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.

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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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The strips were mounted in organ baths[4] containing Tyrode's solution (37 °C, pH 7.2) aerated with 95% O_2/5% CO_2. Contractile activity was monitored by Grass force-displacement transducers (FT O3C) and recorded by a Beckmann Dynograph. Strips were allowed to equilibrate at a resting tension of 0.5 g which was readjusted frequently until holding constant. At this tension, responses should be submaximal[4], and thus we hoped to detect response enhancement most easily. Addition of hormone solutions was done in small quantities, not causing any effects based on volume alone. Between drug additions, the bath fluid (19.75 ml) was changed 3 times and, after a period of 15 min rest, changed 2 more times. Further drugs were added after another 10 min of rest.

PGE_1 was kindly supplied by Dr. J. PIKE (Upjohn Co.) and kept as a stock solution of 2.85×10^{-6} *M*. Synthetic oxytocin (475 IU/mg) was kindly supplied by Dr. R. WALTER, Mt. Sinai School of Medicine, New Vork.

Results and discussion. Mammary strips from both pregnant and lactating rabbits responded to oxytocin. The former were about 100 times less responsive than the latter. In strips from pregnant rabbits, PGE_1 administration prior to oxytocin enhanced the contractile effect of the latter hormone (Figure 1). This increased response occurred when PGE_1 was added either 1 or 15 min prior to oxytocin. Higher doses of PGE_1 caused no further enhancement. The threshold dose of oxytocin was not altered by the presence of PGE_1.

In contrast, when strips from lactating rabbits were tested, PGE_1 administration caused a reduced oxytocin sensitivity (Figure 2). This effect was evident only after long-term exposure (15 min) to PGE_1. We also observed some degree of tachyphylaxis to oxytocin in strips from lactating animals. This allowed only 2 determinations per strip.

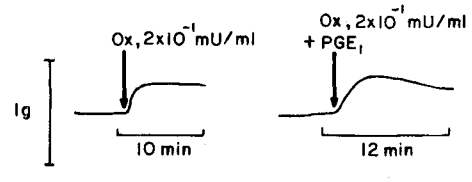

Fig. 1. Potentiation of the oxytocin response in a mammary strip from pregnant rabbit by PGE_1 (15×10^{-8} *M*).

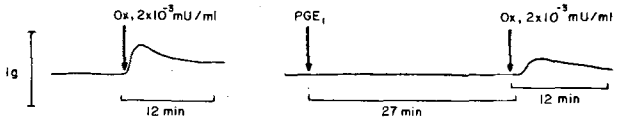

Fig. 2. Inhibition of the oxytocin response in a mammary strip from a lactating rabbit by PGE_1 (1.5×10^{-8} *M*).

Threshold doses for oxytocin were about 1.5 and 0.02 μU/ml in strips from pregnant and lactating animals, respectively; these values changed to 0.6 and 0.4 μU/ml after prior exposure of strips to about 1.5×10^{-8} *M* PGE_1.

The present study provides in vitro confirmation of the in vivo observations of an inhibitory effect of PGE_1 on oxytocin responsiveness of the lactating rabbit mammary gland[1]. Since this effect can be demonstrated on the level of isolated strips, it appears that PGE_1 acts directly on the myoepithelium and does not involve some preceding systemic event.

Since PGE_1 action is functionally opposite in strips from pregnant rabbits compared to strips from lactating animals, this suggests the existence of two different mechanisms of action of prostaglandins, one or both of which may be differentially expressed during periods of glandular development. Conceivably such developmental changes may occur either on the level of PGE_1 action (receptors) or PGE_1 metabolism. Both inhibition and enhancement or potentiation by prostaglandins of smooth muscle contracting agents has been described in the literature[6]. However, to our knowledge, opposing actions in the same organ as a function of its developmental or endocrine state have not been observed to date.

The fact that prostaglandins stimulate adenylate cyclase from mammary gland may be of relevance to the present observations. However, this hormone-sensitive enzyme was thought to be present in secretory cells[3], and it has not yet been established whether or not myoepithelial cells also contain a prostaglandin sensitive cyclase system. Considering the diverse roles of prostaglandins in reproductive physiology as well as the fact that this class of compounds is now in use for therapeutic purposes, it seems of interest to clarify further the possible physiological and pharmacological effects of these agents on the mammary gland.

Summary. PGE_1 administration to isolated strips from pregnant and lactating rabbit mammary gland resulted in different effects on oxytocin-induced contractions. In strips from pregnant animals, oxytocin action was enhanced; in those from lactating animals, it was reduced and threshold doses for oxytocin were markedly higher.

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Antagonistic Effects of Pemoline to Colchicine and Caffeine

After former studies on the medicinal effects of pemoline (5-phenyl-2-imino-4-oxo-oxazoleidine, PIO), the main constituent of Tradon[1] some side-effects of the substance on both animals[2] and plants[3] were noted. BRABEC and RÖPER[4] and RÖPER[5] observed influences of pemoline on mitotic index and mitotic cycle. While studying the effects of pemoline, its influence on the action of colchicine and caffeine was investigated.

Materials and methods. Vicia faba seeds were germinated in moist sand, and after 5–6 days the main root was cut off up to 3 cm. The further culture was done in aerated

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