THE ACTION OF CERTAIN DRUGS ON THE RESPIRATION OF THE SMOOTH MUSCLE OF BLOOD VESSELS

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There is evidence in the literature that the smooth muscle of the blood vessels differs from the other muscular organs in certain aspects of its metabolism.

In particular, the blood vessel wall absorbs much less oxygen than the heart or skeletal muscle [1, 5, 8, 11, 12], resembling more closely in this respect the smooth-muscular organs. Several workers consider that energy formation from carbohydrates (glucose) in the muscle of the vessels takes place largely by glycolysis [8, 10, 12]. The respiration of the smooth muscle of the arterial wall is one of the sources of energy for the physiological processes lying at the basis of muscle tone. The few researches reported in the literature [7, 9] are insufficient to provide a clear indication of the role of tissue respiration in the mechanism of action of vascular drugs.

We have investigated the effect of vasoconstrictor drugs (adrenalin, noradrenalin, etc.) and vasodilator drugs (papaverine, euphyllin, sodium nitrite), widely used in clinical practice, on the respiration and contractility of the smooth muscle of the blood vessels.

EXPERIMENTAL METHOD

Strips of aorta were obtained from rabbits by a method slightly modified [3] from that of Furchgott and Bhadrakom [6]. The thoracic aorta, 4-6 cm long, was extracted from rabbits weighing 2.0-2.5 kg, and placed in Krebs' solution cooled on ice. The aorta was then drawn over the end of a specially adapted Pasteur pipet, freed from connective tissue by means of a razor, and incised longitudinally. The band thus formed from the aorta was divided into separate segments 100-150 mm^2 in area (crude weight 40-70 mg) and placed in the flasks of a Warburg's apparatus, into which the following had been poured: controls – 2 ml of Krebs' solution containing 0.01 M glucose; experimental series – 1.8 ml of the above solution and 0.2 ml of a solution of the drug to be tested. The central portion of the flask contained 0.2 ml of a 5% solution of KOH.

The tissue respiration of the aortic wall was estimated in the Warburg's apparatus in an atmosphere of oxygen for a period of 1 h. The coronary vessels of an ox heart were obtained from a slaughterhouse and immediately placed in cold Krebs' solution. They reached the laboratory in a vacuum flask from 1.5 to 2 h after the animal had been slaughtered. In the experiment we used branches of the coronary vessels 1.5 to 3 mm in diameter. The remainder of the experiment was conducted in the same way as in the case of the rabbits' aortas. The results of the measurements of oxygen absorption were expressed as QO_2 (the number of $\mu M\ O_2$ corresponding to 1 mg dry weight of tissue and to unit time – 1 h).

EXPERIMENTAL RESULTS

The vascular wall is characterized by low rates of tissue respiration, so that we used different variants of experiments in order to obtain the largest possible values. We used different buffer solutions, the wall of the aorta was homogenized or minced, and so on. The largest values of the oxygen consumption were obtained by the use of "vascular disks" prepared as described above in Krebs' solution containing 0.01 M glucose. This agrees with the findings of other workers [4], who also obtained high values of QO_2 by using sections of vessels in their experiments.

In our investigations, the control value of QO_2 for the aortic wall during the first hour was 1.31 ± 0.1 (10 experiments).

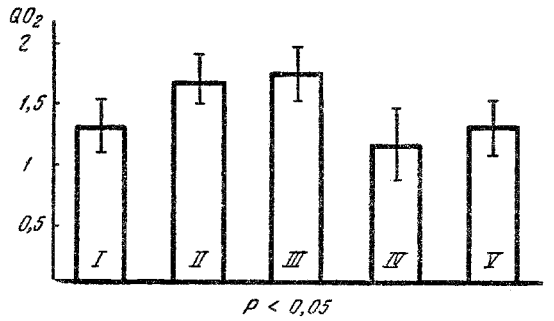

Fig. 1

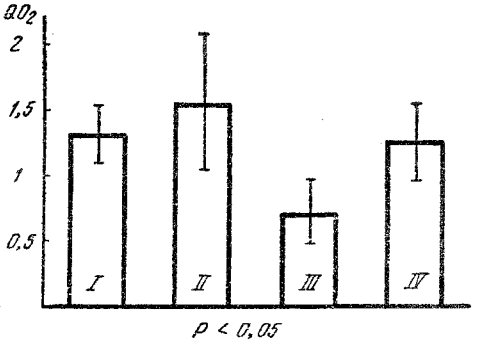

Fig. 2

Fig. 1. Effect of substance causing contraction of a strip of aorta on changes in the respiration of the smooth muscle of the aorta in rabbits. I) Control; II) adrenalin (10^{-5}); III) noradrenalin (10^{-5}); IV) ephedrine (10^{-4}), V) serotonin (10^{-4}).

Fig. 2. Effect of vasodilator drugs on the respiration of the aortic wall in rabbits. I) Control; II) sodium nitrite ($2 \cdot 10^{-3}$); III) papaverine ($2 \cdot 10^{-3}$); IV) euphyllin ($1 \cdot 10^{-4}$).

After the addition of adrenalin in a concentration of 10^{-5}, giving rise to a maximal contraction of the isolated strip [2, 6], the oxygen absorption by the vascular wall was increased (Fig. 1): $QO_2 = 1.68 \pm 0.07$ (7 experiments).

