EFFECT OF SODIUM HYDROXYBUTYRATE ON THE REGIONAL CIRCULATION AND NERVOUS REGULATION OF VASCULAR TONE

É. A. Bendikov and T. S. Gan'shina

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The effect of sodium hydroxybutyrate (40, 100, and 200 mg/kg) on the circulation in the aorta and the carotid, mesenteric, and femoral arteries (using electromagnetic recording of the blood flow), the tonic activity in the sympathetic nerves, and the EEG was studied in experiments on anesthetized and unanesthetized cats and also on immobilized, unanesthetized dogs. Decreased activity of the sympathetic nerves and synchronization of the EEG under the influence of sodium hydroxybutyrate were found to be associated with a marked increase in the circulation in the regional vessels (of the brain, intestine, and limb) and by a decrease in their resistance, which was particularly marked in the system of the common carotid arteries. An effect of sodium hydroxybutyrate on the central regulation of vascular tone is postulated.

KEY WORDS: *regional circulation; vasomotor regulation; sodium hydroxybutyrate.*

In recent years synthetic preparations of γ-aminobutyric acid (GABA) and γ-hydroxybutyric acid (GHBA), namely Gammalon and sodium hydroxybutyrate, have achieved wide popularity in clinical practice [4, 7, 10, 13]. It has been shown that GABA increases the blood flow in the cerebral vessels [8] and inhibits vasomotor reflexes and tonic activity in sympathetic nerves [1]. By contrast, sodium hydroxybutyrate facilitates pressor vasomotor reflexes from spinal afferent fibers [12], increases the blood flow in the splanchnic vessels [7], and has a marked antihypoxic action [6, 9].

It was decided to analyze the action of sodium hydroxybutyrate on the systemic and regional circulation (in the brain, intestine, and limb) and to compare it with changes in tonic activity in the sympathetic nerves.

EXPERIMENTAL METHOD

Experiments were carried out on 33 cats anesthetized with urethane (400 mg/kg) and chloralose (30 mg/kg) and 5 unanesthetized dogs (anesthetic control), immobilized with listhenon. The animals were artificially ventilated and heated. To exclude the effect of the anesthetic, some experiments also were carried out on unanesthetized cats after preliminary implantation of the electromagnetic detector in the abdominal aorta. The resistance of the regional blood vessels and the systemic and regional circulation were monitored by resistography [11] and by recording the blood flow in the ascending arch of the aorta and the mesenteric, femoral, and carotid arteries by

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means of an electromagnetic flowmeter (Nikotron). To compare the central and peripheral cardiovascular effects of sodium hydroxybutyrate, simultaneous recordings were obtained of tonic activity in the sympathetic nerves [2], the EEG (parietal region), the ECG (standard lead II), the pulse and arterial pressure, and the mean and phasic blood flow. Recordings were made on the Mingograph-81 (Elema) apparatus.

Sodium hydroxybutyrate was injected intravenously in doses of 40, 100, and 200 mg/kg.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments on anesthetized cats showed that sodium hydroxybutyrate, in the doses used, rapidly increased the systolic output and minute blood volume (from 2.5-3 to 3.5-4 ml and from 300-350 to 400-450 ml/min respectively), with an accompanying very slight decrease in the heart rate. Parallel with these changes, the flow of blood into the mesenteric, femoral, and carotid artieries was increased by 5-10 ml/min. This effect was observed in both cats and dogs during the first 5 min after injection of sodium hydroxybutyrate, at a time when no changes were present in the EEG and the record of renal and splanchnic sympathetic nerve activity (Figs. 1A and 2A). During the same period the blood pressure was raised by 10-20 mm. The resistance of the regional vessels to the blood flow (measured by resistography) was unchanged during the initial period of action of sodium hydroxybutyrate.

The initial increase in the circulation produced by sodium hydroxybutyrate in the system of the mesenteric, femoral, and carotid artieries was thus due to the cardiac component and not to a change in their tone. These effects were independent of the effect of the drug on central regulation of the circulation.

Further analysis showed that sodium hydroxybutyrate caused a very slight decrease in the intensity of tonic activity in the sympathetic nerves and a gradual decrease in amplitude and frequency of spikes on the EEG of the anesthetized cats 10-15 min after

