EFFECT OF BARBITURATES AND SODIUM HYDROXYBUTYRATE ON HIPPOCAMPAL ELECTRICAL ACTIVITY

G. N. Krolevets

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Responses evoked in the hippocampus by stimulation of the sciatic nerve or of the hippocampus itself were studied in acute experiments on unanesthetized, curarized rabbits. General anesthetics such as thiopental sodium and pentobarbital sodium were found to modify the first type of evoked hippocampal responses much more than the second type. Sodium hydroxybutyrate, a narcotic agent with a new type of action, shows no significant difference in this respect from barbiturates.

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The study of the effect of drugs on synaptic transmission in various parts of the brain is one of the most important aspects of contemporary pharmacology [4, 5]. Interest in this field is particularly great with respect to synaptic transmission in the limbic system, playing an essential role in the regulation of behavioral and emotional responses. The effects of neurotropic drugs on bioelectrical potentials in the limbic system has been investigated principally in relation to spontaneous activity of limbic structures or paroxysmal discharges generated in response to their stimulation [1, 3, 16].

However, there are advantages to be gained from the use of the method of evoked potentials for this purpose, for it gives a more accurate idea of the character of spread of excitation over structures of the limbic system. The object of this investigation was to study effects produced on hippocampal evoked potentials by general anesthetics: the barbiturates thiopental sodium and pentobarbital sodium and a narcotic agent of a new type—sodium hydroxybutyrate.

EXPERIMENTAL METHOD

Acute experiments were carried out on rabbits. The preliminary operations (tracheotomy, trephining of the skull, exposure of the sciatic nerve, insertion of electrodes) were carried out under ether anesthesia, after which the administration of ether was stopped, the rabbit immobilized with flaxedil, and artificial respiration started. To reduce the flow of afferent impulses due to trauma, the wound surfaces were carefully infiltrated with procaine. Responses were recorded after 3-3.5 h, when the EEG began to be dominated by characteristic rhythms of the waking rabbit. Nichrome electrodes 100 μ in diameter with their factory insulation were used; potentials were recorded by a monopolar technique and bipolar electrodes were used for stimulation. Single square pulses (0.08-0.12 msec for hippocampal stimulation and 0.3-0.6 msec for sciatic nerve stimulation) were generated by a "Neurovar" stimulator. The voltage used was 1.2-1.3 times over threshold. Responses were photographed from the screens of S1-4 oscilloscopes. The statistical significance of the results was estimated by the superposition method. In all experiments simultaneous ink recordings were made of the EEG and ECG on an "Alvar" electroencephalograph. Thiopental sodium was injected in a dose of 35 mg/kg, pentobarbital sodium 15-40 mg/kg, and sodium hydroxybutyrate 300, 500, 750, and 1000 mg/kg body weight; all these substances were injected intravenously.

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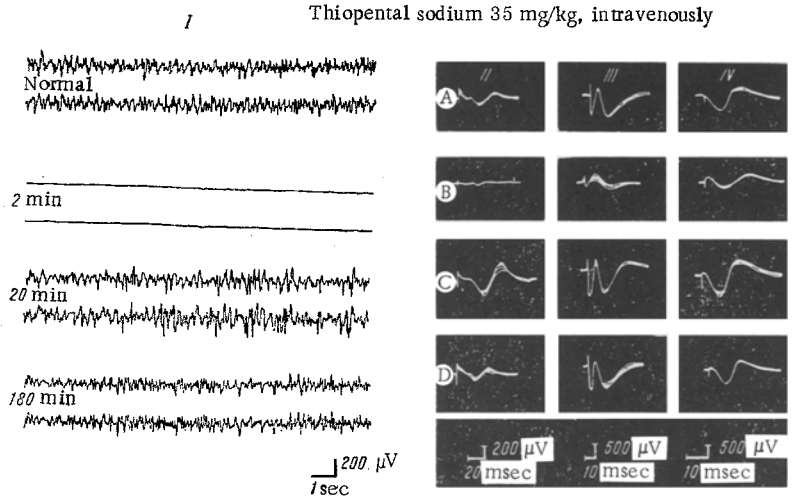

Fig. 1. Effect of thiopental sodium on EEG and hippocampal responses. I) EEG (visual cortex above, hippocampus below); II) somatic hippocampal response; III) local hippocampal response; IV) transcommissural hippocampal response. A) Before injection; B) 2 min, C) 20 min, D) 180 min after intravenous injection of 35 mg/kg thiopental sodium.

EXPERIMENTAL RESULTS AND DISCUSSION

The following types of hippocampal evoked potentials were studied: somatic, local, and transcommissural. The somatic response was recorded in the hippocampus during stimulation of the sciatic nerve. It consists of a combined positive-negative potential with latent period of 15-22 msec and total duration up to 100 msec. In its principal characteristics, this potential closely resembles responses obtained during somatic stimulation by other investigators [7, 10, 12, 13], except for the shorter latent period in the present experiments, presumably due to the fact that unanesthetized animals were used in this case.

