BIOCHEMICAL BASIS OF THE SPASMOLYTIC EFFECT OF ISOQUINOLINE AND PHENOTHIAZINE DERIVATIVES

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Isoquinoline and phenothiazine derivatives have a marked spasmolytic action, but the basis of their myotropic action has not yet been explained. Papaverine, no-shpa, and nonachlazine have been shown to have a malonate-like action on respiration and oxidative phosphorylation of myocardial mitochondria [4]. The writers have accordingly postulated that the spasmolytic action of isoquinoline and phenothiazine derivatives may be realized through inhibition of bioenergetic processes in smooth muscle mitochondria. The present investigation was aimed at confirming this hypothesis.

EXPERIMENTAL METHOD

The action of papaverine (10 μM), no-shpa (25 μM), nonachlazine (50 μM), ethmozine (25 μM), malonate, and hypothermia on the tone of segments of blood vessels and intestine, on the rate of their oxygen consumption and the rate of glycolysis in the veins of the heart was studied in 210 experiments on isolated vascular rings from the great vein and anterior interventricular artery of the pig heart and 80 experiments on isolated segments of the rat small intestine. Smooth muscle tone of the arteries, veins, and intestine was studied by a strain gauge method under isometric conditions [6, 7]. The initial load on the venous rings was 250-400 mg and on the arterial rings and segments of intestine it was 1000 mg. The rate of oxygen consumption by the test objects was studied by polarographic method on the PA-3 polarograph, with open vibrating platinum electrode, lowered into the incubation cell. The rate of anaerobic glycolysis was studied with a photoelectric colorimeter by the method described in [2].

EXPERIMENTAL RESULTS

The spasmolytic activity of the preparations was studied in experiments with veins, arteries, and intestine against a background of steady contraction of smooth muscle induced by addition of a high-potassium Krebs' solution (KCl 60 mM). The results showed that exposure of the preparations after preliminary high-potassium contracture led in every experiment without exception to a rapid and sudden fall of smooth muscle tone of blood vessels and intestine. The drugs under investigation, in the concentrations specified, were shown to abolish the high-potassium contracture of the arterial rings and segments of intestine completely and to reduce the tone of the veins considerably. High-potassium contracture of the veins was reduced under the influence of paraverine, no-shpa, nonachlazine, and ethmozine by 40, 74, 54, and 50% respectively.

Manifestations of this spasmolytic effect in such different systems as arteries and veins of the pig heart and the rat small intestine indicates that the effect may be universal in character and connected with a direct myotropic influence. One possible mechanism of the action of the drugs may be inhibition of glycolysis, as one source of the energy required for maintaining tone. However, the experiments on veins showed that isoquinoline derivatives and phenothiazine derivatives do not affect the rate of lactic acid formation.

Another probable mechanism of the plasmolytic action, in our opinion, is inhibition of energy production in the smooth muscle mitochondria. Proof of this hypothesis is given by

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the results of several series of the present experiments. For instance, the level of tone was found to depend to a considerable degree on the oxygen concentration in the Krebs' solution. Aerated high-calcium Krebs' solution caused the arterial tone to rise by 50% more than the nonaerated solution. High-potassium contracture increased several times faster in the aerated than in the nonaerated solution. It was also found that cooling the Krebs' solution from 37 to 20°C reduces the high-potassium contracture by 30%. Meanwhile hypothermia within these limits did not reduce the rate of anaerobic glycolysis at all, but it sharply reduced the velocity of respiration (the rate of oxygen consumption by arterial rings, for example, was reduced by more than fivefold). Smooth muscle tone of veins, arteries, and intestine is thus oxygen-dependent, i.e., the energy required to maintain a high tone is formed during oxidative phosphorylation in the mitochondria. Proof of this is given also by experiments with 2,4-DNP and potassium cyanide [1, 3].

As well as reducing high-potassium contracture, the drugs also sharply reduced the velocity of respiration of the test objects. For instance, the velocity of respiration of the venous rings was reduced in the presence of papaverine, no-shpa, nonachlazine, and ethmozine by 34, 44, 54, and 50% respectively, the velocity of respiration of the arterial rings was reduced by 41, 29, 30, and 66% respectively, and the velocity of respiration of intestinal segments by 43, 30, 27, and 60% respectively. It can be tentatively suggested that the decrease in the velocity of respiration of the vascular rings and intestine in the presence of these drugs is a secondary reaction in response to the lowering of tone. However, this is not so. A decrease in the velocity of respiration was observed before the decrease of tone, and the established decrease in the velocity of respiration remained unchanged with a fall in tone. We also know that papaverine, no-shpa, and nonachlazine, in these same concentrations, can exert a direct malonate-like action on mitochondria [4, 5]. Consequently, there is an independent mechanism of action of these drugs on respiration of the vessels and intestine, which is manifested even before the smooth muscle tone begins to fall, and is independent of the level of tone and can probably be attributed to a malonate-like action on the mitochondria. A fall in the intensity of respiration and phosphorylation in smooth muscle mitochondria, however, leads to a decrease in energy formation and is one cause of the lowering of tone in the presence of these drugs; in other words, it is one of the mechanisms of their spasmolytic action.

Further proof that this mechanism participates in the realization of the spasmolytic effect of these drugs is given by the results of experiments with malonate, a specific inhibitor of mitochondrial succinate dehydrogenase. Malonate (10 mM) completely abolished the high-potassium contracture of arterial rings and intestinal segments, while reducing the velocity of respiration by 56 and 58% respectively, and in a concentration of 2 mM malonate reduced the tone of the venous rings by 39% and reduced the velocity of respiration by 56%.

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