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THE EFFECT OF PROPRANOLOL ON THE RESPONSE OF THE RAT ISOLATED HEART TO NORADRENALINE

BY

I. BRICK, K. J. HUTCHISON AND I. C. RODDIE

From the Department of Physiology, The Queen's University of Belfast

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Ahlquist (1948) has suggested that the positive inotropic and chronotropic effects of catecholamines on the heart are due to stimulation of sympathetic β-receptors. This hypothesis is supported by the fact that the β-receptor antagonists dichloroisoprenaline (Moran & Perkins, 1958) and pronethalol (Benfey & Varma, 1964) inhibit the effects of catecholamines on the heart.

In the present experiments we have studied the effect of propranolol, a recently developed β-receptor antagonist (Black, Crowther, Shanks, Smith & Dornhorst, 1964), on the response of the rat isolated heart to noradrenaline.

METHODS

Albino rats, weighing between 300 and 600 g, were killed by a blow on the head. Immediately after death the heart was removed and perfused via the aorta. The perfusate contained (g/l.): NaCl 7.6; $NaHCO_3$ 2.1; KCl 0.42; $NaHPO_4$ 0.286; $CaCl_2$ 0.12; dextrose 2.0; and sucrose 4.5. It was equilibrated to *p*H 7.25 ± 0.05 by bubbling with 95% oxygen and 5% carbon dioxide. Two glass reservoirs, in which the fluid level was maintained at 90 ± 1 cm above the tip of the cannula, fed the perfusate through two heating columns maintained at 28° C. The heart could be perfused from one or other reservoir, as required, by operation of two taps. Thus, to administer a drug, one side of the apparatus was filled with the drug diluted in the perfusate and, when required, was made to perfuse the heart by reversing the two taps.

Strength of contraction was recorded using a spring-loaded lever with magnification 1:20 and diastolic loading between 4 and 6 g. The level was attached to the heart by thread and a hook was fixed to the wall of the right ventricle close to its centre point. The apex of the heart was anchored. Rate was recorded by an impulse counter coupled to a phototransistor device.

Noradrenaline was given as −l-noradrenaline bitartrate (Bayer), and propranolol as hydrochloride (I.C.I.).

RESULTS

In seven experiments (propranolol series) the effect of propranolol on the response to noradrenaline was examined. The results of a typical experiment are shown in Fig. 1. Noradrenaline was given in concentrations of 0.01, 0.1 and 1 μg/ml. for 30 sec periods. Rate and strength of contraction were increased in each case and the greater the concentration of noradrenaline the greater were the responses. Propranolol, 1 μg/ml., was then

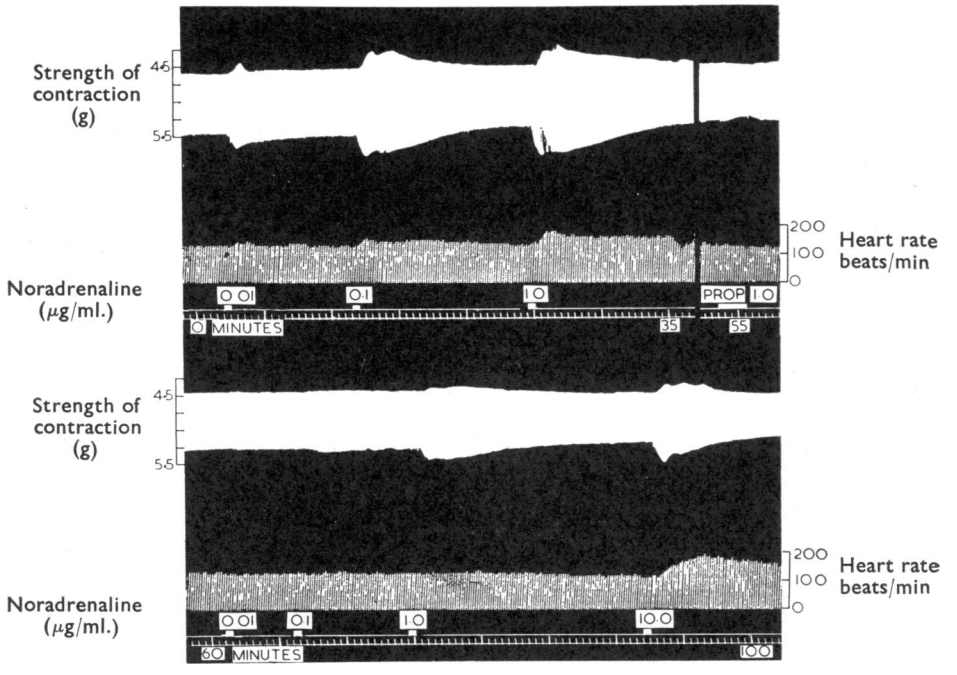

Fig. 1. The strength of contraction (contraction downwards) and rate responses of a rat's isolated heart to the perfusion of noradrenaline before (upper record ; 0.01, 0.1 and 1 μg/ml. for 30 sec each) and after (lower record ; 0.01, 0.1, 1 and 10 μg/ml. for 30 sec each) propranolol, 1.0 μg/ml. for 2 min. Periods of drug infusion are shown by the white rectangles under the concentration values.

perfused for 2 min. This caused a small reduction in strength of contraction but no change in heart rate. After propranolol, noradrenaline was again given in concentrations of 0.01, 0.1 and 1 μg/ml. and the responses were greatly reduced.

Five experiments (control series) were carried out using the same procedure as in the above seven experiments but without propranolol in the second reservoir ; there was only a small reduction in the respective responses.