In order to differentiate between the effects of different drugs on the afferent pathways by which impulses reached the hippocampus and effects on conduction in the hippocampus itself, the next two types of evoked potentials which are entirely formed in the hippocampus, i.e., are evoked by its stimulation and are recorded in this hippocampus itself, also were studied. One of these types, which will be called local in the future [8], is recorded in the hippocampus when the stimulating electrodes are placed side by side with the recording electrode and not more than 2 mm away from it; the other – the transcommissural evoked potential – is recorded in one hippocampus during stimulation of the symmetrical parts of the opposite hippocampus [9, 11].

When the electrodes were inserted into the hippocampus to the usual depth of 200-300 μ, the local response consisted of a negative wave with latent period of less than 1 msec and duration 10-20 msec, and if the strength of stimulation was increased this was followed by a slower (up to 40 msec) positive wave. The transcommissural response had a latent period of 4-8 msec. It consisted of a negative wave up to 15-20 msec in duration, preceded in the case of above-threshold stimulation by a positive wave of up to 10 msec.

The study of the effect of thiopental sodium on these hippocampal responses showed that these changes are phasic in character and that changes in hippocampal responses of different origin also differ in degree. In the phase of deep thiopental anesthesia, marked by complete absence of EEG potentials [14, 15] or by the presence of single low-amplitude oscillations against the background of the isoelectric line (Fig. 1, I, B), a decrease in amplitude of the hippocampal responses was observed (Fig. 1, III, IV, B). It is important to emphasize that, whereas the amplitude of the local response (Fig. 1, III, B) was reduced by only 10-15%, and that of the commissural response by 20-30% compared with its original value, the somatic response (Fig. 1, II, B) was suppressed to a much greater degree, especially on acount of the positive wave which almost disappeared. Thiopental anesthesia of moderate depth, manifested on the EEG as slow, high-ampli-

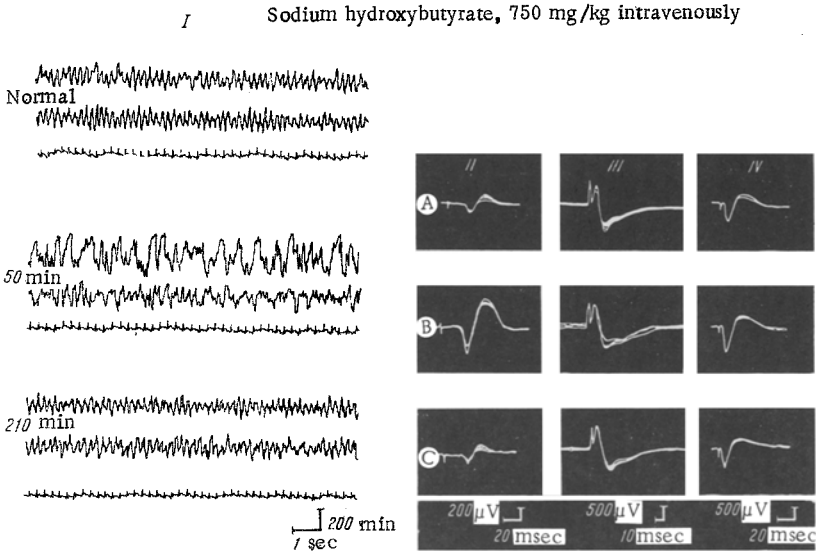

Fig. 2. Effect of sodium hydroxybutyrate on EEG and hippocampal responses. I) EEG (from above down—visual cortex, hippocampus) and ECG; II) somatic hippocampal response; III) local hippocampal response; IV) transcommissural hippocampal response. A) Before injection; B) 50 min, C) 210 min after injection of 750 mg/kg sodium hydroxybutyrate intravenously.

tude potentials and spindle-shaped groups, was characterized by an increase in amplitude of the responses (Fig. 1C), the amplitude of the local responses (Fig. 1, III, C) increasing by 10-15%, that of the commissural by 30-40%, and that of the somatic by 100-200% compared with initially (Fig. 1, II, C). Pentobarbital sodium produced similar changes in the hippocampal responses and EEG, but its action was characterized by a rather different temporal relationship between the phases: deep depression of hippocampal potentials on the EEG which, after injection of thiopental, did not exceed 10 min in duration, compared with 4-5 h after injection of pentobarbital sodium; the period of slow, high-amplitude potentials and of spindle-shaped groups also was longer in duration.

