EFFECT OF SODIUM HYDROXYBUTYRATE ON THE CEREBRAL CIRCULATION AND REGIONAL VASOMOTOR REFLEXES

É. A. Bendikov, T. S. Gan'shina, and R. S. Mirzoyan

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Experiments on cats in which electromagnetic and resistographic methods were used showed that sodium hydroxybutyrate (100 mg/kg) considerably increases the cerebral circulation. It also increases the blood flow into the brain during the period of formation of pressor blood pressure reflexes. An increase in blood flow also is observed in the system of the femoral arteries, whereas in the intestinal artery, on the other hand, the increase in the blood flow is reduced during vasomotor reflexes. Reflex changes in the resistance of the regional vessels also differ in character: depression of pressor reflexes in the cerebral vessels accompanied by facilitation in the intestinal and femoral arteries and potentiation of the dilator phase of the reflex in the limb vessels. These differences are evidently based on differences in the sensitivity of sympathetic formations in the central components of the different regional vasomotor reflexes to hydroxybutyrate.

KEY WORDS: sodium hydroxybutyrate; cerebral blood flow; nervous regulation of the cerebral circulation.

Sodium hydroxybutyrate causes an increase in the blood flow in various regional vessels [1] and has a marked antihypoxic action [3, 6]. It also affects the central regulation of the circulation [1] and changes the character of pressor and depressor vasomotor reflexes [8].

The object of this investigation was to study the effect of sodium hydroxybutyrate on the cerebral circulation and on the formation of vasomotor reflexes in different arterial systems.

METHODS

Experiments were carried out on 56 cats (3-4 kg) under general anesthesia (urethane, chloralose) and artificial ventilation of the lungs and on six waking animals.

The cerebral blood flow as determined by an electromagnetic flowmeter (Nihon Kohden) and an RKE-2-BI resistograph in the carotid arterial system with simultaneous recording of the EEG from the parietal region, the ECG in lead II, and the arterial pressure [5]. The inflow of blood was recorded by an electromagnetic method in the systems of the common carotid, femoral, and intestinal arteries [1]. To record the resistance of the arterial systems of the brain, hind limb, and intestine, the method of resistography was used [4, 7].

Reflex changes in the circulation and resistance of the regional vessels were induced by electrical stimulation of afferent fibers of A and C groups of the tibial nerve (10-20 V, 20 stimuli/sec). Sodium hydroxybutyrate was injected intravenously in a dose of 100 mg/kg. The experimental results were subjected to statistical analysis.

RESULTS

The experiments showed that sodium hydroxybutyrate has a marked effect on the cerebral circulation. In a dose of 100 mg/kg the compound increased the blood supply to the brain on average by 40 ± 5.2% (Fig. 1). At the same time sodium hydroxybutyrate lowered the vascular tone by an equal degree in the carotid (10 ± 0.8%) and vertebrobasilar (14 ± 2.2%) arterial

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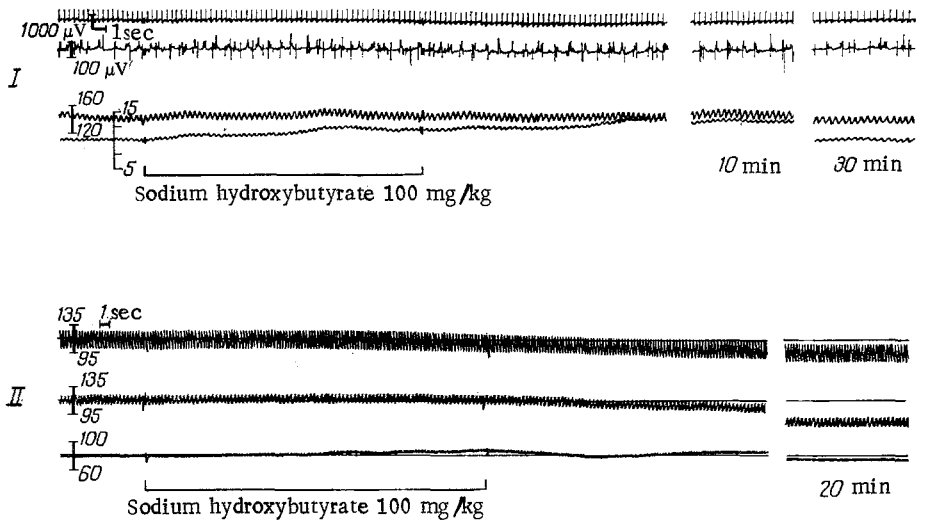

