiments was carried out to study the action of sodium hydroxybutyrate on the dendritic response (DR), i.e., on the potentials arising around the electrodes stimulating the surface of the cortex. The DR recorded from the rabbit's cortex in response to a threshold stimulus consists of a negative wave up to 10-20 msec in duration if the strength of stimulation is increased considerably this is followed by a slow positive wave). If sodium hydroxybutyrate is injected, the amplitude of the principal negative component of the DR is slightly increased, but these changes do not reach the degree of the changes in the analogous component of the TCR, and this is seen particularly demonstratively if both responses are recorded in one experiment. Concurrently with the slowing and increase in amplitude of the rhythms of the spontaneous EEG, the amplitude of this response also increases. The changes in DR do not show this parallel trend and are less marked in degree: even in the case of very marked synchronization of the EEG, when the amplitude of the negative TCR is increased up to 2-3 times, the negative DR is not increased by more than 1.3-1.5 times. The changes in the positive component of the DR are somewhat more marked: they approximate to the changes in the TCR.

In individual experiments a further interesting aspect of the action of sodium hydroxybutyrate on the cortex was observed. Whereas paroxysmal discharges were produced by the frequently repeated stimulation of the cortex, subsequent application of 1% hydroxybutyrate to one side led to shortening of the convulsions on this side. If the convulsions arose repeatedly, they were confined to the side not treated with sodium hydroxybutyrate; as soon as the hydroxybutyrate was rinsed off the cortex, the convulsions arising on one side immediately spread to the other.

The TCR is produced entirely at the cortical level: the impulse arises on account of stimulation of the callosal neurons located mainly in layers III-IV of the cortex [5], and is transmitted along the axons of the corpus callosum—a structure containing no cell relays or collaterals. The callosal axon has a synaptic connection only at the symmetrical point of the opposite hemisphere. The distribution of the neurons in the layers of the cortex can be seen to correspond: axons leaving deep neurons terminate on the opposite side in the deep layers of the cortex, while axons of relatively superficial neurons have their endings in more superficial layers of the cortex [4, 6]. Both waves of the TCR are postsynaptic potentials, the positive arising in the deeper layers and the negative in the more superficial layers of the cortex.

Hence, the TCR as a whole reflects processes of synaptic transmission taking place entirely at the cortical level, in connection with which the ability of hydroxybutyrate to evoke changes in the TCR can be regarded as an indication of the cortical effect of this compound. The fact that a similar increase in TCR can be obtained by application of hydroxybutyrate to the cortex, which entirely rules out its action through subcortical structures, confirms their cortical character. The initial depression of the TCR is nonspecific in character, as most investigators recognize for a substance metabolically similar to hydroxybutyrate—γ-hydroxybutyric acid [2]. It spreads mainly to the negative component as a result of its connection with the more superficial layers of the cortex. The fact that the sensitivity of the negative components of the DR and TCR to sodium hydroxybutyrate differs, revealed by these experiments, is interesting from the point of view of the study of the chemical sensitivity of various cortical reactions: the negative dendritic potential, produced entirely at the level of the superficial layer of the cortex, is less sensitive to the action of sodium hydroxybutyrate than the negative wave of the TCR, associated with additional relays between the deep and superficial layers of the cortex. This may evidently explain the fact that the positive component of the DR changes more than the negative, for it has been shown [3] that the positive part of the DR results from involvement of the deep layers of the cortex following intensive stimulation of its surface.

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