EFFECT OF VERAPAMIL ON THE CEREBRAL CIRCULATION

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In acute experiments on anesthetized cats verapamil (0.05, 0.1, and 0.5-1 mg/kg, intravenously) lowered the tone of the cerebral vessels and the systemic arterial pressure. Changes in the volume velocity of the cerebral blood flow were phasic in character depending on the tone of the cerebral vessels and the blood pressure level; the blood flow in the cerebral cortex increased more than in the reticular formation. pO_2 in the cerebral cortex correlated with the blood flow. The diameter of the pial arteries increased both after intravascular injection of verapamil and after its local application. Blockade of the β-adrenoreceptors, muscarinic cholinoreceptors, and histamine receptors and preliminary injection of a sympatholytic did not abolish the vasodilator effect of verapamil. It is suggested that the vasodilatation is myotropic in character and possibly connected with electrolyte metabolism.

KEY WORDS: verapamil; cerebral circulation.

Among the many coronary dilators, verapamil (isoptin) is of particular interest because its vasodilator action is accompanied by a reduction in the oxygen consumption of the heart muscle and definite changes in the electrolyte balance in the myocardium [5, 14]. The combination of these properties may also be interesting in the treatment of ischemic states of the brain, but there is no information in the literature on the character of the action of verapamil on the cerebral circulation, and the investigation described below was accordingly carried out to study this problem.

EXPERIMENTAL METHOD

Experiments were carried out on 116 cats weighing 2.5-4 kg, anesthetized with urethane (0.8-1 g/kg). The character of the vascular responses of the brain and its blood supply was judged from the results of resistography, rheoencephalography, recording the total and local cerebral blood flow, measurement of the diameter of the pial arteries, polarographic determination of pO_2 in the cerebral cortex, and recording the systemic blood pressure. The methods of investigation are described in the literature [1-4, 7, 9]. Most series of experiments were carried out with artificial respiration. Verapamil (isoptin) was injected intravenously (0.05, 0.1, and 0.5-1 mg/kg) and into the carotid artery (0.01 mg/kg). The experimental results were subjected to statistical analysis.

EXPERIMENTAL RESULTS AND DISCUSSION

Resistography showed that intravenous injection of verapamil in doses of 0.05, 0.1, and 0.5-1 mg/kg caused a significant ($P < 0.001$) reduction in tone of the cerebral vessels on average by 8 ± 1, 12.2 ± 1, and $15.8 \pm 1.2\%$ respectively. The effect was observed immediately after injection of the drug, reached a maximum after 1 min (Fig. 1A), and lasted for between 8 and 40 min depending on the dose. Similar changes were found in the systemic blood pressure and the tone of the extracranial vessels.

The results of rheoencephalography showed that verapamil (0.1 mg/kg, intravenously) caused a significant increase in the amplitude of the rheographic wave by $36.1 \pm 8.6\%$, a decrease in the duration of the anacrotic phase by $33.5 \pm 2.2\%$, a decrease in the index of peripheral resistance by $59.2 \pm 5.3\%$, and an increase in the value of t by $42 \pm 8.1\%$. The effect was observed immediately after injection of the drug, it reached a maximum after 1 min (Fig. 1b), and lasted for 10-15 min. Analysis of the changes observed in the rheoenceph-

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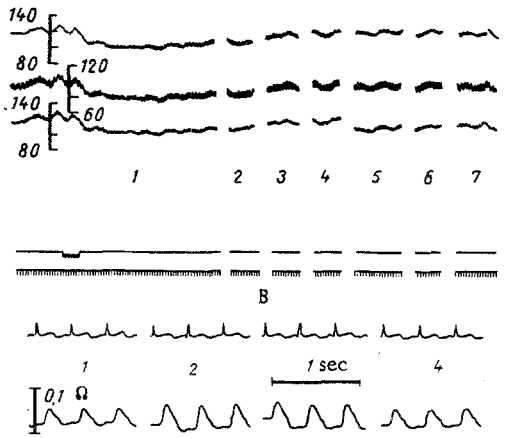

Fig. 1

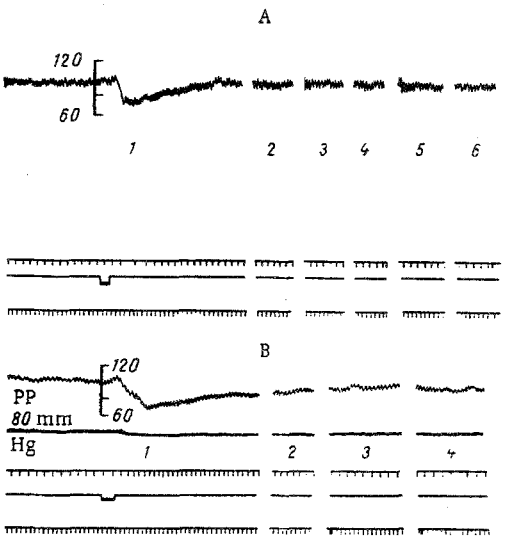

Fig. 2

Fig. 1. Effect of verapamil (0.1 mg/kg intravenously) on tone of cerebral vessels. A) Data of resistography. From top to bottom; systemic blood pressure, resistogram of intracranial vessels, resistogram of extracranial vessels, marker of injection of verapamil, time marker 3 sec. 1) Initial data at moment of injection of drug, 2-7) 3, 5, 10, 15, 20, and 30 min, respectively, after injection of verapamil. B) Data of rheoencephalography. Top curve – ECG, bottom curve – REG. 1) Initial data, 2-4) 1, 5, and 20 min, respectively, after injection of verapamil.