Fig. 1. Effect of sodium hydroxybutyrate (100 mg/kg, intravenously) on cerebral circulation. I) Changes in cerebral blood flow; from top to bottom: ECG in lead II, EEG from parietal region, blood pressure in femoral artery, inflow of blood into brain through internal maxillary artery. II) Changes in tone of arterial systems of the brain; from top to bottom: perfusion pressure in internal maxillary arteries, vertebral arteries, arterial pressure.

system of the brain. The cerebrovascular effect of the compound developed immediately after its injection and lasted 20-40 min.

Investigation of nervous regulation of the cerebral circulation began with the study of the effect of sodium hydroxybutyrate on the blood supply to the brain during the pressor vasomotor reflex from afferents of A and C groups of the tibial nerve. The circulation in the femoral and intestinal arteries also were studied for comparison. Sodium hydroxybutyrate was shown to cause a marked increase in the inflow of blood into the brain during the formation of the vasomotor reflex (Fig. 2). After administration of the compound the reflex increase in blood flow was 47 ± 8%, compared with 21 ± 4.6% in the control ($P < 0.02$). Sodium hydroxybutyrate also increased the circulation in the vessels of the hind limbs on average by 14 ± 1.2%, whereas characteristically in the control the blood flow was reduced during the pressor vasomotor (mean value 21 ± 2%; $P < 0.01$). In the intestinal artery, on the other hand, the increase in the blood flow was reduced during the formation of the vasomotor reflex (12 ± 1.7%) compared with the control response (23 ± 4%; $P < 0.05$).

Sodium hydroxybutyrate considerably facilitated suppressor reflex responses of the arterial pressure (20 ± 1.1% in the control, 53 ± 6.2% in the experiment. These changes were combined with a decrease in the amplitude and frequency of EEG spikes.

In the waking animals similar changes were observed under the influence of sodium hydroxybutyrate: facilitation of the pressor vasomotor reflexes, a significant increase in the inflow of blood in the systems of the common carotid and femoral arteries in the period of formation of the vascular reflexes.

It was interesting to study to what extent the differences in the responses of the regional circulation under the influence of sodium hydroxybutyrate in the period of formation of the pressor vasomotor reflexes were due to changes in the resistance of the regional vessels. Experiments by the resistographic method showed that sodium hydroxybutyrate considerably weakened the constrictor responses of the cerebral vessels due to stimulation of afferents of A and C groups of the tibial nerve. Reflex responses in the carotid and vertebrobasilar arteries were inhibited by 40 ± 7.2 and 44 ± 4.6% respectively. Meanwhile, under the influence of hydroxybutyrate facilitation of the reflex increase in vascular tone in the sys-

