PROTECTIVE ACTION OF DOPA AND DOPAMINE IN EXPERIMENTAL CORONARY INSUFFICIENCY

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A number of facts suggests that dopamine, which plays the part of the immediate precursor of noradrenalin, possesses physiological functions of its own often differing essentially from the functions of the other catecholamines [6, 8]. In particular, it may give rise to very characteristic vascular effects [5, 7], possibly causing redistribution of the blood in favor of the internal organs.

The object of the present investigation was to study the effect of dopamine on the course of severe acute experimental coronary insufficiency.

EXPERIMENTAL METHOD

Acute coronary insufficiency was produced in anesthetized dogs by ligation of the anterior descending branch of the left coronary artery immediately below the origin of the circumflex branch by the method described previously [1]. After the end of the experiment the heart was removed from the animals and injected with an oily suspension of white lead under manometric control. Roentgenograms were then taken of the preparations, opened out by Schlesinger's method, and of transverse sections of the heart. Attention was concentrated on the activity of the interarterial anastomes within the heart, which was judged from the intensity of vascularization of portions of the myocardium corresponding to the ramification of the the anterior descending branch of the left coronary artery after injection of the roentgenographic contrast material into the circumflex branch.

Dopamine (10 μg/kg) was injected intravenously 30 min before ligation of the coronary artery. To raise the tissue level of dopamine, its precursor 3, 4-dihydroxyphenylalanine (DOPA) was injected intravenously in doses of 10 and 50 mg/kg.

EXPERIMENTAL RESULTS

High ligation of the descending branch of the left coronary artery led to an extensive ischemic lesion affecting the greater part of the anterior surface of the heart. The ECG taken immediately from the zone of ischemia showed the characteristic changes of severe, acute coronary insufficiency: elevation of the S-T segment and an increase in amplitude of the R wave, usually to the extent of producing a monophasic curve. The results of the high ligation of the descending branch of the left coronary artery in the control dogs were uniform in pattern: during the first minutes after occlusion the animals developed arrhythmia, quickly transformed into ventricular fibrillation. Of the 44 control dogs 42 developed fibrillation, and these animals died.

Small doses of the dopamine precursor (DOPA) and of dopamine itself had a definite protective action on this model of severe, acute coronary insufficiency. This was manifested above all in the sharp decrease in the number of animals developing ventricular fibrillation (see table).

In relation to the degree of its antifibrillatory properties dopamine was similar to the monoamine oxidase (MAO) inhibitors, while DOPA surpassed them; both preparations were much more effective than novocainamide [2]. The onset of fibrillation was prevented only by small doses of DOPA; if the dose was increased fivefold tachycardia often developed, and the proportion of cases developing fibrillation was not significantly different from the proportion in the control series.

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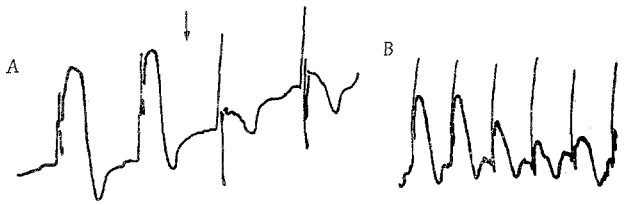

Fig. 1. Changes in the epicardial electrogram as the electrode is moved from the center of the ischemic zone toward the intact myocardium. A) control: sharp transition from elevation of S-T segment to its decline corresponds to a sharp visible border (indicated by the arrow); recording speed 50 mm/sec; B) after injection of DOPA (10 mg/kg): gradual decline of S-T segment; recording speed 25 mm/sec.

Effect of Dopamine and DOPA on Development of Ventricular Fibrillation in Dogs

Preparation	Dose (in mg/kg)	No. of experiments	Results ligation of coronary artery		
			Fibrillation absent	Fibrillation developed	P (compared with control)
Dopamine	0.01	8	4	4	< 0.05
Dopa	10	10	7	3	< 0.001
Control	—	44	2	42	

The electrocardiographic changes arising after ligation of the coronary artery against the background of DOPA and dopamine were similar to the changes observed in the control animals, although the impression was gained that they were slightly less marked. The electrographic border of the ischemic zone was less sharply defined. As the electrode was moved from the center of the ischemic zone of the myocardium toward the undamaged part, as a rule the S-T segment was lowered gradually, and the sudden change from the rise of the S-T segment to its fall characteristic of the control dogs was not found (Fig. 1). This obliteration of the electrographic border of the ischemic zone was similar to that observed during the action of MAO inhibitors, causing activation of the intercoronary anastomoses [1, 2], and it was therefore decided to investigate the arterial system of the heart.

The functional activity of the intercoronary anastomoses in the heart of the control dogs was very small: in two-thirds of the experiments the contrast material injected into the circumflex artery almost completely failed to enter the system either of the anterior descending branch of the left coronary artery or of the right coronary artery (Fig. 2). In the other cases a "relative ischemia" was observed—the contrast material entered the vessels of the anterior descending branch but they were filled to a much lesser degree than the vessels of the circumflex system.

