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ACUTE EFFECTS OF PROPRANOLOL ON THE CIRCULATION AND ON OXYGEN UPTAKE IN CONSCIOUS RATS

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1 The acute effect of orally administered propranolol (100 mg/kg) on blood pressure, heart rate, cardiac output, venous pressure, haemoglobin concentration and oxygen uptake was studied in conscious rats.

2 Oxygen uptake was measured in a closed circuit respirometer and cardiac output determined by the direct Fick method. Other variables were measured by means of chronically implanted cannulae.

3 Significant falls occurred in heart rate (8.9%), cardiac output (30.5%), derived stroke volume (21.3%) and oxygen uptake (12.2%).

4 There were significant rises in arterial blood pressure (12.9%), derived arterial resistance (69%), arterio-venous oxygen difference (31.5%) and arterial haemoglobin concentration (6.3%).

5 A rise in venous pressure occurred in lightly anaesthetized rats but was only of borderline significance.

6 Correlations between the different variables revealed only one significant relationship, between heart rate and oxygen uptake.

7 It is concluded that only one primary site of action of propranolol has to be postulated to account for these findings, that of the well known negative inotropic and chronotropic effect on the heart.

Introduction

The acute effects of propranolol on the circulation have been described by a number of workers in man and in experimental animals and although the findings are generally in agreement, contradictory findings in regard to the effect on blood pressure have been made. In man, no change in blood pressure has been found acutely (Ulrych, Frohlich, Dustan & Page, 1968; Hansson, Zweifler, Julius & Hunyor, 1974). Brundin, Edhag & Lundman (1976) did find a marginal rise in humans but this was not significant. In rats however, a significant acute rise in blood pressure has been reported (Struyker-Boudier, Smits & Van-Essen, 1979). Few observations have been made on the acute effect of propranolol on oxygen utilization (Brundin *et al.*, 1976) and the relationship of the circulatory changes to the changes in oxygen utilization have not been specifically studied. The present work is concerned with a study of the acute circulatory effects of propranolol and of their relationships to oxygen uptake in conscious rats and forms part of a wider study of the various factors concerned in oxygen delivery and their modification to meet changing oxygen requirements of the body.

Methods

Experimental animals

Female Wistar rats of approximately 200 g were subjected to a two week conditioning period during which they were placed in a restraining cage for 1 h daily; in the second week the cage was placed in a specially constructed respirometer for half the daily conditioning period. The restraining cages were of transparent perspex construction and of adjustable dimensions to permit uninterrupted vision and a certain degree of movement. The cage prevented the rats engaging in excessive activity or interfering with the cannulae leads but did not subject them to stress. At the end of the conditioning period and during experiments the rats sat quietly in the cage; the absence of stress was indicated by their restful pose and normal heart rates.

During the second week cannulae were implanted in the abdominal aorta (pp10 polythene tubing) following the technique of Weeks & Jones (1960) and in the right ventricle (00 nylon tubing) by the technique

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of Popović, Kent & Popović (1963). Cannulae were heparin filled and plugged with stainless steel at their exit at the back of the neck. Observations were started at least two days after cannulae implantation.

Oxygen uptake

The respirometer apparatus was of closed circuit type; by introducing 5 ml increments of oxygen from a side-limb to the main circuit when the pressure fell to a fixed level, the pressure and composition of gas in the circuit was maintained very nearly constant. The whole circuit was maintained in a water bath and the temperature kept within 0.2°C during the observation period. The temperature selected was in the range 28°C–32°C which lay in the thermo-neutral range for the rat. Very stable oxygen uptake curves were obtained and were accepted if the rat exhibited no restlessness throughout the observation period.

Haemodynamic observations

Cardiac output was determined by the direct Fick method using arterial and mixed venous (right ventricular) blood samples. Haemoglobin and oxygen saturation were measured on 20 μl blood samples in a hemoximeter (Radiometer OSM2). Two paired blood samples were withdrawn during the oxygen uptake measurement period and were immediately replaced with an equal volume of donor blood. Blood pressure was continuously monitored except during blood sampling, by means of a Statham P23G pressure transducer and a u.v. recorder. Heart rate was obtained from the pressure reading.