Fig. 2. Effect of verapamil (0.1 mg/kg, intravenously) on volume velocity of cerebral blood flow with perfusion pressure (PP) unstabilized (A) and stabilized (B). From top to bottom: systemic blood pressure; cerebral blood flow (distance between markers 3 ml); marker of injection of verapamil; time marker 5 sec. 1) Initial data at moment of injection; 2-6) 3, 5, 10, 20, and 30 min, respectively, after injection of verapamil.

alogram (REG) [6, 8] showed that verapamil reduces the elastic–tonic properties of the cerebral vessels, including the main trunks, and increases pulse fluctuations in their blood volume.

Intravenous injection of verapamil (0.1 mg/kg) under conditions of an unstabilized arterial pressure caused biphasic changes in the volume velocity of the total cerebral blood flow in most (five of eight) experiments. Immediately after injection of the drug the blood flow was briefly reduced by 11-31%, after which it rose again quickly, and after 3 min it was already 6-14% greater than initially (Fig. 2A). In two experiments the blood flow increased without any previous decrease, and in one experiment there were no appreciable changes in the blood flow. Statistical analysis of the results of measurement of the blood flow showed that the initial decrease, on average by 11.6 ± 5%, and the subsequent increase by 8 ± 3% were significant ($P < 0.05$). The character of the changes in pO_2 in the brain tissue corresponded on the whole to the blood flow. The blood pressure in all the experiments of this series fell briefly (3-5 min) on average by 10%. In some experiments the cerebral blood flow thus increased, despite the general hypotension.

A particularly clear increase in the cerebral blood flow (on average by 33.1 ± 9.3%) after intravenous injection of verapamil (0.1 mg/kg)was observed when the perfusion pressure was stabilized (Fig. 2B). In this series of experiments there was no initial phase of decrease in the blood flow.

Investigation of the local cerebral blood flow by the hydrogen clearance method revealed an increase in the blood flow under the influence of verapamil (0.1 mg/kg, intravenously) in the cerebral cortex on average by 37.7 ± 6.6 % and in the reticular formation by 21.2 ± 5%. In this series of experiments no initial phase of a decrease in blood flow was observed, possibly on account of the inertia of the method.

The results of serial photography of the vessels on the surface of the brain, taken through a "window" in the skull, showed a mean increase in the diameter of the pial arteries of 14% after injection of verapamil (0.01 mg/kg) into the carotid artery and by 22% after local application of a 0.02% solution of verapamil.

The mechanism of the vasodilator action of verapamil has not been finally elucidated. The problem of its antiadrenergic properties remains disputed [10-12]. Previous statements on the β-adrenoblocking action of verapamil have not been confirmed by subsequent investigations. The definite vasodilator response to verapamil cannot be reconciled at all with β-adrenoblocking activity.

In some series it was found that denervation of the carotid sinuses, or preliminary injection of anaprilin (propranolol), atropine, reserpine, and dimedrol (diphenhydramine), in doses blocking the corresponding synaptic structures and receptors, did not abolish the cerebrovascular effect of verapamil; moreover, after anaprilin and atropine the vasodilator action of verapamil was potentiated somewhat.

The dilator response of the cerebral vessels is evidently manifested after their direct contact with verapamil and it is evidently myotropic in character. However, the myotropism of verapamil differs from that of papaverine and euphylline. For instance, there is evidence [13] that verapamil, unlike papaverine and euphylline, does not lower the phosphodiesterase activity of the smooth muscles of the isolated guinea pig intestine and does not cause accumulation of cyclic AMP, characteristic features of papaverine and euphylline. Meanwhile high concentrations of calcium did not inhibit the spasmolytic effect of papaverine and euphylline, but abolished only that of verapamil.

The role of electrolyte (especially calcium) metabolism in the mechanism of the antiarrhythmic action of verapamil has frequently been discussed in the literature [5]. Verapamil, as a calcium antagonist, evidently lowers the excitability not only of the myocardium, but also of the smooth muscles of the blood vessels. To elucidate the complex mechanism of action of verapamil on electrolyte metabolism further investigations must be carried out in order to study many problems concerned with the function of the CNS, including the mechanisms of regulation of vascular tone.

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