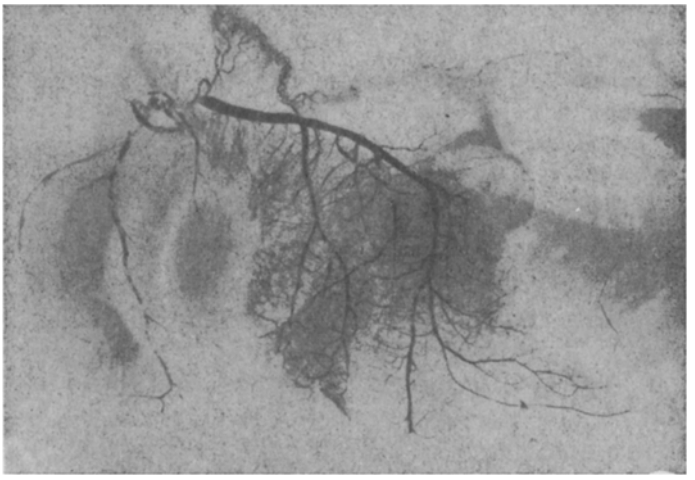

Fig. 2. Almost complete absence of anastomoses between the systems of the circumflex branch, into which the contrast material was injected, and of the ligated anterior descending branch of the left coronary artery of a control dog. The arrow points to the site of ligation. Angioroentgenograms of ventricles opened out by Schlesinger's method.

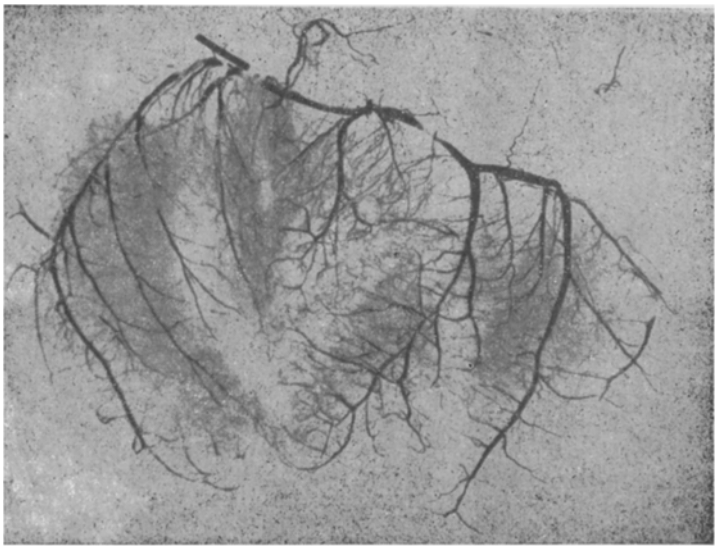

Fig. 3. Angioroentgenogram of an opened-out dog's heart. Dopamine (10 mg/kg) was injected 30 min before high ligation of the anterior descending branch of the left coronary artery. No fibrillation developed.

A different picture was observed in the angioroentgenographic study of the heart of the animals receiving DOPA and dopamine. Of the 14 hearts investigated among the animals of this group (fibrillation was prevented in 11), the presence of a zone of ischemia sharply demarcated from the surrounding region, with the almost complete absence of anastomoses, characteristic of the control dogs, was found in only two animals. Three animals had "relative ischemia," and in the heart of nine dogs receiving dopamine or DOPA, the region of ischemia was hardly distinguishable angioroentgenographically from the surrounding myocardium (Fig. 3). On the angioroentgenograms of these dogs numerous vessels could be seen entering the zone of ischemia from the intact areas. Not only did the contrast material pass from the system of one branch of the left coronary artery into the system of another of its branches, but it also entered the branches of the right coronary artery.

Dopamine and small doses of DOPA thus had a marked protective action on the ischemic heart, increasing the functional activity of the intercoronary anastomoses, obliterating the sharp enectrographic border between the ischemic and the intact regions of the myocardium, and preventing the onset of ventricular fibrillation.

This property of activating intercoronary anastomoses after only a single injection is possessed by very few substances besides dopamine and DOPA. It is interesting to note that these include the MAO inhibitors [1, 2] and another catecholamine – noradrenalin [3].

On the other hand, it may be considered that in natural conditions the rhythmic activity of the heart is related to the tissue dopamine level. In contrast to noradrenalin, for instance, dopamine is known to be concentrated mainly in the region of the pacemakers – the sino-atrial and atrio-ventricular nodes [4].

LITERATURE CITED

1. E. A. Zhuk, N. K. Popova, et al., Pat. Fiziol., No. 5, 36 (1964).
2. N. K. Popova, Farmakol. i Toksikol., No. 1, 44 (1966).
3. A. V. Sapozhkov, Byull. éksp. Biol., No. 8, 72 (1964).
4. E. T. Angelakos, Circulat. Res., 16, 39 (1965).
5. J. N. Eble, J. Pharmacol. Exp. Ther., 145, 64 (1964).
6. P. L. McGeer, J. Neuropsychiat, 4, 247 (1963).
7. J. L. McNay R. H. McDonald, Jr, et al., Circulat. Res., 16, 510 (1965).
8. T. L. Sourkes, Biochemical and Neurophysiological Correlation of Centrally Acting Drugs, Praha 35 (1964).