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REFERENCES

ANDÉN, N.-E. & MAGNUSSON, T. (1967). *Acta physiol. scand.*, **69**, 87–94.
BERTLER, Å., CARLSSON, A. & ROSENGREN, E. (1958). *Ibid.*, **44**, 273–292.
CARLSSON, A. & LINDQVIST, M. (1962). *Ibid.*, **54**, 87–94.
HÄGGENDAL, J. (1963). *Ibid.*, **59**, 242–254.
GREEN, H. & ERICKSON, R. W. (1964). *Int. J. Neuropharmac.*, **3**, 315–320.
KAHLSON, G., ROSENGREN, E. & THUNBERG, R. (1963). *J. Physiol., Lond.*, **169**, 467–486.
SADAVONGVIVAD, C. (1970). *Br. J. Pharmac.*, **38**, 353–365.
SCHILDKRAUT, J., SCHANBERG, S. M., BREESE, G. R. & KOPIN, I. J. (1969). *Biochem. Pharmac.*, **18**, 1971–1978.
WIEGAND, R. G. & SCHERFLING, E. (1962). *J. Neurochem.*, **9**, 113–114.

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Inhibitory effect of propranolol on the vasoconstrictor response to sympathetic nerve stimulation

Propranolol enhances the vasoconstrictor effect of noradrenaline in skeletal muscle (Brick, Hutchinson & Roddie, 1967, Shanks, 1967), spleen (Ross, 1967a) and the mesenteric circulation (Ross, 1967b), an effect thought to be a consequence of inhibition of the effect of noradrenaline on vasodilator β-adrenergic receptors. Whether propranolol, through the same mechanism, may also enhance the vasoconstrictor response to sympathetic nerve stimulation has received less attention. Burks & Cooper (1967) did find propranolol to increase the vasoconstrictor responses both to exogenous noradrenaline and to sympathetic nerve stimulation in canine isolated perfused mesenteric arteries. We have compared the effect of propranolol on the vasoconstrictor responses to peripheral sympathetic nerve stimulation and to intra-arterially injected noradrenaline in the hind leg of the anaesthetized cat.

Cats, 2·5–3·1 kg, were anaesthetized with pentobarbitone sodium, eviscerated, and the lumbar sympathetic chain on one side cut at L3-L4 and a bipolar electrode placed on the distal part of the nerve. The femoral artery on the same side was catheterized in both directions, and the blood flow to the leg passed through a constant-flow Sigmamotor pump. The perfusion pressure to the leg, recorded by means of a Statham transducer on an Offner Dynograph, was initially adjusted to correspond to the systemic arterial pressure. The blood flow to the paw was occluded by means of a tight ligature.

The sympathetic nerves were stimulated for 90 s with impulses of supramaximal voltage, 4 ms duration and a frequency (1–2 impulses/s) (Grass S4 stimulator) that produced an increase of perfusion pressure of 50–80 mm Hg. Nerve stimulations were alternated according to a standardized time schedule with intra-arterial injections of noradrenaline in a dose (0·25–1 μg) that also increased the perfusion pressure 50–80 mm Hg. When stable responses to nerve stimulation and injected noradrenaline had been established, propranolol was infused intravenously during 5 min in a dose of 0·1 mg/kg, followed after 45 min by another infusion of 0·5 mg/kg propranolol. Three responses to each of the vasoconstrictor stimuli were recorded after each dose of

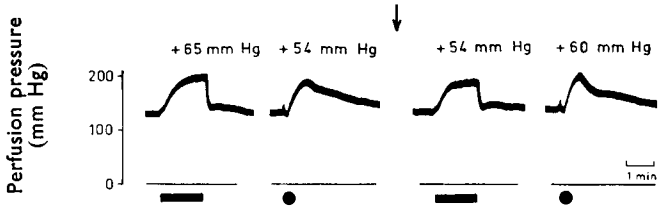

FIG. 1. Influence of (±)-propranolol (0·1 mg/kg, i.v. at arrow) on the effects of electrical stimulation of the lumbar sympathetic nerve (2 impulses/s, 4 ms impulse duration, 6 V shown by bars) and intra-arterially injected noradrenaline (0·5 μg, ●) on the perfusion pressure in a constant-perfused hind leg of an anaesthetized cat.

propranolol. Five experiments were made with (±)-propranolol. In addition five experiments were made in the same way with (+)-propranolol.

Fig. 1 shows typical responses recorded before and after 0·1 mg/kg (±)-propranolol. After this dose the vasoconstrictor response to sympathetic nerve stimulation was consistently reduced (on the average 14 ± 3·7%, $P < 0.025$), while the response to injected noradrenaline was slightly increased or unchanged (average increase 6 ± 3·5%). After 0·5 mg/kg (±)-propranolol the response to noradrenaline was significantly augmented (mean increase 20 ± 6·8%, $P < 0.05$), while the response to nerve stimulation was decreased less than after the lower dose of (±)-propranolol (mean decrease 5 ± 2·8%). (+)-Propranolol, 0·1 and 0·5 mg/kg, elicited on the average no change either of the response to nerve stimulation or of that to injected noradrenaline.

The decreased response to sympathetic nerve stimulation caused by (±)-propranolol concomitant with an unchanged or augmented response to injected noradrenaline indicates that (±)-propranolol reduced the noradrenaline output from the nerve endings. The effect is probably due to β-adrenergic receptor blockade as (+)-propranolol was inactive. The results of cross-circulation experiments, where (±)-propranolol was given exclusively to the leg of the studied animal indicate that the reduced response to sympathetic nerve stimulation was due to a peripheral site of attack.

Our experimental results are not necessarily at variance with those of Burks & Cooper (1967) since these authors reported that after propranolol the vasoconstrictor responses to sympathetic nerve stimulation were less enhanced than those to added noradrenaline. This finding combined with those reported here may indicate that propranolol can influence the vasoconstrictor response to sympathetic nervous stimulation differently, dependent upon whether the reduced release of noradrenaline from the nerve endings or the enhanced sensitivity to it at the smooth muscle cells is of predominant importance for the resultant effect.

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REFERENCES

BRICK, I., HUTCHINSON, K. J., & RODDIE, I. C. (1967). *Br. J. Pharmac. Chemother.*, **30**, 561–567.
BURKS, T. F., & COOPER, T. (1967). *Circ. Res.*, **21**, 703–715.
ROSS, G. (1967a). *Am. J. Physiol.*, **213**, 1079–1083.
ROSS, G. (1967b). *Ibid.*, **212**, 1037–1042.
SHANKS, R. G. (1967). *Br. J. Pharmac. Chemother.*, **29**, 204–217.