GABA-ERGIC COMPONENTS OF THE CEREBROVASCULAR EFFECT OF SODIUM HYDROXYBUTYRATE

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The writers showed previously that sodium hydroxybutyrate increases the blood supply to the brain and has a selective depriming effect on nervous regulation of the cerebral circulation [2]. Accordingly it appeared interesting to study the neuromediator mechanisms of the cerebrovascular effect of this compound. Sodium hydroxybutyrate is known to be a GABA analog, and to resemble it in several of its effects: In particular, it increases the cerebral blood flow and lowers the tone of the brain vessels [8]. GABA has a central depriming effect on nervous regulation of the cerebral circulation [4, 9], and by contrast with sodium hydroxybutyrate, it inhibits vasomotor reflexes [3, 5, 10, 14]. Finally, reports have been published to the effect that the brain vessels contain receptors sensitive to GABA [11-13].

The above data formed the basis for a suggestion that the cerebrovascular effects of sodium hydroxybutyrate may be mediated through GABA-ergic mechanisms. To shed light on this problem the effect of sodium hydroxybutyrate was studied under conditions when GABA receptors were blocked with bicuculline.

EXPERIMENTAL METHOD

Experiments were carried out on 29 cats weighing 3-4 kg under general anesthesia (urethane, chloralose) with artificial ventilation. The blood flow into the brain through the internal maxillary artery was determined with an electromagnetic flowmeter. The EEG in the parietal region, ECG in lead II, and blood pressure in the femoral artery were recorded simultaneously; the tonic activity and reflex responses in sympathetic nerves of the renal plexus and stellate ganglion also were recorded [1]. The vascular component of the action of the substances on the cerebral hemodynamics was differentiated with the aid of a technique of separate bilateral perfusion of the carotid and vertebral arteries [7]. In all experiments the partial pressure of carbon dioxide (pCO_2) was determined in samples of arterial blood by means of the ABC-1 apparatus and maintained between limits of the control values (35-40 mm Hg). The test substances were injected intravenously: sodium hydroxybutyrate in a dose of 100 mg/kg and bicuculline in a dose of 0.15-0.2 mg/kg. The animals were killed with a mixture of urethane and chloralose.

EXPERIMENTAL RESULTS

When the GABA receptors were blocked with bicuculline, sodium hydroxybutyrate was able to increase the volume velocity of the cerebral blood flow. Between 10 and 15 min after injection of bucuculline sodium hydroxybutyrate caused an increase in the blood supply to the brain by 31 ± 4.5%. In the control experiments the compounds increased the circulation in brain tissue by 40 ± 5.2%. Against the background of the action of bicuculline sodium hydroxybutyrate caused changes in the blood pressure similar to those observed in intact animals. The results of experiments with recording cerebrovascular tone showed that when GABA receptors were blocked sodium hydroxybutyrate lowered the resistance in the carotid system by 9 ± 2.3% and in the vertebrobasilar system by 11 ± 3.2%. In the control experiments the

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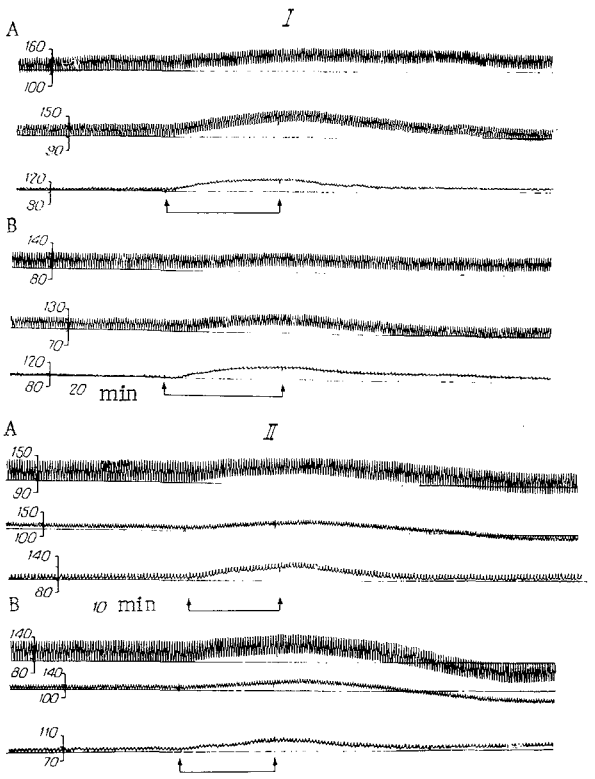