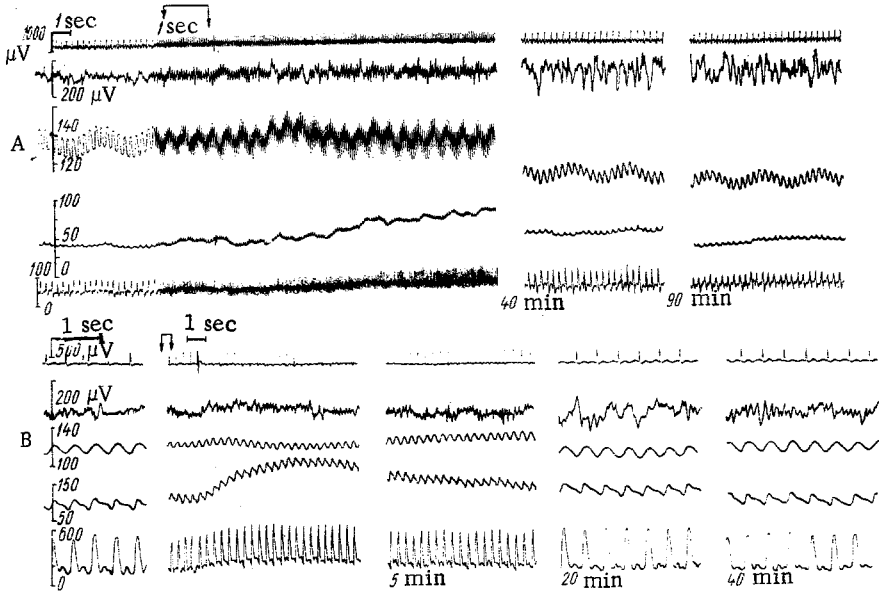

Fig. 1. Effect of sodium hydroxybutyrate (100 mg/kg) on unanesthetized, immobilized dog (A) and on freely behaving cat (B). From top to bottom: ECG; EEG; pulse pressure; averaged and phasic blood pressure in femoral artery (A) or abdominal aorta (B). Arrows mark time of injection of sodium hydroxybutyrate.

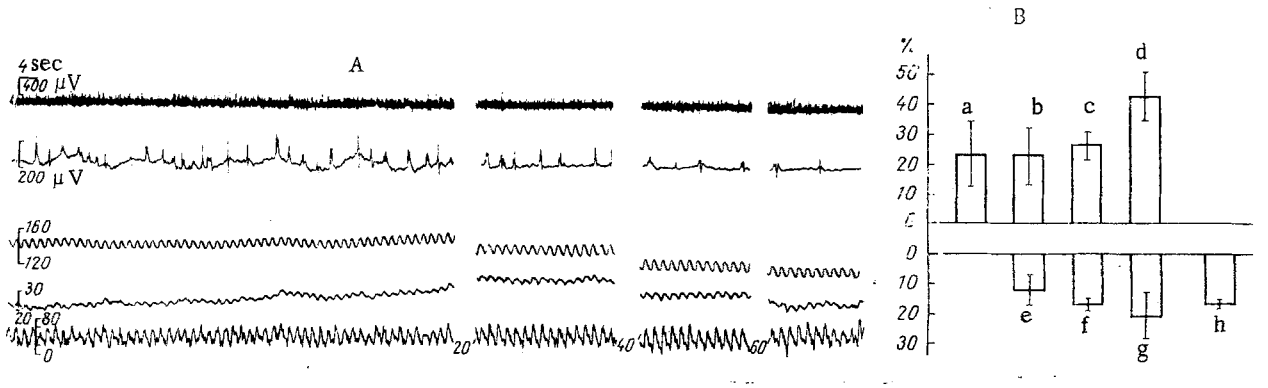

Fig. 2. Effects of sodium hydroxybutyrate (100 mg/kg) on anesthetized cat. A: Legend as in Fig. 1; tonic activity in renal nerve shown above, averaged and phasic blood flow in common carotid artery recorded below. B: a) Blood flow in ascending arch of aorta; b) in mesenteric, c) in femoral; d) in common carotid artery; e, f, g) tone of corresponding vessels; h) arterial pressure. Indices given as percentages of initial levels. Values of M ± 2.5 m given.

its injection (Fig. 2A). Parallel with the changes in sympathetic nerve activity, a decrease was observed in the arterial pressure (on the average by 16.7 ± 0.32%) and in the tone of the regional vessels, which was particularly marked in the system of the common carotid artery (mean decrease 20.8 ± 2.8%; Fig. 2B). These changes led to a redistribution of the mass of circulating blood with a considerable increase in the flow of blood into the carotid artery (on the average by 41.8 ± 3.2%). The increase in the blood flow in the ascending arch of the aorta and the mesenteric and femoral arteries observed under these conditions was much smaller ($P < 0.05$). The duration of the effect varied from 40 to 90 min depending on the dose of sodium hydroxybutyrate. Similar results were obtained in experiments in which the blood flow was recorded in the femoral artery of unanesthetized dogs and in the abdominal aorta of freely behaving cats (Fig. 1). In these animals the hemodynamic changes and moderate bradycardia were accompanied by synchronization of the EEG, and in the unanesthetized cats by a sedative effect also.

The lowering of sympathetic tone, synchronization of the EEG, and increase in the blood flow in the carotid arteries, supplying blood to the brain [14], are associated with stimulation of oxidative processes in the brain by GHBA [3, 7]. Meanwhile the differences in sensitivity of the regional vascular system to sodium hydroxybutyrate, allowing for changes in tone of the sympathetic innervation [15], suggest that its effect on vasomotor regulation can be regarded in the light of the synaptic theory of action of neurotropic agents [5].

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