During histamine infusion in the same four dogs, propranolol had no effect on the secretory plateau and negligible effect on gastric mucosal blood flow. In another experiment on one of these dogs histamine-induced secretion increased during propranolol administration.

Propranolol had no clear effect on acid secretion induced by bethanecol. In six experiments in five dogs secretion increased twice, decreased twice and was unchanged twice.

These experiments show that propranolol increases gastric acid secretion in response to pentagastrin but not to histamine. This is not inconsistent with the hypothesis that histamine is involved in the secretory response to pentagastrin.

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REFERENCES

ASSEM, E. S. K. & FEIGENBAUM, J. J. I. (1972). Effect of adrenergic drugs on histamine forming capacity of human leucocytes. *Br. J. Pharmac.*, **46**, 519–520P.

BLACK, J. W., DUNCAN, W. A. M., DURANT, C. J., GANELLIN, C. R. & PARSONS, E. M. (1972). Definition and antagonism of histamine H_2 receptors. *Nature (Lond.)*, **236**, 385–390.

CURWAIN, B. P. & HOLTON, P. (1971). Radioactive aniline clearance from canine gastric pouches for the measurement of gastric mucosal blood flow. *Br. J. Pharmac.*, **41**, 384P.

CURWAIN, B. P. & HOLTON, P. (1972). The effects of isoprenaline and noradrenaline on pentagastrin-stimulated gastric acid secretion and mucosal blood flow in the dog. *Br. J. Pharmac.*, **46**, 225–233.

CURWAIN, B. P. & HOLTON, P. (1973). The measurement of dog gastric mucosal blood flow by radioactive aniline clearance compared with amidopyrine clearance. *J. Physiol. Lond.*, **229**, 15-31.

CURWAIN, B. P., HOLTON, P. & SPENCER, J. (1972). The effects of β_2-adrenoceptor stimulants, salbutamol and terbutaline on gastric acid secretion and mucosal blood flow in conscious dogs with Heidenhain pouches. *Br. J. Pharmac.*, **46**, 566–567P.

CURWAIN, B. P., HOLTON, P. & SPENCER, J. (1973). Evidence that the inhibitory effect of burimamide on gastric secretion is not due to decreased gastric mucosal blood flow. *J. Physiol. Lond.* (In the press.)

KAHLSON, G. & ROSENGREN, E. (1971). Biogenesis and physiology of histamine, p. 145. London: Arnold.

The blocking effects of propranolol, practolol and ICI-66082 on the peripheral vascular responses to isoprenaline

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Some β-receptor blocking drugs are known to be different in their ability to block the response of the heart and the arterial blood pressure to infused isoprenaline (Dunlop & Shanks, 1968). In this study we examined the effects of propranolol, practolol and ICI-66082 on the responses of arterial and venous resistance to infusion of isoprenaline.

Dogs were anaesthetized with chloralose and a hind limb was vascularly isolated from the rest of the circulation by strong nylon snares tightened round the muscle groups at the upper end of the thigh. The snares excluded the femoral vessels and the femoral and sciatic nerves. The femoral artery was perfused at constant flow with blood from a carotid artery; changes in perfusion pressure indicated arterial resistance changes. A vein near the ankle was perfused at constant flow. Blood from the limb was drained from the femoral vein to maintain a constant femoral venous pressure, and pumped back into an external jugular vein. Changes in pressure gradient between the ankle vein and femoral vein indicated venomotor changes.

The responsiveness of each preparation was shown by stimulation of the lumbar sympathetic nerve at supra-maximal intensity and 5 Hz. The average response in 14 dogs was an increase in arterial resistance of 68% and in venous resistance of 395%. Infusion of isoprenaline at 5–10 μg/min caused an increase in heart rate of 61 beats/min and a decrease in arterial resistance of 27%. Isoprenaline caused venous dilatation only if the vein was previously constricted by sympathetic nerve stimulation.

Propranolol (0·5 mg/kg) in 2 dogs abolished the heart rate, arterial and venous responses to isoprenaline infusion. Practolol (2 mg/kg) in 6 dogs reduced the heart rate response to isoprenaline by 85% and the arterial response by 10%. ICI-66082 (2 mg/kg) in 6 dogs reduced the heart rate response to isoprenaline by 84% and the arterial response by 40%. After either drug, isoprenaline still caused dilation in a

previously constricted vein. These blocking effects of both practolol and ICI-66082 were overcome by increasing the rate of infusion of isoprenaline.

This study has demonstrated that propranolol is effective in blocking both heart rate and peripheral vascular responses to infused isoprenaline, but practolol and ICI-66082 are less effective in blocking peripheral vascular responses.

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REFERENCE

DUNLOP, A. D. & SHANKS, R. G. (1968). Selective blockage of adrenoceptive beta-receptors in the heart. *Br. J. Pharmac. Chemother.*, **32**, 201–208.

Central hypotensive effect of propranolol in the rabbit

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The action of propranolol in the treatment of hypertension is not well understood. The effective dose in chronic oral treatment may be very high (Prichard & Gillam, 1969) and although propranolol induces a rapid fall in cardiac output, the fall in arterial pressure is usually a gradual one. Several antihypertensive drugs exert actions on noradrenergic pathways in the central nervous system (CNS) and this is a possible site of action for propranolol, which achieves high CNS concentrations.

Intracerebroventricular (ICV) injection of (±)-propranolol (500 μg) produced a rapid rise in mean arterial pressure (MAP) in the conscious rabbit, 27·5±6·0 mmHg at 5 min, followed by a prolonged fall, 8·8±3·3 mm Hg at 4 h. A similar early rise in MAP was produced by (+)-propranolol 500 μg ICV, 42·2±4·5 mmHg, but there was no late fall. Procaine (1 mg) ICV produced a similar rise, 51·0±10 mm Hg at 5 min. The pressor effect of both (+)-propranolol and procaine were both abolished by pentobarbitone anaesthesia. This early rise in MAP may be related to the membrane stabilizing action shared by procaine and both isomers of propranolol.

(−)-Propranolol 500 μg ICV raised MAP 20·8±4·1 mm Hg at 5 min, but the subsequent fall was greater than that produced by the racemate (14·6±4·5 mmHg at 4 h). The central hypotensive effect of (−)-propranolol was abolished by pretreatment of rabbits one week previously with intracisternal 6-hydroxydopamine (500 μg/kg), which destroys CNS noradrenergic neurones.

Isoprenaline (50 μg ICV) caused a transient fall in MAP, 10·0±0·4 mmHg at 5 min. In rabbits pretreated with 500 μg (−)-propranolol ICV 2 h previously, this response to central isoprenaline was abolished.

It appears therefore that propranolol can lower arterial pressure in the rabbit by an action on the CNS. This action is dependent on the integrity of noradrenergic neurones and the effect is related to β-adrenoceptor blocking activity and not to local anaesthetic activity.

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REFERENCE

PRICHARD, B. N. C. & GILLAM, P. M. S. (1969). Treatment of hypertension with propranolol. *Brit. Med. J.*, **1**, 7–16.

Rabbit monoarticular arthritis and synovial prostaglandins

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An immune arthiritis is produced in the rabbit using a modification of the method of Dumonde & Glynn (1962). Essentially, this consists of sensitizing the animals intra-