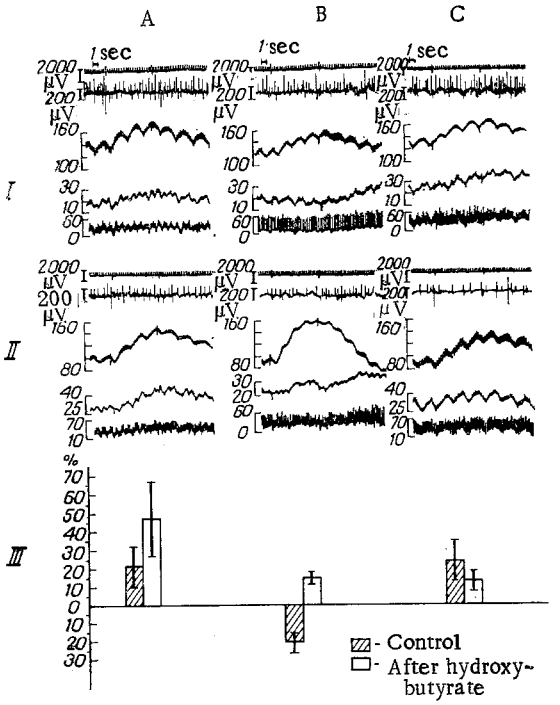

Fig. 2. Changes in blood supply of brain (A), lower limb (B), and intestine (C) under influence of sodium hydroxybutyrate (100 mg/kg, intravenously) during period of formation of pressor vasomotor reflexes. 1) Control responses; II) 15 min after injection of sodium hydroxybutyrate; III) mean data for changes in blood flow in regional vessels, in % of initial level during electrical stimulation of afferent fibers of tibial nerve (15 V, 20 stimuli/sec, 1 msec). I and II) from top to bottom: ECG in lead II, EEG in parietal region, arterial pulse pressure, averaged and phasic blood flow.

tem of intestinal arteries was observed (23.5 ± 3.3%). At the same time, sodium hydroxybutyrate potentiated the constrictor and dilator phases of the reflex in the hind limb vessels on average by 24 ± 2.8 and 41 ± 1.3% respectively.

Sodium hydroxybutyrate thus considerably increases the cerebral circulation and strengthens the flow of blood into the brain in the period of formation of the vasomotor reflex. It facilitates pressor vascular reflexes and, under these circumstances, gives rise to dissimilar changes in the blood supply to the brain, the hind limb, and intestine, because of the differences in the character of reflex changes in the tone of the regional blood vessels. These differences are evidently based on differences in the sensitivity of the synaptic formation in the central components of the different regional vasomotor reflexes to sodium hydroxybutyrate, in agreement with the results of investigations by Zakusov and his collaborators [2], who found a broad spectrum of sensitivity of the central synapses to this substance. The increase in the blood supply to the brain and hind limbs under conditions of facilitation of vasomotor reflexes from muscular afferent fibers may play an important role in the mechanism of the antihypoxic action of sodium hydroxybutyrate and in the increase in physical working capacity caused by this compound.

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THE USE OF MINI PIGS — A NEW KIND OF EXPERIMENTAL ANIMAL — TO STUDY THE EMBRYOTROPIC ACTION OF PHENAZEPAM

B. I. Lyubimov, N. M. Smol'nikova, S. N. Strekalova, S. S. Boiko, A. N. Yavorskii, V. A. Dushkin, and P. R. Poznakhirev

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Experiments on a Siberian breed of mini pigs showed that phenazepam, in a dose of 1 mg/kg internally throughout the period of organogenesis, has neither embryotoxic nor teratogenic action. Parallel determinations of the blood level of the compound were made in pregnant animals. It can be concluded from the results of this investigation that mini pigs are a promising species with which to test the embryotropic activity of drugs.

KEY WORDS: embryotropic action; mini pigs; phenazepam.

In many countries, mini pigs are being used with increasing frequency as experimental animals in recent years. The reason is that the structure and functions of the principal physiological systems and the character of feeding and metabolism, including drug metabolism of these animals are closer to those of man than in any other experimental animal except, perhaps, monkeys [6]. It is difficult to enumerate all the fields of application of mini pigs in medico-biological research. Appropriate surveys on this subject can be consulted [2, 4, 6].

The study of the embryotropic action of drugs is made much more difficult because of the absence of a perfect experimental model. Experiments nowadays are carried out chiefly on small laboratory animals (rodents), which are cheap and convenient from the technical point of view. However, the results of such experiments have limited prognostic value for extrapolation to man. The use of mini pigs in this branch of research is a promising development, for these animals different from ordinary pigs in their more precocious development and higher fertility, and the physiology of reproduction and embryogenesis of these animals has been adequately studied. Mini pigs readily tolerate such surgical procedures as removal of fetuses at different stages of pregnancy.

Various factors, including genetic, hypoxia, irradiation, and virus infections, may cause teratogenesis both in man and in pigs. Malformations induced in pigs are similar clinically and pathologically to those observed in man. The difference in structure of the placenta (epitheliochorial in the pig, hemochorial in man) is not a serious obstacle, for the distance between the maternal and fetal blood is very small because of the development of sub- and intraepithelial capillaries in the maternal and fetal parts of the placenta.

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