BIOCHEMISTRY AND BIOPHYSICS

A STUDY OF THE METABOLISM OF PHOSPHORUS COMPOUNDS IN THE HEART, WITH THE AID OF RADIOACTIVE PHOSPHORUS

COMMUNICATION III. THE EFFECT OF THE PAVLOV REINFORCING NERVE ON THE RATE OF EXCHANGE OF HIGH-ENERGY PHOSPHORUS COMPOUNDS IN THE NORMAL AND IN THE PATHOLOGICALLY ALTERED HEART

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In a previous discussion [3], we undertook the study of the effect of the cardiac reinforcing nerve, discovered by I. P. Pavlov [2], on the metabolism of adenosine triphosphate, phosphocreatine and inorganic phosphorus in the heart of healthy dogs. On the basis of the comparison of the specific activity of the indicated fractions, 15 minutes after radiophosphorus was administered intravenously under normal conditions and with irritation of the reinforcing nerve, we drew inferences as to an increase in the turnover rates of ATP and phosphocreatine in the heart, under the influence of this nerve.

However, those data, obtained within a given period after the administration of P^{32}, did not preclude the possibility of a different pattern of dynamics operating in the penetration of P^{32} into the compounds under discussion, under normal conditions and upon irritation of the reinforcing nerve, and more precise studies of the dynamics involved were therefore in order. In accord with the above, the present discussion sets out, first of all, to determine the effect of the reinforcing nerve on the rate of exchange of ATP and phosphocreatine in the heart, with the aid of P^{32} incorporation studies at different intervals after administration of the label, and, secondly, to find out how the effect of reinforcing nerve on the exchange of these substances varies in response to pathological conditions.

The results obtained by B. A. Vinokurov [1] are, of the data available in the literature, the ones bearing the most direct relation to the problem under discussion. The author disclosed that, on asphyxia brought about in experiments on animals by way of cessation of artificially induced respiration, and on hypoxemia, caused by forcing a gas mixture deficient in oxygen into the lungs of animals, a sharp drop-off in the positive effect resulting from stimulation of the reinforcing nerve is observed. In severe degrees of hypoxia, this effect disappears entirely, while in especially severe cases of oxygen starvation, irritation of the reinforcing branches often contributes to the onset of palpitations on the part of the ventricles of the heart.

Data on variations in the influence of the extracardial nerves on exchange processes in the heart under pathological conditions are not available in the literature, as far as we were able to determine. Of various pathological states, we considered it most interesting to make a study of the changes ensuing in the course of the turnover processes of ATP and phosphocreatine, taking place in the heart in response to reinforcing nerve actions when a myocardial infarct is induced experimentally.

EXPERIMENTAL METHOD

The experiments were carried out on 64 dogs. In all cases, the thorax was opened up while the dogs were under morphine-barbamyl* narcosis, and the cardiac reinforcing nerve was prepared with the animals under artificially induced respiration. Radioactive phosphorus was administered intravenously to some of the animals 15 minutes after this. In the other animals, myocardial infarction was brought about by ligating the left descending coronary artery, and 15 minutes after the ligature, when the electrocardiogram disclosed symptoms of acute local impairment of coronary circulation. Radiophosphorus was also administered to these animals. At preassigned intervals thereafter (5,10,15,20,25,30, and 60 minutes), an abscission of the apex of the heart was performed, while, in the infarction experiments, the section of the heart cut away contained both a portion of the ischemia and the tissue surrounding it.

The heart studies carried out in the first series of experiments took place on a background of normal performance and on irritation of the reinforcing nerve in normal animals; in the second series of experiments, on a background of normal performance and on irritation of the reinforcing nerve in dogs suffering from a myocardial infarct.

The part of the heart cut away was quickly frozen in liquid nitrogen, carefully ground to a fine power and subjected to biochemical investigation. The research technique utilized has already been described in a previous communication and will not be repeated in the present discussion. In all the experiments, arterial pressure and the electrocardiogram were recorded as a control of the functional state of the heart.

EXPERIMENTAL RESULTS

A physiological analysis of the data which we obtained revealed a considerable drop in the reinforcing effect resulting from irritation of the reinforcing nerve in response to myocardial infarction.