The average dose/response curves for strength of contraction and rate are shown in Fig. 2. The responses for each dose of noradrenaline were calculated by subtracting the value 1 min before the dose was administered from the value at the peak change. In the control series, the dose/response curve for the second exposure to noradrenaline was shifted slightly to the right of that for the first exposure, but the differences between the responses to identical doses were not significant. Propranolol caused a shift to the right in both dose/response curves. The reductions in the average inotropic responses to the administration of noradrenaline, 0.01, 0.1 and 1 μg/ml. were all significant ($P<0.01$). The reductions in the average chronotropic responses to noradrenaline, 0.1 and 1 μg/ml. were both significant ($P<0.05$).

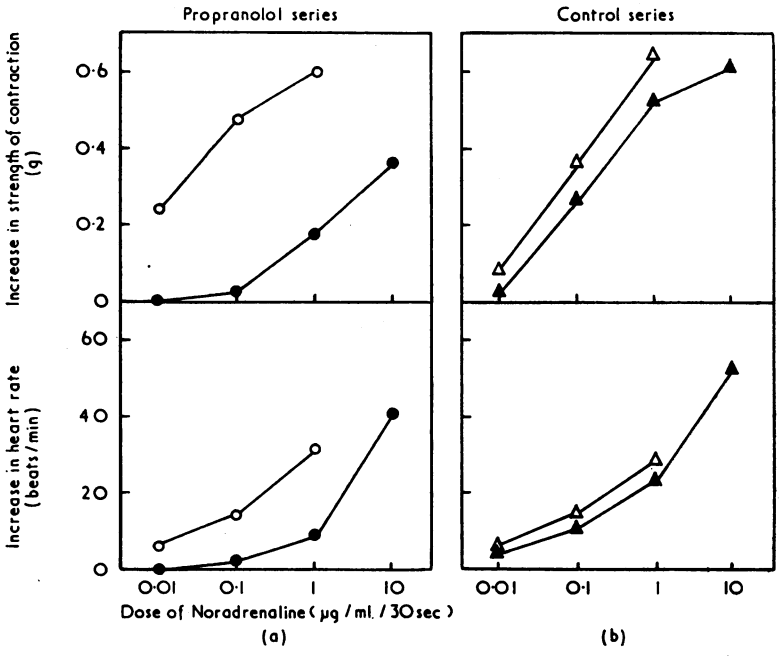

Fig. 2. Average dose response curves for the inotropic and chronotropic effects of noradrenaline. (*a*) before (○) and after (●) propranolol, 1.0 μg/ml. for 2 min (seven experiments); and (*b*) before (△) and after (▲) perfusate without propranolol (five experiments).

DISCUSSION

The experiments show that propranolol inhibits both the inotropic and the chronotropic effects of noradrenaline on the rat isolated heart. The reduction in responses to noradrenaline after propranolol might have been due to tachyphylaxis but the results of the control experiments show that this is unlikely. Previously, the positive inotropic and chronotropic effects of noradrenaline have been shown to be antagonized by dichloroisoprenaline in rabbit isolated heart (Moran & Perkins, 1958) and by pronethalol in the guinea-pig isolated atrium (Benfey & Varma, 1964).

The dose/response curves for the strength of contraction response before and after propranolol are approximately parallel (see Fig. 2). This is a characteristic pattern of competitive antagonism (Arunlakshana & Schild, 1959) and has also been observed on the guinea-pig isolated atrium using adrenaline and propranolol (Black, Duncan & Shanks, 1965), isoprenaline and propranolol (McInerny, Gilmour & Blinks, 1965) and noradrenaline and pronethalol (Benfey & Varma, 1964). In the present experiments parallel dose/response curves were not found for the rate responses, though evidence of antagonism of the chronotropic action of noradrenaline was demonstrated.

The direct effects of propranolol in the concentration used in these experiments were not significant. Black *et al.* (1965) also found no stimulation of the heart with propranolol—unlike pronethalol, which had a sympathomimetic effect.

SUMMARY

1. The effect of propranolol was studied using the isolated perfused heart of the rat.

2. By itself propranolol had no significant inotropic or chronotropic effect.

3. After exposing the heart to propranolol the dose/response curves for the positive inotropic and chronotropic effects of noradrenaline were shifted to the right; in other words, propranolol antagonizes these effects of noradrenaline.

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REFERENCES

AHLQUIST, R. P. (1948). A study of the adrenotropic receptors. *Am. J. Physiol.*, **153**, 586–600.

ARUNLAKSHANA, O. & SCHILD, H. O. (1959). Some quantitative uses of drug antagonists. *Br. J. Pharmac. Chemother.*, **14**, 48–58.

BENFEY, B. G. & VARMA, D. R. (1964). Inhibition of sympathomimetic effects on the heart. *Br. J. Pharmac. Chemother.*, **23**, 399–404.

BLACK, J. W., CROWTHER, A. F., SHANKS, R. G., SMITH, L. H. & DORNHORST, A. C. (1964). A new adrenergic beta-receptor antagonist. *Lancet*, **i**, 1080–1081.

BLACK, J. W., DUNCAN, W. A. M. & SHANKS, R. G. (1965). Comparison of some properties of pronethalol and propranolol. *Br. J. Pharmac. Chemother.*, **25**, 577–591.

MCINERNY, T. K., GILMOUR, D. P. & BLINKS, J. R. (1965). Comparison of effects of propranolol and other cardiac adrenergic blocking agents on inotropic and chronotropic actions of catecholamines. *Fedn. Proc. Fedn. Am. Socs, exp. Biol.*, **24**, 712.

MORAN, N. C. & PERKINS, M. E. (1958). Adrenergic blockade of the mammalian heart by a dichloro analogue of isoproterenol. *J. Pharmac. exp. Ther.*, **124**, 223–237.