Effect of Dipyridamole on the Glycogen Metabolism in the Normal and Ischemic Canine Myocardium

In the preceding paper[1], we reported that pretreatment of the dog with nitroglycerin inhibited the rate of acceleration of utilization of myocardial glycogen induced by ligation of the coronary artery. In the present study, the effect of dipyridamole on the myocardial utilization of glycogen and levels of high-energy phosphate compounds were investigated. Dipyridamole was chosen because it is relatively ineffective against anginal attack, inspite of having a powerful coronary dilating action[2,3]. Since nitroglycerin is the most effective antianginal agent, inspite of having only a moderate coronary dilating action[2,3], we expected that the effect of dipyridamole on the myocardial metabolism during coronary ligation would probably be different from that of nitroglycerin.

The methods employed in the present study are the same as described in our preceding report[1]. Mongrel dogs anesthetized with pentobarbital were used. In experiments with ischemic hearts, one of the small branches of the left coronary artery was ligated 5 min after i.v. injection of saline or dipyridamole (250 μg/kg). The hearts were removed 1.5, 3, 7, or 30 min after the coronary ligation, and immediately frozen with freezing clamps. The endo- and epicardial portions of the left ventricular wall, which had been perfused by the ligated coronary artery, were carefully taken for determination of glycogen, glucose-6-phosphate (G6P), lactate, adenosine triphosphate (ATP) and phosphocreatine (PCr), and activities of phosphorylase *a* and *a* + *b*. In experiments with non-ischemic hearts, the hearts were removed 5 min after the injection without ligation of the coronary artery.

Results. Results are shown in the Figure and the Table. Since the results concerning the control (saline-injected) dogs were essentially the same as those obtained in our preceding study, the data on control dogs shown in the Figure and the Table are cited from our preceding experiments[1].

Experiments with non-ischemic hearts. Pretreatment with dipyridamole influenced neither levels of glycogen, G6P, lactate, ATP and PCr, nor activities of phosphorylase *a* and *a* + *b*, in each of the endo- and epicardial layers of the left ventricle.

Experiments with ischemic hearts. Pretreatment with dipyridamole modified the pattern of acceleration of glycogenolysis and glycolysis induced by the coronary ligation as described below. After the coronary ligation, glycogen decreased temporarily followed by a secondary slow decrease in the control dogs, but in the dipyridamole-injected dogs it decreased only slowly. Duration of increase in G6P after the coronary ligation was relatively short in the dipyridamole-injected dogs. The anaerobic lactate production due to the coronary ligation was markedly augmented by the pretreatment with dipyridamole in the endo- and epicardial layers, especially in the former. During the coronary ligation, ATP changed little in the control dogs, but in the presence of dipyridamole it slightly decreased. Both the endo- and epicardial PCr levels decreased slowly after the coronary ligation, followed by a gradual increase in the control dogs; but in the presence of dipyridamole, these levels decreased rapidly after the coronary ligation without a following increase. Activity of phosphorylase *a* in the endo- and epicardial layers increased markedly after the coronary ligation in the control dogs, but in the presence of dipyridamole it did not increase markedly.

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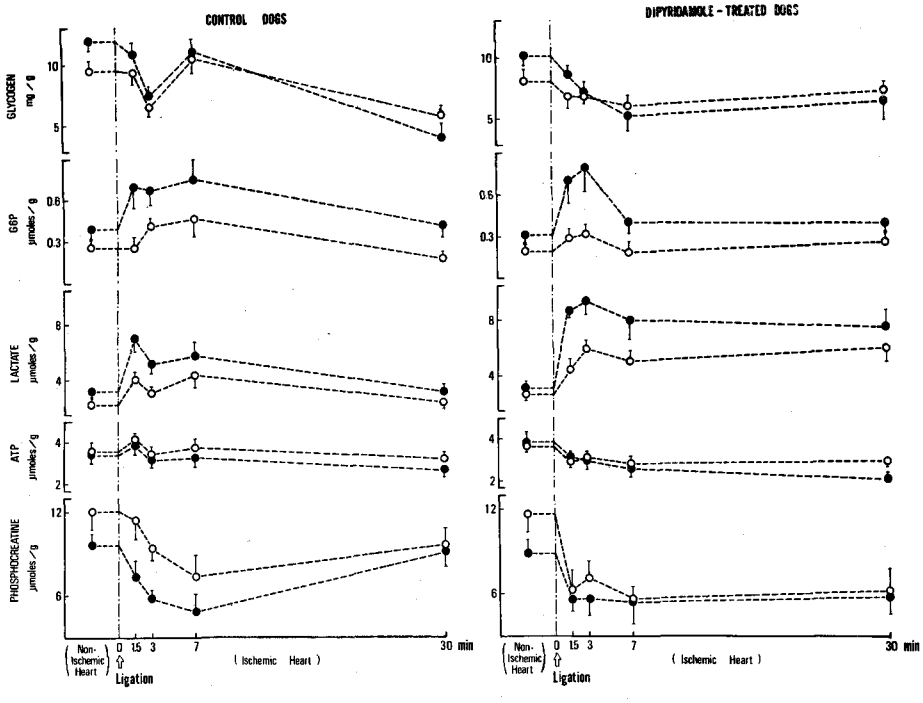

The effect of ligation of one of the small branches of the anterior descending coronary artery on the endocardial (solid circle) and epicardial (open circle) levels of glycogen, G6P, lactate, ATP and PCr in control (saline-injected) and dipyridamole-treated dogs. The small branch was ligated 5 min after the injection. The dose of dipyridamole injected i.v. is 250 μg/kg. Each point with a bar represents mean ± SEM of 6 to 8 hearts. The data on control dogs are cited from our preceding report[1].