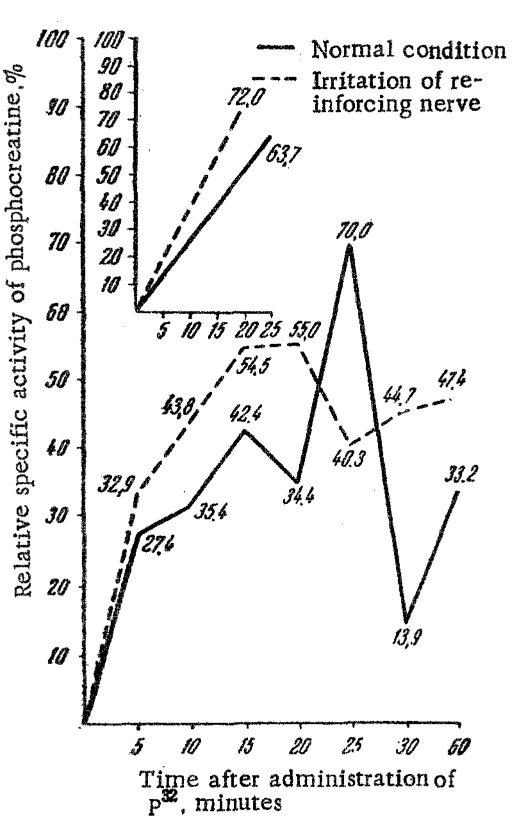

Fig. 1. Variations in the relative specific activity of phosphocreatine in the heart in response to irritation of the reinforcing nerve in normal dogs.

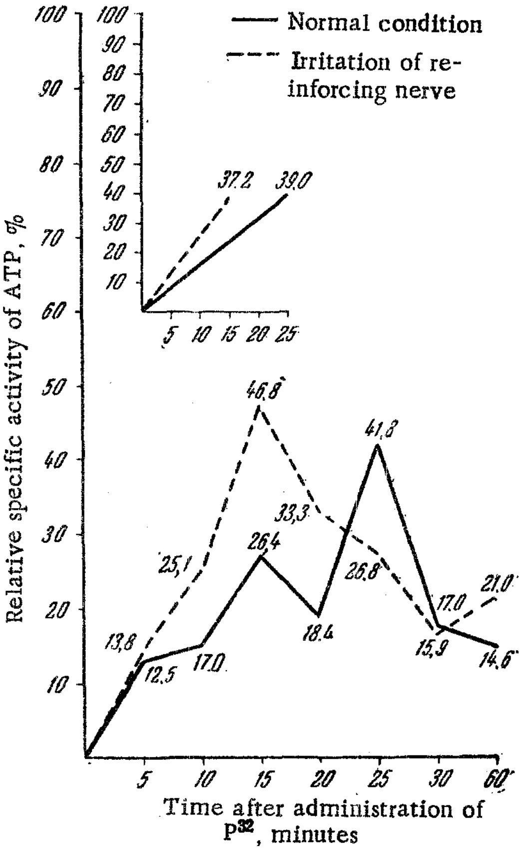

Fig. 2. Variations in the relative specific activity of ATP in the heart in response to irritation of the reinforcing nerve in normal dogs.

* Russian trade name.

The biochemical data were first computed in terms of the specific activities of inorganic phosphorus, phosphocreatine and ATP, and plotted as curves. A comparison of the curves of the specific activities of ATP and of phosphocreatine bring confirmation to the conclusion drawn in the previous communication relating to the increases in ATP and phosphocreatine turnover in response to irritation of the reinforcing nerve. However, these findings still do not justify our inferring that the exchange rates of these substances are stepped up, since the intensified turnover rates of ATP and phosphocreatine could be the result of an exchange taking place with inorganic phosphorus at a high turnover rate. To preclude that possibility, we expressed our data in terms of relative specific activity, referring the specific activities of ATP and of phosphocreatine to the specific activity of tissue inorganic phosphorus taken as the standard. Taking into account the fact that the activity of the latter might show an increase due to blood inorganic phosphorus present in cardiac muscle, the specific activity of the last mentioned being far from uniform at different intervals after the administration of P^{32}, we first introduced into the specific activity values for tissue inorganic phosphorus the corresponding corrections. For this purpose, the specific activity of blood inorganic phosphorus was determined for all the experiments and the amount of blood present in the cardiac muscle was ascertained on the basis of hemoglobin content in the aqueous extract, by spectrophotometric measurement.

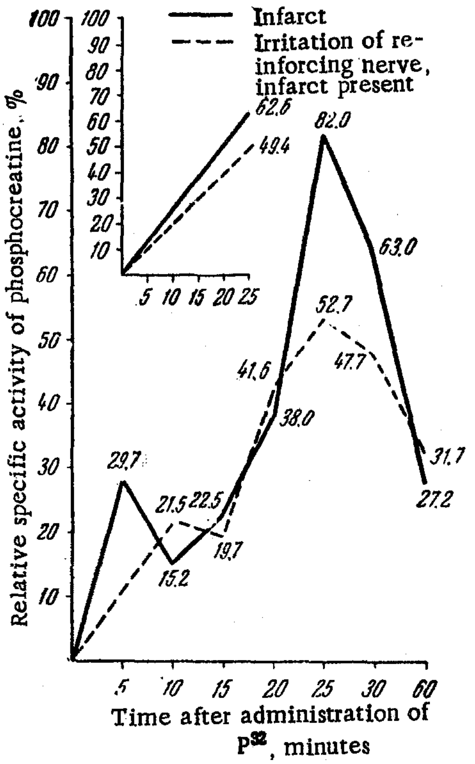

Fig. 3. Variations in the relative specific activity of phosphocreatine in the heart in response to irritation of the reinforcing nerve in dogs suffering from a myocardial infarct.

