Les micro-injections d'apomorphine dans le noyau caudé de rat déterminent la survenue de mouvements stéréotypés. La stimulation locale du Piribédil est moins importante. Parmi les métabolites injectés localement, seul le S 584 induit une assymétrie du tonus à dose faible. La différence entre les résultats obtenus après administration locale et après injection i.p. de S 584, dépendrait de la vitesse d'élimination élevée de ce métabolite, ou d'un franchissement difficile de la barrière hémato-encéphalique lorsqu'il est administré par voie i.p. La constatation d'une teneur suffisante de S 584 au niveau du néostriatum du Rat pourrait étayer l'hypothèse d'une participation de ce métabolite aux effets pharmacologiques du Piribédil. Il existe des différences notables entre d'une part, les effets du Piribédil administré dans le noyau caudé et par voie i.p. et, d'autre part, les effets produits par les trois métabolites actuellement synthétisés. Ces différences ne permettent pas d'exclure la possibilité d'une stimulation des structures centrales par la molécule de Piribédil elle-même.

Summary. The effects of Piribedil on central dopaminergic receptors were compared with the effects elicited by 3 metabolites of this drug. One of them S-584 = [1-(2-pyrimidyl)-4 (3–4 dihydroxyphenyl) piperazine] showed dopaminergic stimulant properties when administered by the i.p. route, in unilateral nigro-neostriatal lesioned rats. Other metabolites: S 3284 = [1–(2-pyrimidyl)1*N*-oxydo-4 piperonyl piperazine] and S 3473 = [1-(5 hydroxy 2 pyrimidyl)-4 piperonyl piperazine] were ineffective.

J.-C. Poignant, F. Lejeune, E. Malecot, M. Petitjean, G. Regnier et R. Canevari

Division des Recherches Pharmacologiques et Division des Recherches Chimiques, Science-Union et Cie., Groupe de Recherche des Laboratoires Servier, 14, rue du Val d'Or, F-92150 Suresnes (France),
23 juillet 1973.

Effects of PGE_1 on the Frog Ventricular Strip

In previous publications[1–3], the effects of PGE_1 on perfused frog heart were described. According to these papers, PGE_1 has no effect on the heart rate but increases contractile force. It was also suggested that PGE_1 and catecholamines have rather similar effects on the cardiac tissue of the frog[4]. A study[5] on the cat isolated papillary muscle showed that the effect of PGE_1 is mainly mediated by an adrenergic mechanism. PGE_1 increased the sensitivity of isolated rabbit atria to ouabain[6].

These results prompted us to investigate the effects of PGE_1 on frog ventricular strip after α-blockade, beta blockade and sodium pump inhibition. The present paper describes the results of this investigation.

Methods. Isolated frog ventricular strips were prepared from *Rana esculenta*. Hearts were excised and dropped into Ringer solution (per 1000 ml: 6.5 g NaCl, 0.2 g $CaCl_2$, 0.2 g KCl and 0.1 g $NaHCO_3$). The atria were cut away without injury to the ventricle. A strip extending from the heart base to apex was prepared by cutting spirally ventricle. Isolated strips were mounted in a 22 ml. volume bath in Ringer solution and aerated with oxygen. Experiments were performed at room temperature. An isotonic frontal lever exerted a tension of 2 g on the strip and was kept constant in all experiments. Preparations were allowed to equilibrate for 1 h. The ventricle thus prepared showed regular and spontaneous contraction at a rate of about 30 beats/min. Contractions were magnified 17-fold and recorded on smoked drum. The contact time with PGE_1 was 2 min. After this, the tissue was washed with fresh solution and allowed to restore normal ventricular function for 15

[1] F. Berti, R. Lentati and M. M. Usardi, Med. Pharmac. exp. *13*, 233 (1965).
[2] S. Bergström, L. A. Carlson and J. R. Weeks, Pharmac. Rev. *20*, 1 (1968).
[3] S. Arienti, F. Piccini and P. Pomarelli, Boll. Soc. ital. Biol. sper. *43*, 521 (1967).
[4] A. J. Vergroesen and J. de Boer, Eur. J. Pharmac. *3*, 171 (1968).
[5] R. K. Türker, B. K. Kiran and H. Vural, Arzneimittel-Forsch. *21*, 989 (1971).
[6] R. S. Tuttle and M. M. Skelly, in *Prostaglandin Symposium of the Worcester Foundation for Experimental Biology* (Eds. P. W. Ramwell and J. E. Shaw; Interscience Co., New York 1968), p. 309.