Fig. 1. Effect of sodium hydroxybutyrate (100 mg/kg, intravenously) on reflex constrictor responses of brain vessels in intact cat (I) and after preliminary intravenous injection of 0.2 mg/kg bicuculline (II). A) Control reactions, B) after injection of sodium hydroxybutyrate. From top to bottom: perfusion pressure in carotid basin, in vertebrobasilar system, blood pressure in carotid basin, in vertebrobasilar system, blood pressure (mm Hg), marker of stimulation (20 V, 20 stimuli/sec, 1 msec, 15 sec).

compound reduced the tone of the cerebral arterial systems by 10 ± 0.8 and 14 ± 2.2%, respectively.

There was thus no difference in the effects of sodium hydroxybutyrate on the cerebral circulation in the intact animals and when GABA receptors were blocked by bicuculline. Consequently, the increase in the blood supply to the brain observed under the influence of sodium hydroxybutyrate is not mediated through GABA-ergic mechanisms. These effects of the drugs are evidently due to its ability to exert a direct relaxing action on the cerebral vessels.

Meanwhile bicuculline had a significant effect on the ability of sodium hydroxybutyrate to act on nervous regulation of the cerebral circulation. When GABA receptors were blocked the drug had no depriming action on constrictor responses of blood vessels in the carotid and vertebrobasilar systems evoked by stimulation of afferent fibers of the tibial nerve (Fig. 1, II), and in some experiments it actually enhanced them. In control experiments the drug inhibited constrictor responses of the brain vessels in both arterial systems by 40 ± 7.2 and 44 ± 4.6%, respectively (Fig. 1, I). In intact cats sodium hydroxybutyrate considerably increased the inflow of blood into the brain during the pressor vasomotor reflex (+133 ± 18.9%). Bicuculline blocked the ability of hydroxybutyrate to influence changes in the cerebral blood flow during formation of the pressor vasomotor reflex (+12 ± 10.1%), although it also potentiated the pressor response of the arterial pressure. It can accordingly be postulated that against the background of the action of bicuculline, sodium hydroxybutyrate does not cause any further enhancement of the pressor response of the arterial pressure.

When GABA receptors were blocked by bicuculline, sodium hydroxybutyrate had no depriming action on somatosympathetic reflexes. In particular, the gradual inhibition of reflex responses during the period of high-frequency stimulation of afferents A- and C-groups of tibial nerve fibers, characteristic of sodium hydroxybutyrate, was not observed. Consequently, GABA-ergic mechanisms do participate in the depriming effect of sodium hydroxybutyrate on nervous regulation of the cerebral circulation. These results are in agreement with observations by Kozhechkin [6], who found that sodium hydroxybutyrate, if injected by microiontophoresis, evoked depression of unit activity. This effect was abolished by bicuculline, evidence that GABA receptors participate in the manifestation of the inhibitory effect of the drug on the CNS.

The present experiments thus showed that two different mechanisms are concerned in the realization of the cerebrovascular effects of sodium hydroxybutyrate. Whereas dilatation of the brain vessels and an increase in the inflow of blood into the brain under the influence of the compound are not mediated through GABA receptors and are evidently determined by the direct relaxing effect of the drug on the brain vessels, an important role in the depriming effect of sodium hydroxybutyrate on nervous regulation of the cerebral circulation undoubtedly belongs to central GABA-ergic processes.

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