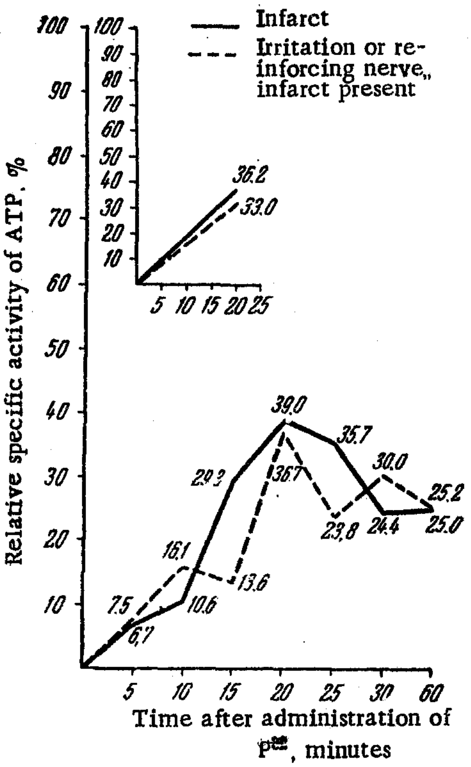

Fig. 4. Variations in the relative specific activity of ATP in the heart in response to irritation of the reinforcing nerve in dogs suffering from a myocardial infarct.

The curves obtained for the relative specific activities of ATP and phosphocreatine under normal conditions and upon irritation of the reinforcing nerve are shown in Figs. 1 and 2. The turnover rates for ATP and phosphocreatine find their expression in the slope of the curves. However, the shape of these curves, each point on which represents an arithmetic mean of determinations from several animals, renders more complicated the quantitative calculation of the general trend of the process. To facilitate the operation, we carried out a statistical treatment of the data obtained using the method of least squares, making the assumption that the rate of incorporation of P^{32} into the fraction studied per element of the curve over a range from 0 to the maximum was proportional to time. As a result of that treatment, we obtained straight lines corresponding to those elements of the curve. A comparison of the slope of those lines revealed, with greater clarity than was the case with the corresponding curves, that the exchange of ATP and of phosphocreatine, on irritation of the reinforcing nerve, underwent an acceleration.

Other measurements were obtained by irritation of the reinforcing nerve in dogs having a myocardial infarct. The curves associated with the relative specific activity of ATP and phosphocreatine and on irritation of the reinforcing nerve in dogs with a myocardial infarct are shown in Figs. 3 and 4.

A comparison of these curves and the corresponding straight lines plotted according to the method of least squares demonstrated that the rate of ATP and phosphocreatine exchange, with myocardial infarct present, not only did not increase in response to irritation of the reinforcing nerve but, conversely, showed a decline.

The absence of any increase in the rate of ATP and phosphocreatine exchange characteristic of the influence of the reinforcing nerve is evidently linked to the fact that the compensatory possibilities which exist in the heart for enhancing the exchange of those substances turns out to be exhausted when an acute impairment of coronary circulation in the heart takes place, and a subsequent stepping up of the rate of exchange of those substances, in response to irritation of the reinforcing nerve, becomes impossible.

In this manner, as a result of the disturbances occurring in the heart in myocardial infarction, cardiac muscle, exposed to the corresponding actions of the nerve, is deprived of the possibility of intensifying its contractions by virtue of the stepping up of the exchange of the basic energy sources, adenosine triphosphate and phosphocreatine.

SUMMARY

The results of study of the rapidity of metabolism of adenosinetriphosphate (ATP) and phosphocreatine (PC) in the heart in stimulation of Pavlov reinforcing nerve are presented. Experiments were performed with the aid of radioactive phosphorus both on healthy dogs and in animals with myocardial infarction. Increased heart contractions caused by this nerve in healthy dogs are associated with a more rapid metabolism of ATP and PC in the cardiac muscle. The effect of stimulation of reinforcing nerve in myocardial infarction is less pronounced. This is probably connected with the fact that the metabolism of ATP and PC in the heart is not accelerated but, on the contrary, delayed in these conditions.

LITERATURE CITED

[1] B. A. Vinokurov, Influence of the Efferent Nerves on the Heart in Asphyxia and Hypoxemia, Thesis, reports of session devoted to problems of the physiology and pathology of the cardiovascular system, Leningrad, (1955).*

[2] I. P. Pavlov, Efferent Cardiac Nerves, Thesis, (1889).*

[3] M. E. Raiskina, "Exchange studies of phosphorus-containing compounds in the heart with the aid of radioactive phosphorus; Communication II; Influence of the Pavlov reinforcing nerve of the rate of turnover of phosphorus-containing compounds in the dog heart," Byull. Eksptl. Biol. i Med., No. 5, 44-47 (1956).**

* In Russian.

** Original Russian pagination. See C.B. Translation.