Noradrenalin, like adrenalin, stimulated the absorption of oxygen by the arterial wall: $QO_2 = 1.75 \pm 0.08$ (5 experiments). Hence, no appreciable differences in the action of these two catecholamines on the respiration of the blood vessel wall could be detected.

In the face of these findings, the question arises, is the stimulation of tissue respiration associated with the ability of the catecholamines to cause a contraction of the smooth muscle of the aorta, or is it a specific property of these drugs? In an attempt to elucidate this question, we used substances which also cause the contraction of the isolated strip of rabbit's aorta under experimental conditions: ephedrine (10^{-4}) and serotonin (10^{-4}). It will be clear from Fig. 1, however, that these substances had hardly any effect on the respiration of the vascular wall.

We attempted to obtain additional data by studying the peculiarities of the metabolism of those vessels which are relaxed by adrenalin. For this purpose experiments were carried out on the coronary vessels of the ox heart. These showed that adrenalin had a tendency to stimulate the tissue respiration. In the control series (10 experiments), for instance, $QO_2 = 0.328 \pm 0.06$, while after the action of adrenalin $QO_2 = 0.442 \pm 0.07$ (9 experiments).

Consequently, these results afforded further evidence of the unique mechanism of action of the catecholamines and of the fact that the contraction of the smooth muscle of the blood vessels may take place without any increase in the tissue respiration. The action of vasodilator drugs on the contractility of the smooth muscle of the vessels was determined by their ability to suppress the contraction caused by adrenalin (10^{-9}).

The vasodilator drugs affected the tissue respiration in different ways (Fig. 2). Euphyllin (10^{-4}), which did not affect the contractility of the smooth muscle of the blood vessels, caused almost no change in the oxygen absorption by the vascular wall: $QO_2 = 1.24 \pm 0.095$ (5 experiments).

Sodium nitrite, which appreciably depressed the contractile reaction of the aortic muscle to adrenalin, had a tendency to increase the tissue respiration of the vascular wall: $QO_2 = 1.54 \pm 0.18$ (5 experiments). This increase in the oxygen absorption by the aortic wall was presumably due to the ability of sodium nitrite to block oxidative phosphorylation, because 2,4-dinitrophenol, which is, like sodium nitrite, a poison of the blocking type, also depresses the contractile reaction of the smooth muscle of blood vessels.

An interesting parallel was observed in the experiments with papaverine (Fig. 3). Papaverine ($2 \cdot 10^{-3}$) depressed the respiration of the isolated aortic wall: $QO_2 = 0.71 \pm 0.08$ (8 experiments); in a concentration of 10^{-4} this drug reduced the amplitude of the contraction of the isolated aortic strip in rabbits due to adrenalin (10^{-9}). In the control tests the amplitude of the contraction was 7.0% ± 0.412 (more than 30 experiments), and during the action of papaverine 3.8% ± 0.1 (9 experiments). After administration of adrenalin (10^{-5}) and papaverine (10^{-3}) together, a depression of the tissue respiration was recorded: $QO_2 = 0.48 \pm 0.047$ (7 experiments).

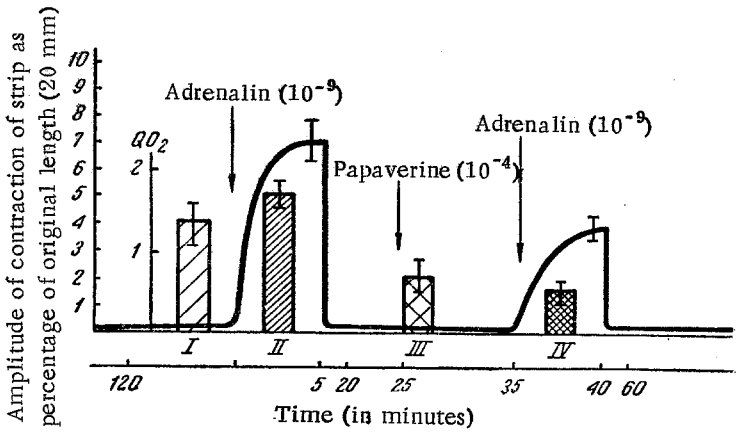

Fig. 3. Action of adrenalin and papaverine on the contractility and respiration of the smooth muscle of the rabbit's aorta. Continuous line - contraction of the aortic strip; columns - values of absorption of oxygen by the rabbit's aorta. I) Control; II) adrenalin (10^{-5}), III) papaverine (10^{-3}), IV) adrenalin (10^{-5}) + papaverine (10^{-3}).

Hence, the vasoconstrictor effect of adrenalin and the vasodilator effect of papaverine may take place at some point in the chain of tissue respiration. The discovery of the points of action of adrenalin and papverine in the respiratory chain would shed additional light on the understanding of the mechanism of action of the catecholamines and vasodilator drugs.

SUMMARY

As experimentally demonstrated, adrenalin and noradrenalin increased the oxygen uptake by the aortic wall in concentrations of 10^{-5} causing the maximal contraction of the isolated rabbit aortic band. Ephedrine and serotonin, which also caused contraction of the vascular band, had almost no effect on the respiration of the aortic smooth muscles.

Of the vasodilating substances, euphylline does not change the tissue respiration, sodium nitrite has a tendency to increase the QO_2 as compared to control values, whereas papaverine depresses the tissue respiration. There is a parallelism between the capacity of papaverine to depress the adrenalin-induced contraction and reduction of oxygen uptake by the isolated rabbit aortic band in conjoint administration of adrenalin and papaverine.

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