of rise of pressure in the left ventricle (dP/dt max) in a preparation in which heart rate and mean aortic pressure were held constant (Furnival, Linden & Snow, 1970). Cardiac reflexes were prevented from occurring by section of vagal and sympathetic nerves to the heart.

ICI-66082 (0·1–2·0 mg/kg) antagonized the increase in heart rate and dP/dt max induced by isoprenaline, an effect which could be overcome by increasing the infusion rate of isoprenaline, e.g. in five dogs an increase in heart rate of 40–50 beats/min was produced by an infusion rate of 1–2 μg/min of isoprenaline in the absence of 66082 and by 10–15 μg/min in the presence of 66082 (dose 0·1 mg/kg). In three dogs ICI-66082 (0·25–4 mg/kg) reduced the control measurement of dP/dt max by a mean value of 661 mmHg/s; this effect is due to β-receptor blockade of circulating catecholamines by ICI 66082 in this preparation, as described previously for propranolol (Harry, Linden & Snow, 1972). In three dogs depleted of catecholamines by reserpine ICI-66082 (up to 3 mg/kg) produced no change in dP/dt max.

In five isolated papillary muscle preparations, set up as described by Harry, Linden & Snow (1971), ICI-66082 (1–1,000 μg/ml) produced no depression of the twitch response to electrical stimulation.

It is concluded that ICI-66082 is a β-adrenoceptor blocking drug, with no intrinsic stimulating action and without negative inotropic activity on the heart in high doses.

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Enhancement by propranolol of gastric acid secretion in response to pentagastrin in conscious dogs.

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In conscious dogs, both β-adrenoceptor agonists (Curwain & Holton, 1972; Curwain, Holton & Spencer, 1972) and burimamide (Black, Duncan, Durant, Ganellin & Parsons, 1972; Curwain, Holton & Spencer, 1973) decrease pentagastrin-induced gastric acid secretion. It has also been shown that β-adrenoceptor agonists decrease, and that propranolol increases (Assem & Feigenbaum, 1972), histamine formation in human leucocytes. If histamine formation is involved in the effect of pentagastrin on the gastric mucosa, as has been suggested by Kahlson & Rosengren (1971), the action of β-adrenoceptor agonists on gastric secretion might be secondary to their action on histamine formation. If this were so, propranolol would be expected to increase histamine formation and hence gastric secretion in response to pentagastrin but not in response to histamine. We have therefore investigated the effects of propranolol on gastric acid secretion in conscious Heidehain pouch dogs.

Secretion was induced by a constant infusion of pentagastrin (1–2 [μg/kg]/h) histamine acid phosphate (1–2 [μg/kg]/min) or bethanechol hydrochloride (0·5–1·0 [μg/kg]/min). Increasing doses (0·1, 0·3, 0·6 and 1·0 mg/kg) of (±) propranolol hydrochloride were injected intravenously at 30–60 min intervals. In some experiments gastric mucosal blood flow was measured by radioactive aniline clearance (Curwain & Holton, 1971, 1973).

In each of four experiments in four dogs, propranolol (0·4–2·0 mg/kg total dose) caused a prolonged increase of 53% ± 22·7% (S.E. of mean) in pentagastrin-induced gastric secretion (mean maximum increase of 81% over control; range 33–120%). Propranolol also increased gastric mucosal blood flow in parallel with the increased secretion.

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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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