EFFECT OF CALCIUM ON RELATIONSHIP BETWEEN THE STRENGTH OF CONTRACTION AND THE CORONARY BLOOD FLOW OF THE ISOLATED HEART

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The isolated hearts of rats and guinea-pigs were perfused through the aorta. A latex balloon of constant volume was fixed inside the left ventricle. The pressure developed in the balloon and the coronary blood flow were measured for 1 min. An increase in the Ca^{++} concentration in the perfusion fluid from 2.5 to 5 meq/liter led to a marked increase in the pressure developed and to a definite increase in the coronary flow. With a further increase in the Ca^{++} concentration to 20 meq/liter, the pressure developed increased still further, but the coronary flow was reduced. In the course of the experiment the decrease in the developed pressure and in the coronary flow took place more rapidly when the Ca^{++} concentration was increased.

When the action of Ca^{++} on the coronary circulation has been studied both vasoconstrictor [18, 20] and vasodilator [6, 8, 17] effects have been observed. These results were obtained in experiments on whole animals with an uncontrolled heart rate and they did not permit the effect of Ca^{++} on the coronary vessels to be compared with its effect on the heart muscle.

In the investigation described below the action of Ca^{++} was studied on the isolated heart when contracting at constant rate, with simultaneous measurement of the strength of its contractions and the rate of the coronary flow.

EXPERIMENTAL METHOD

The isolated hearts of rats and guinea-pigs were perfused with Krebs' solution saturated with 95% O_2+5% CO_2 at 37°C. An atrioventricular block was produced and the ventricles were made to contract by electrical stimulation at the rate of 120 beats/min. The heart was perfused through the aorta under a constant perfusion pressure of 70 mm. A latex balloon was introduced into the left ventricle through the left atrium and the pressure inside it reflected the strength of ventricular contraction. The volume of the balloon corresponding to maximal strength of contraction was first established and this volume remained constant throughout the experiment. Fuller details of the method were given previously [1]. In the course of the experiment the coronary flow was measured by collecting the fluid expelled by the right ventricle.

EXPERIMENTAL RESULTS AND DISCUSSION

During perfusion of the isolated rat heart by a solution with normal (5 meq/liter) or with half the normal (2.5 meq/liter) Ca^{++} concentration a direct relationship was found between the coronary flow and the developed pressure (Fig. 1). In the course of the experiment these indices fell gradually, but they did so

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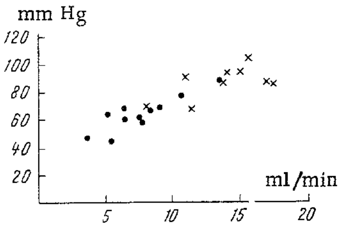

Fig. 1

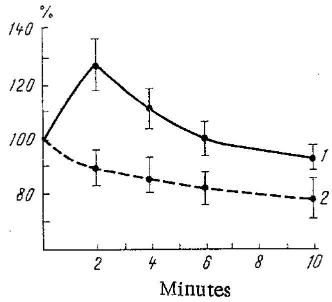

Fig. 2

Fig. 1. Relationship between coronary flow (abscissa) of the isolated rat heart and pressure developed in the left ventricle (ordinate) with normal (dots) and half the normal (crosses) Ca^{++} concentration (each dot or cross corresponds to a separate experiment).

Fig. 2. Dynamics of pressure developed (1) and of coronary flow (2) of the isolated rat heart in response to a twofold increase in the normal Ca^{++} concentration (in percent of initial values; $M \pm m$).

more sharply if the hearts were perfused with a solution containing a normal Ca^{++} concentration. If, however, the increase in Ca^{++} concentration in the solution from 2.5 to 5 meq/liter took place actually in the course of the experiment, after 5-7 min the developing pressure increased on the average by 102 ± 8%, but the coronary flow increased by only 8 ± 2% compared with its initial value.

With a further increase in the Ca^{++} concentration in the solution from 5 to 10 meq/liter (Fig. 2), the developing pressure at first increased, whereas the coronary flow fell immediately after the replacement of the solutions.

Since the rat's myocardium differs from the myocardium of other mammals in certain of its responses which are based on changes in the Ca^{++} metabolism (by the relationship between the frequency and strength of contraction [12], and by its lower sensitivity to glycosides [3] and to paired stimulation [9]), the experiments in which the Ca^{++} concentration was successively increased were carried out on the hearts of guinea pigs.

These experiments showed (Fig. 3) that the greatest increase in Ca^{++} concentration (up to 5 meq/liter) was accompanied by a marked increase in the strength of contraction and a substantial increase in the coronary flow. An increase in the Ca^{++} concentration above the normal level, however, led to a decrease in the coronary flow, despite a further increase in the pressure developed.

The results of the experiments on the hearts of guinea-pigs and rats show conclusively that an increase in the Ca^{++} concentration from 2.5 to 5 meq/liter is accompanied by consistent changes in the strength of the contractions and in the rate of the coronary flow.

In large doses Ca^{++} disturbs the relationship usually observed between the strength of contraction and the rate of the coronary flow.

The results of experiments on dogs to study the effect of Ca^{++} on the coronary blood flow are in agreement with this view. Analysis of the results of these experiments showed that the vasodilator effect of injection of Ca^{++} on the coronary vessels was always combined with an increase in the minute volume and in the arterial pressure [6, 17], while the absence of this effect or, conversely, a vasoconstrictor effect was combined with absence of an increase in the minute volume and a decrease in the rate of contraction [14, 20], i.e., a change which itself led to a decrease in the coronary blood flow [4, 16].

During prolonged injection of Ca^{++} the coronary blood flow falls after its initial increase, despite a further increase in the minute volume [17].

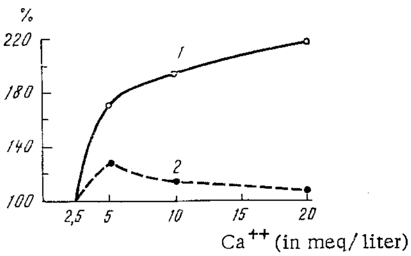

Fig. 3. Effect of an increase in Ca^{++} concentration in the solution on pressure developed (1) and coronary flow (2) of the isolated guinea pig heart (in percent of initial values; M ± m).

When the causes of this effect of Ca^{++} are analyzed it must be remembered that Ca^{++} is an important link in the chain of processes coupling excitation and contraction not only in heart muscle [2, 5, 13, 15], but also in the smooth muscles of the blood vessels [7, 10, 11, 19].

The direct effect of Ca^{++} on the vessels is thus to increase their tone. However, this effect in the working heart can be masked by the opposite vasodilator effect of the increase in the strength of the contractions. The end result is determined by the combination of these factors. The relative predominance of the direct vasoconstrictor effect of Ca^{++} (Figs. 2 and 3) can be limited to the function of the heart muscle. It is understandable that in the healthy organism, in which the Ca^{++} concentration in the plasma is under strict control, such a situation cannot arise. However, if the mechanisms regulating the Ca^{++} level in the blood are disturbed or after administration of large doses of catecholamines, one of the important components of whose action on the cell is an increase in Ca^{++} metabolism, the direct vasoconstrictor effect of Ca^{++} may evidently be one cause of the development of necrotic changes in the myocardium.

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