The activities of phosphorylase in the normal and ischemic hearts and the effect of dipyridamole on these activities (μmoles Pi released/g-wet tissue/min)

		Phosphorylase *a* (without AMP)		Phosphorylase *a* + *b* (with AMP)		
		Endocardial layers	Epicardial layers	Endocaridal layers	Epicardial layers	
Control dogs[a]						
Time after ligation						
Before	(8)	5.0 ± 0.5	3.2 ± 0.4	16.6 ± 0.5	12.6 ± 0.3	(Non-ischemic)
1.5 min	(7)	8.3 ± 1.4	7.9 ± 1.3	16.8 ± 1.7	12.7 ± 1.4	
3	(8)	9.3 ± 1.0	7.1 ± 1.2	15.8 ± 1.4	12.9 ± 1.4	(Ischemic)
7	(7)	6.0 ± 0.4	3.9 ± 0.3	16.4 ± 0.7	11.9 ± 0.8	
30	(6)	4.7 ± 0.3	2.8 ± 0.6	14.9 ± 1.1	11.3 ± 1.2	
Dipyridamole-treated dogs						
Time after ligation						
Before	(8)	3.6 ± 0.8	2.6 ± 0.4	15.7 ± 0.6	13.2 ± 0.4	(Non-ischemic)
1.5 min	(6)	6.4 ± 0.8	3.6 ± 0.8	13.4 ± 1.3	12.3 ± 0.4	
3	(6)	5.0 ± 0.4	3.1 ± 0.7	16.2 ± 1.0	13.3 ± 1.1	(Ischemic)
7	(6)	4.5 ± 0.4	3.2 ± 0.5	14.6 ± 0.9	12.8 ± 0.9	
30	(6)	3.9 ± 0.5	3.6 ± 0.4	16.2 ± 1.1	12.6 ± 0.4	

Values are mean ± SEM. Number of animals in parenthesis. [a]The data on control dogs are cited from our preceding report[1].

These results indicate that the effect of dipyridamole is different from that of nitroglycerin. It should also be noted that the degree of reduction in myocardial ATP and PCr levels induced by myocardial ischemia was augmented by the pretreatment with dipyridamole, although there are reports[4,5] indicating that dipyridamole considerably increases myocardial ATP level which has been reduced by anoxia.

Summary. Pretreatment of the dog with dipyridamole tended to increase the rate of acceleration of anaerobic metabolism in the myocardium induced by ligation of a small branch of the coronary artery.

K. Ichihara and Y. Abiko

Department of Pharmacology, Asahikawa Medical College, 3-13 Kaguraoka, Asahikawa (Japan 071-01), 20 May 1975.

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Modification of the Contractile Responses of Rabbit Mammary Strips to Oxytocin by Prostaglandin E_1

The development and the physiological functions of the mammary gland are dependent upon the sequential action of several hormones. To date, possible effects of prostaglandins on this organ have been investigated only to a very limited extent. It has been noted that prostaglandin E_1 (PGE_1) inhibits the milk ejection response to oxytocin in lactating rabbit mammary glands[1], and that prostaglandins possess milk-ejecting activity[2] in the guinea-pig, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ being considerably more potent than PGE_1. In our laboratory it was established that prostaglandins effectively stimulate adenylate cyclase activity from rabbit mammary tissue[3]. We present here some initial observations on the interaction of PGE_1 and oxytocin in isolated strips from mammary gland of pregnant and lactating rabbits.

Materials and methods. Pregnant White New Zealand rabbits were sacrificed 3 days before expected term or 11 days post partum. Since oxytocin responsiveness begins several days before parturition and reaches a maximum between the 9th and 44th day after parturition[4], we hoped our timing would reflect both minimal and optimal glandular responsiveness.

Prior to surgery, animals were stunned and subjected to cervical dislocation. Glandular tissue was exposed by dissecting and retracting the covering skin, ligating arterial and venous vessels supplying the glands and dissecting the entire glandular mass. The procedure lasted about 10 min. After removal, the glands were rinsed with cold Krebs bicarbonate solution (pH 7.4) to remove blood and milk. Strips (about 100 × 10 × 4 mm) were cut using, however, a different cutting orientation than other workers. Radial strips[5] and strips cut along the plain of the abdomen[4], extending from one teat to another across the midline, have been used by others. We cut strips in a circumferentially disposed fashion with respect to the teat. Strips were placed into cold Tyrode's solution (pH 7.2) aerated with 95% O_2/5% CO_2 and stored at 4 °C until used 48 h later. Prior to mounting in an organ bath, strips were trimmed with razor blades to final dimension of about 60 × 2–3 × 2–3 mm. Care was taken to remove excess connective tissue.

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