Percent increase of contraction (mean ± S.E.)

	PGE_1 50 ng/ml	PGE_1 100 ng/ml	PGE_1 200 ng/ml	PGE_1 400 ng/ml	Norepinephr. 500 ng/ml	Norepinephr. 1000 ng/ml	Epinephrine 250 ng/ml	Epinephrine 500 ng/ml
Untreated	8.54 ± 1.50 $n = 23$	12.34 ± 2.28 $n = 23$	15.99 ± 2.75 $n = 23$	21.66 ± 2.85 $n = 23$	15.14 ± 2.67 $n = 16$	28.31 ± 5.52 $n = 12$	25.29 ± 6.00 $n = 7$	36.82 ± 6.66 $n = 7$
Treated with Phenoxybenzamine 500 ng/ml	10.26 ± 1.05 $n = 7$	13.08 ± 1.79 $n = 7$	16.31 ± 2.05 $n = 7$	26.76 ± 3.53 $n = 7$	18.43 ± 4.22 $n = 7$	28.35 ± 5.16 $n = 7$	32.15 ± 7.18 $n = 7$	40.46 ± 5.29 $n = 7$
Treated with Propranolol 500 ng/ml	9.90 ± 2.86 $n = 9$	13.46 ± 2.86 $n = 9$	14.79 ± 2.75 $n = 9$	20.81 ± 2.94 $n = 9$	0.94 ± 0.57[a] $n = 9$	0.35 ± 1.35[a] $n = 5$	—	—
Treated with Ouabain 20 ng/ml	10.48 ± 1.21 $n = 7$	15.70 ± 2.01 $n = 7$	20.32 ± 4.12 $n = 7$	27.55 ± 5.02 $n = 7$	—	—	—	—

n = Number of experiments. [a] $p < 0.001$ differs from untreated group.

min. For blocking agents and ouabain, the contact time was about 30 min. The inotropic effect was expressed as % increase of contraction. Chronotropic action was evaluated by measuring the sponaneous beats of strip.

Statistical analysis of the results was carried out using Student's *t*-test. Stock solution of PGE_1 was prepared from crystalline PGE_1 by dissolving in alcohol, and was kept at 0 °C.

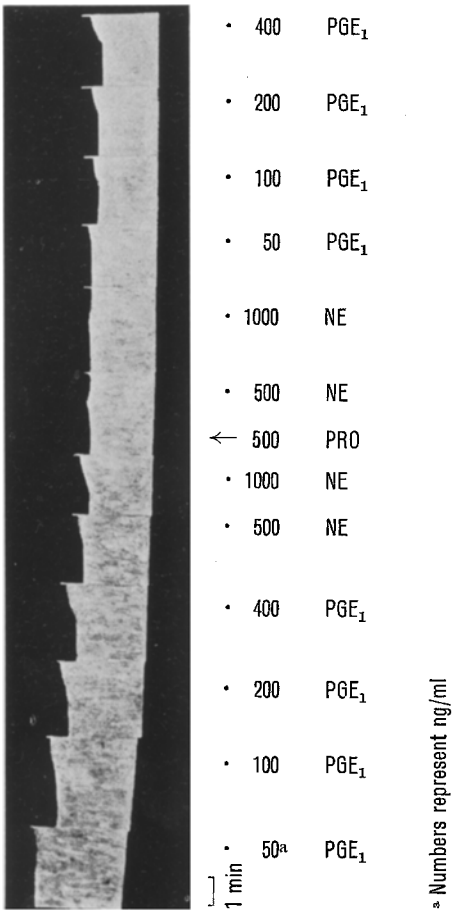
Results. PGE_1 at the concentration range of 50 ng/ml to 400 ng/ml increased the contractile force of strip. Its activity was dependent on the dose. The inotropic effect of various doses of PGE_1 is shown in the Table. Figure illustrates a typical tracing of one experiment. PGE_1 did not cause any significant change in the rate of ventricular beats.