Sodium hydroxybutyrate evoked slow, high-amplitude potentials in the hippocampus similar to those described for other parts of the brain [17]. The character of the EEG after injection of hydroxybutyrate was similar to that of the EEG for moderately deep thiopental anesthesia, except for the smaller number of spindle-shaped groups in the first case (Fig. 2, I, B). The degree of the synchronizing effect for the same dose of sodium hydroxybutyrate varied considerably depending on the initial background of cortex and hippocampus. When active rhythms were more marked in the hippocampus than in the cortex, synchronization took place mainly in the cortex (Fig. 2, I, B), although in experiments in which the hippocampal rhythm was not normally dominant, it was equally marked in the hippocampus and cortex. The phase of deep depression was not observed after injection of sodium hydroxybutyrate. The deepest level of anesthesia produced by sodium hydroxybutyrate in a dose of 1 g/kg is the phase of K-complexes. Just as in thiopental anesthesia of moderate depth, under the influence of hydroxybutyrate the amplitude of the hippocampal responses was increased, that of the somatic response (Fig. 2, II, B) being increased much more (by 100-200%) than the amplitude of the local (by 10-20%) or commissural (by 30-40%) response compared with their initial levels, (Fig. 2, III, IV, B).

The study of the effect of barbiturates and sodium hydroxybutyrate on hippocampal evoked potentials showed that the effects are similar in character: in both cases a phase of marked EEG synchronization occurred, accompanied by an increase in amplitude of the responses. This would seem to destroy some of the grounds for Winter's assertion [18] that the increase which he found in cortical evoked responses under the influence of hydroxybutyrate can be regarded as a manifestation of a paroxysmal effect, and that the action of hydroxybutyrate in this respect is opposite to that of thiopental, which reduces the response. The reason for these differences is that Winter did not take into account the character of the EEG but compared re-

sponses taking place in states of anesthesia of different depths: deep thiopental anesthesia, marked by suppression of spontaneous and evoked activity, and anesthesia caused by hydroxybutyrate, which never reached that depth. These substances also act in a similar manner on intracortical connections [6].

If the degree of change in hippocampal responses is compared within the same phase, it becomes clear that under the influence of hydroxybutyrate and barbiturates the local and commissural responses were changed to a lesser degree than the somatic. The local response is known to reflect the spread of excitation within the limits of one hippocampus, while the transcommissural response reflects its spread along fibers connecting symmetrical parts of opposite hippocampi. Generation of the somatic response in the hippocampus is associated with conduction of the impulse along complex pathways including the extralemniscal system of the brain stem [2, 3]. The fact that the somatic response undergoes a greater degree of change indicates that the anesthetics studied act to a greater degree on the pathways along which afferent impulses reached the hippocampus than on conduction in the hippocampus itself. The parallel between changes in the somatic response and the degree of EEG synchronization suggests that they are the result of the effect of these drugs on activating mechanisms of the brain stem.

LITERATURE CITED

1. L. Allikmets, Zh. Nevropatol. i Psikhiatr., 64, 1241 (1964).
2. A. V. Val'dman, in: Investigations of the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian], Leningrad (1961), p. 11.
3. A. V. Val'dman, in: Current Problems in the Pharmacology of the Reticular Formation and Synaptic Transmission [in Russian], Leningrad (1963), p. 9.
4. V. V. Zakusov, Pharmacology of the Nervous System [in Russian], (1953).
5. V. V. Zakusov, The Pharmacology of Synaptic Transmission, Paper read at the 26th Session of the General Assembly of the Academy of Medical Sciences of the USSR [in Russian], Moscow (1968).
6. V. V. Zakusov and R. U. Ostrovskaya, Byull. Éskperim. Biol. i Med., No. 11, 85 (1967).
7. F. N. Serkov and R. F. Makul'kin, Electrophysiology of the Central Nervous System. Proceedings of the 5th All-Union Conference [in Russian], Tbilisi (1966), p. 274.
8. P. Andersen, T. C. Eccles, and Y. Loyning, Nature, 198, 541 (1963).
9. B. Y. Cragg and L. H. Hamlin, J. Physiol. (London), 135, 460 (1957).
10. C. W. Dunlop, Electroenceph. Clin. Neurophysiol., 10, 297 (1958).
11. J. D. Green, Handbook of Physiology, Neurophysiology, The Hippocampus, Vol. 2 (1960), p. 1373.
12. J. D. Green and W. R. Adey, Electroenceph. Clin. Neurophysiol., 8, 245 (1956).
13. T. S. McKenzie, Electroenceph. Clin. Neurophysiol., 17, 428 (1964).
14. V. Y. Longo, No. 4, Elsevier, Amsterdam (1962).*
15. F. Rinaldi and H. A. Himwich, Ann. New York Acad. Sci., 61, 27 (1955).
16. C. Stumph, Rev. Neurobiol. Vol. 8, Academic Press, New York (1965), p. 77.
17. S. Schneider et al., Agressologie, 4, 55 (1963).
18. W. Winter and C. Spooner, Electroenceph. Clin. Neurophysiol., 18, 287 (1965).

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