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GLUCONEOGENETIC EFFECT OF PROSTAGLANDIN $F_{2\alpha}$ UNDER NORMAL CONDITIONS AND IN MYOCARDIAL INFARCTION

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KEY WORDS: myocardial infarction; prostaglandin $F_{2\alpha}$; carbohydrate and nitrogen metabolism; gluconeogenesis.

Biological and physiological aspects of the action of prostaglandins (PG) under normal and pathological conditions are widely familiar [1, 8]. Studies in the field of cardiology have been particularly numerous [2, 6, 9, 10]. It is not disputed that the differences in the action of PG of different classes may be ultimately due to changes in metabolism. However, the metabolic action of PG, especially at the whole body level, remains virtually unstudied.

The aim of this investigation was to study changes in gluconeogenesis in rats with myocardial infarction (MI) by comparison with normal rats. Gluconeogenesis is the resultant of major components of metabolism and it undergoes significant changes in MI [4].

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 232 g. The animals were divided into two groups. Animals of group 1 received no PG, those of group 2 received $PGF_{2\alpha}$. Both groups 1 and 2 included normal rats (control) and rats with MI (3rd, 10th, and 20th day after injection of $PGF_{2\alpha}$ and ligation of the coronary artery).

To discover the dose of PG, the preparation was injected into the caudal vein of rats in doses of 25, 50, or 100 μg/kg body weight. The glucose concentration was then determined in their peripheral blood after 30 sec, 1, 3, 5, 10, and 30 min, and 1, 2, 3, 4,5, and 24 h. The greatest rise of the rats' blood glucose level occurred 5 min after injection of $PGF_{2\alpha}$ in a dose of 50 μg/kg. This time and dose were working values and were used to study the metabolic action of PG. The rats were starved beforehand for 24 h. MI was induced by the method in [5], and its presence was monitored histologically and electrocardiographically.

Concentrations of glucose and lactate in the blood were determined by enzymic methods, pyruvate by a modified Umbreit's method, urea with the help of diacetylmonooxime, ammonia, and glutamine [7]. The glycogen concentration was determined in the liver and heart and skeletal muscles, and activity of the two key enzymes of gluconeogenesis, namely glucose-6-phosphatase (G6Pase) and fructose-1,6-diphosphatase (F-1,6-DPase) was determined in tissues of the liver and renal cortex by methdos in [11, 12]. Protein was determined by Lowry's method. The experimental results were subjected to statistical analysis by "Yamaha" computer.

EXPERIMENTAL RESULTS

After intravenous injection of $PGF_{2\alpha}$ the blood glucose level of the normal rats showed a statistically significant increase ($p < 0.02$) but the lactate and pyruvate levels rose by 25 and 18% respectively (Table 1). Meanwhile the blood urea of the rats rose by 2.44 times, and glutamine by 1.24 times, whereas the ammonia concentration showed a tendency to fall ($p > 0.05$). $PGF_{2\alpha}$ probably stimulates glucose synthesis in normal rats from noncarbohydrate, mainly

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TABLE 1. Effect of $PGF_{2\alpha}$ on Some Parameters of Carbohydrate and Nitrogen Metabolism in the Blood (in mM) of Normal Rats and Rats with MI (M ± m)

Group of animals	Day after ligation of coronary artery	Parameters					
		glucose	lactate	pyruvate	ammonia	urea	glutamine
I	Control (1)	3,20±0,12	1,140±0,075	0,328±0,021	0,0405±0,0029	2,98±0,15	0,0657±0,0049
	3 (2)	4,50±0,18*	2,790±0,193*	0,400±0,030	0,0822±0,0076*	7,04±0,39*	0,0696±0,0029
	10 (3)	3,60±0,11*	2,470±0,170*	0,470±0,037*	0,0558±0,0050*	5,61±0,42*	0,0850±0,0040*
	20 (4)	3,30±0,10	2,130±0,076*	0,409±0,026*	0,0481±0,0031	3,94±0,22	0,0759±0,0062
II	Control (1)	4,00±0,23*	1,42±0,230	0,390±0,028	0,0344±0,0035	7,27±0,64*	0,0814±0,0019*
	3 (2)	4,90±0,34*, **	2,15±0,100*, **, ***	0,660±0,034	0,0570±0,0079*, **, ***	4,14±0,41*, **, ***	0,1273±0,0075*, **, ***
	10 (3)	4,70±0,28*, **, ***	2,10±0,190*, **	0,350±0,017	0,0505±0,0052**	4,03±0,21*, **, ***	0,1169±0,0067*, **, ***
	20 (4)	3,90±0,31*, ***	1,76±0,160***	0,470±0,055	0,0423±0,0025	5,22±0,87*	0,0889±0,0047*

Legend. *) Differences from group 1/I significant; **) compared with 1/II ***) comparison of 2, 3, and 4 of group I/2, 3, and 4 of group II. Number of animals in each group 10-20.