When propranolol (PRO) was added to the bath at the concentration of 500 ng/ml, it inhibited frequency of ventricular rate. This effect was significant ($P < 0.001$). In addition, the spontaneous activity had more regular rhythm after propranolol. Propranolol did not cause any significant inhibition on the response of muscle to PGE_1 (Table). However, it antagonized positive inotropic action of norepinephrine (NE) ($P < 0.001$).

Phenoxybenzamine did not change the effect of PGE_1 at concentration of 500 ng/ml (Table). The action of catecholamines was also not affected by alpha blockade. This drug significantly reduced the frequency of ventricular rate ($P < 0.005$).

Ouabain, at the concentration of 20 ng/ml, was used to inhibit the sodium pump. After this treatment no significant change was observed in the inotropic action of PGE_1 (Table). However, Na pump inhibition significantly slowed the spontaneous rhythm of strip ($P < 0.001$). It occasionaly caused premature beats.

Discussion. The results of the present study indicate that the effect of PGE_1 on frog ventricular strip is not mediated by catecholamine release or adrenergic receptor stimulation. Here, although propranolol at this concentration did not change the action of PGE_1, it significantly antagonized the response of tissue to norepinephrine. This finding is not in agreement with the effect of beta blockade on the cat isolated papillary muscle. These investigators[5] have observed that propranolol inhibited the effect of PGE_1 on the tension of muscle. Contradictory findings may be explained by the species specifity of PGE_1. The action of propranolol on ventricular rate may be due to β adrenergic blocking activity or quinidine-like actions of this drug. Phenoxybenzamine neither blocked PGE_1-induced change nor inhibited the effect of catecholamines. These results strongly indicate that ventricular adrenergic receptors of frog are of the beta type. The haloalkylamines have a transient direct depressant effect on the myocardium[7]. This effect may account for the action of phenoxybenzamine on the strip rate. After pretreatment with ouabain, we could not observe any significant change in the effect of PGE_1. This led us to the conclusion that PGE_1-induced change is not directly related to sodium pump. However, a study[6] indicated that PGE_1 increased the sensitivity of isolated rabbit atria to ouabain.



Frog ventricular strip.

Résumé. Les effets de la PGE_1 ont été étudiés sur les bandelettes ventriculaires isoleés de la grenouille. La PGE_1 augmente la force de contraction de ces préparations. Le propranolol antagonise significativement les effets de la noradrenaline sans altérer les réponses à la PGE_1. Un bloqueur des récepteurs α-adrenergiques, la phénoxybenzamine n'inhibe pas les effets induits par la PGE_1 ou les catécholamines. L'inhibition de la pompe à sodium par l'ouabaine ne modifie pas la réponse du tissu à la PGE_1.

F. BAYSAL and H. VURAL[8]

Department of Pharmacology, Faculty of Medicine, Diyarbakır (Turkey),
24 April 1973.

[7] M. NICKERSON, in *The Pharmacological Basis of Therapeutics*, 4th edn. (Eds. L. S. GOODMAN and A. GILMAN MacMillan Co., London 1970), p. 554.

[8] We should like to thank Prof. D. A. VAN DORP (Unilever Research Vlaardingen) for supplying PGE_1.

Phentolamine and Propranolol on Isoprenaline Induced Responses on Rabbit Aortic Strips

Whether isoprenaline contracts or relaxes smooth vascular muscle in the rabbit aortic strips, depends upon the dose given. Low doses provoke relaxation and high doses contraction (FURCHGOTT[1]).

DOREVITCH[2] suggests that, in rabbit aortic strips, some of the β-receptors may be excitatory and the contractile effect produced by large doses of isoprenaline may be mediated by both α- and β-receptors, since a β-antagonist,