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.

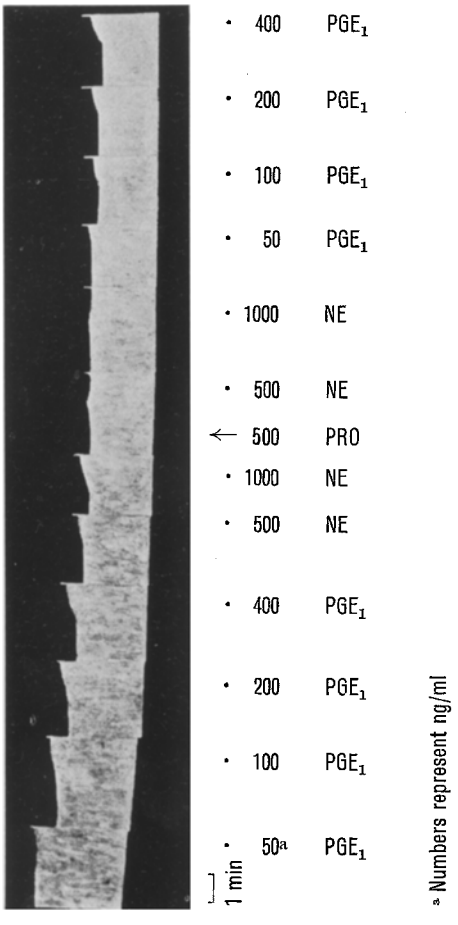
Results. PGE_1 at the concentration range of 50 ng/ml to 400 ng/ml increased the contractile force of strip. Its activity was dependent on the dose. The inotropic effect of various doses of PGE_1 is shown in the Table. Figure illustrates a typical tracing of one experiment. PGE_1 did not cause any significant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

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24 April 1973.

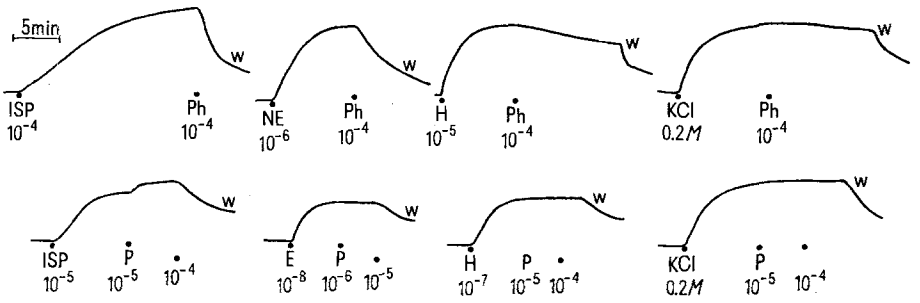
[7] M. NICKERSON, in *The Pharmacological Basis of Therapeutics*, 4th edn. (Eds. L. S. GOODMAN and A. GILMAN MacMillan Co., London 1970), p. 554.

[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,



Typical responses of rabbit aortic strips. Effect of Phentolamine mesylate (Ph) on Isoprenaline hydrochloride (ISP), Noradrenaline bitartrate monohydrate (NE), Histamine diphosphate (H) and KCl induced contractions (upper curves). Effect of Propranolol hydrochloride (P) on the contractions induced by the same agonists though adrenaline hydrochloride (E) was used instead Noradrenaline (lower curves). All concentrations are expressed in g/ml and refer to the concentrations of the salts added to the bath of 10 ml, except the concentration of KCl, expressed in molarity, which refers to the total concentration into the bath.
The upper curves were evoked in one strip and the lower curves in another different one. Between each curve, and after washing (W), a recovery time of 90 min was observed.

propranolol, partially blocked its contractile effect, when administered before them.

EYRE[3] described an α-adrenergic response to isoprenaline on the pulmonary artery of the calf during β-adrenergic blockade with propranolol. LEWIS[4] has also described an α-adrenergic response to isoprenaline on the pulmonary artery of the guinea-pig, as confirmed by α-blockade with phentolamine and phenoxibenzamine.