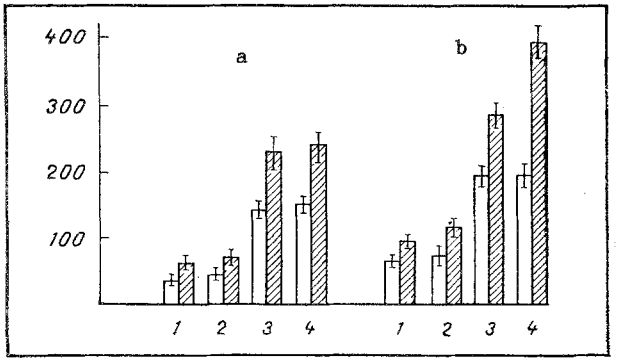

Fig. 1. Changes in G6Pase and F-1,6-DPase activity of enzymes (in μmoles inorganic phosphorus/g protein/min at 37°C). 1) Healthy rats, 2) healthy rats receiving $PGF_{2\alpha}$; 3) rats 3 days after ligation of coronary artery; 4) similar animals receiving $PGF_{2\alpha}$. Unshaded columns – G6Pase; shaded – F-1,6-DPase.

nitrogenous, compounds. It might be supposed that elevation of their blood glucose level is the result of intensified glycogenolysis. However, this was not so. On the contrary, injection of $PGF_{2\alpha}$ increased the glycogen content in the liver on average by 3.14 times, in the heart by twice, and in the skeletal muscle by 2.59 times. The possibility cannot be ruled out that $PGF_{2\alpha}$ promotes accumulation of glycogen in the tissues by a mechanism of gluconeogenesis. This hypothesis was tested specially.

For this purpose, activity of the two key enzymes of gluconeogenesis was determined in the liver and the renal cortex – principal organs for glucose synthesis de novo. Figure 1 shows that $PGF_{2\alpha}$ increased the activity of G6Pase and F-1,6-DPase significanty in normal rats. The shifts in the parameters of carbohydrate and nitrogen metabolism and in the glycogen concentration in the organs and tissues, and changes in the activity of the key enzymes of gluconeogenesis thus indicate that $PGF_{2\alpha}$ increases the intensity of synthesis of glucose de novo in normal rats.

The effect of $PGF_{2\alpha}$ on the above-mentioned parameters was then studied in rats with extensive MI. The writers showed previously for the first time that the rate of glucose synthesis from noncarbohydrate compounds is sharply increased in rats with MI [3, 4]. $PGF_{2\alpha}$ always raised blood levels of glucose, lactate, pyruvate, urea, and glutamine in rats with MI (Table 1), whether compared with normal intact rats or with healthy rats which received a single dose of PG. In other words, more marked shifts of nitrogen and carbohydrate metabolism are induced in rats with MI by $PGF_{2\alpha}$ than in animals of the corresponding control groups. PG evidently potentiate the functioning of systems responsible for de novo synthesis of glucose – a metabolite which is particularly essential for maintaining the additional work of the injured myocardium. This conclusion can also be deduced from the following data.

A single injection of $PGF_{2\alpha}$ into rats with MI was shown to lead to the production of more newly formed glucose, on average by 0.7 mM/day than in the same animals but not receiving

PG. This result is connected with increased transformation of lactate into glucose ($r = 0.94$; $p < 0.001$). Meanwhile PG inhibited tissue protein breakdown in rats.

The writers showed previously that ligation of the coronary artery leads to a sharp fall in the tissue glycogen level of rats [3]. However, after injection of $PGF_{2\alpha}$, the glycogen concentrations in the liver and heart and skeletal muscles were almost identical, normal in value, and higher than in rats with MI not receiving PG, by 9.1, 5.2, and 3.9 times, respectively (3rd day), by 3.4, 2.7, and 3.2 times (10th day), and by 2.7, 2.0, and 2.6 times, respectively (20th day of the experiment). Consequently, in rats with MI, glycogenolysis is intensified under the influence of $PGF_{2\alpha}$, and this has a marked cardioprotective action with respect to glycogen.

Further confirmation of the above was obtained by the study of G6Pase and F-1.6-DPase activity (Fig. 1): the increase in activity of these enzymes was greater in rats with MI due to coronary occlusion, and receiving PG injections. This reflects the higher rate of transformation of noncarbohydrate compounds into glucose.

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EFFECT OF FLUORINE ON CARDIAC ARRHYTHMIAS IN RATS

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KEY WORDS: calcium chloride arrhythmias; fluorine; blockade; inward calcium current.

Since hyperactivation of cardiomyocytes and the development of cardiac arrhythmias are linked with intensive inflow of Ca^{++}, blockers of slow Ca channels have been found to be effective antiarrhythmic agents [2, 6, 7]. Considering data showing that intracellular injection of fluorine ions induces blockade of the inward Ca current in the somatic membrane of neurons [5, 8], it was decided to test the antiarrhythmic activity of fluorine in experiments with a calcium chloride model of cardiac arrhythmia.

EXPERIMENTAL METHOD

Experiments were carried out on 58 control and 56 experimental noninbred male rats weighing 260-350 g. Throughout the experiment the animals were kept in the animal house of the Institute on a standard diet (pellet food, milk products). Sodium fluoride was used in tablet

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