The purpose of this paper is to present some qualitative tests which can clarify the mechanisms involved in the contracting effect of isoprenaline on rabbit aortic strips, as well as in the blocking effect of propranolol on the induced contraction by high doses of isoprenaline.

Methods. Spiral strips of rabbit thoracic were prepared as described previously by FURCHGOTT and BHADRAKOM[5].

Two series of experiments were carried out. In the first series, the action of an α-blocking agent, phentolamine, on isoprenaline, noradrenaline, histamine and KCl induced contractions was tested. In the second series of experiments, the effects of a β-blocking agent, propranolol, was similary tested against the same agonist though adrenaline was used instead of noradrenaline. Each series was repeated 6 times on different aortic strips.

Results. Phentolamine (10^{-4}) induced a strong relaxing effect when administered after isoprenaline and noradrenaline, whereas no apparent effect was observed after histamine and KCl (Figure; upper curves).

Propranolol at dose 10^{-5} enhanced the contraction induced by isoprenaline, but depressed those induced by adrenaline. However, larger doses of propranolol, 10^{-4}, also depressed the contractile effect evoked by isoprenaline. Neither one of the propranolol doses tested, produced effects on histamine and KCl induced contractions (Figure; lower curves).

Discussion. Whether the contraction induced by isoprenaline is mediated through α-receptors may be supposed, since the relaxing effect of an α-blocking agent, phentolamine, on isoprenaline-induced contraction, was identical to those produced on the contraction induced by a typical α-adrenergic agent as noradrenaline. However phentolamine did not relaxed the contraction induced by drugs such as histamine and KCl whose contractile effect is not mediated through α-adrenergic receptors.

The fact that a β-blocking agent, propranolol, at dose 10^{-5} increased and at dose 10^{-4} decreased the contractile effect induced by isoprenaline, and, on the other hand, at dose 10^{-5} caused a relaxing effect on adrenaline-induced contraction, can be explained, because adrenaline combined with a significant fraction of α-receptors and only with a small amount of β-receptors, whereas isoprenaline has a higher affinity for β-receptors than for α-receptors. Thus, according to FURCHGOTT[1], high concentrations of isoprenaline may interact with β-receptors, but with α-receptors too, and then the contracting effect over-rides the relaxing effect. In this manner, the dose of propranolol 10^{-5} would displace, by competitive mechanism, the isoprenaline from the β-receptors, developing more intensively the α-contractile effect. A higher dose of propranolol (10^{-4}) might remove simultaneously isoprenaline from the α-receptors, inhibiting the α-activity and developing a relaxing effect. On the other hand, although adrenaline is fixed in a much larger amount to α- than to β-receptors, a lower concentration of propranolol (10^{-5}) might be enough to produce, besides a complete displacement of adrenaline from β-receptors, also a partial displacement of its fixing points in α-receptors, therefore developing a relaxing effect.

This explanation is supported by the fact that propranolol did not modify the contraction induced by drugs without affinity for adrenergic receptors, such as histamine and KCl.

These findings suggest that the contractile effect of large doses of isoprenaline on rabbit aortic strips, is mediated through α-receptors and that a β-blocking agent, propranolol, besides its β-blocking effect, can also act, at least partially, as α-adrenergic blocking agent.

Resumen. El efecto contractil de altas dosis de Isoproterenol en tiras de aorta aislada de conejo parece ser debido a estimulación α-adrenérgica. El Propranolol a la concentraciön 10^{-5} incrementa y a 10^{-4} relaja la contracción inducida por Isoproterenol, mientras que la concentración 10^{-5} relaja la contracción inducida por Adrenalina. Es posible que el Propranolol además de su efecto β-bloqueante, actúe también como bloqueante α-adrenérgico.

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