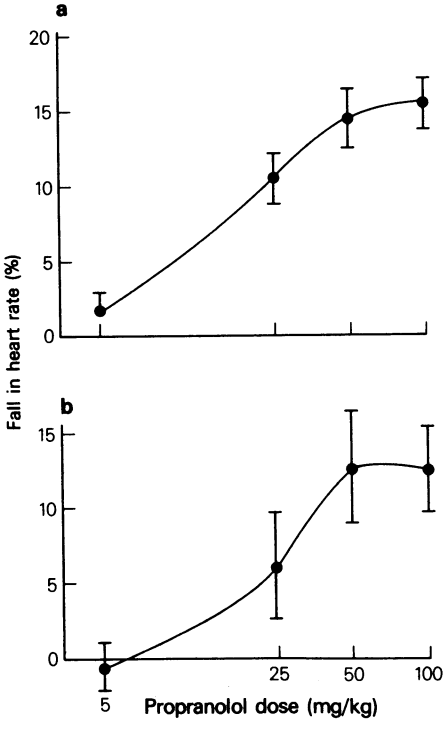

Figure 1 Dose-response of heart rate versus propranolol concentration at 1 (a) and 2 hours (b) in conscious rats. Vertical lines indicate s.d.

Propranolol administration

Initial observations were made on blood pressure, cardiac output and oxygen uptake after which the rats were removed from the cage. After 2 h they received by gavage, either 20 mg propranolol (I.C.I. (±)-propranolol hydrochloride) in 0.6 ml water, i.e. 100 mg/kg (experimental group) or 0.6 ml distilled water alone (control group). Observations were repeated in the period 40 to 60 min after the administration of the drug.

The amount of propranolol given was selected on the basis of observations on heart rate in a separate group of (8) cannulated rats. The change in heart rate 1 and 2 h after administration of 1, 5, 10 and 20 mg propranolol by gavage (0.6 ml) was measured as is shown in Figure 1. After 1 h there was a significant reduction in heart rate with doses of 5, 10 and 20 mg but not with 1 mg. The reduction in heart rate increased significantly with doses up to 10 mg; a further reduction between 10 and 20 mg was not significant. The depression in heart rate was diminished after 2 h.

Venous pressure

Venous pressure measurements were made through a cannula (pp10 polythene tubing) previously implanted in the inferior vena cava. It proved impossible to obtain reproducible and stable measurements in unanaesthetized animals and a study of the effect of propranolol on venous pressure was conducted in the lightly anaesthetized state in a separate series of experiments. After anaesthetizing with ether, the rat was placed prone and a continuous recording made of venous pressure with a Statham P23D pressure transducer up to the period of waking, the value obtained just prior to waking being accepted as the definitive venous pressure. The zero reference point was arbitrarily defined as 1 cm above the floor of the support. Observations were made before and 40 min after the administration of propranolol or water in the manner described above.

Statistics

The significance of changes (both absolute and percentage) in the variables studied was assessed by Student's t test, used as a paired test for changes

Table 1 Acute haemodynamic changes in propranolol-treated rats and controls

		No. of rats	*Initial (s.d.)*		*Final (s.d.)*		*Mean change*	*Mean % change*
Heart rate (min^{-1})	Propranolol	9	355.4	(38.8)	319.2	(22.5)	−36.2*** (*)	−8.9** (*)
	Control	6	376.0	(44.2)	375.0	(45.8)	−1.4	−0.36
Cardiac output ($ml\ min^{-1}\ 200\ g^{-1}$)	Propranolol	10	73.2	(14.4)	50.2	(8.9)	−23†† (††)	−30.5†† (††)
	Control	7	67.4	(15.7)	62.2	(14.5)	−5.3*	−7.25*
Mean arterial blood pressure (mmHg)	Propranolol	10	101.6	(5.0)	114.3	(5.2)	+12.7†† (†)	+12.9†† (†)
	Control	6	95.9	(6.4)	96.5	(7.9)	+0.61	+0.59

Significance within and between (in parentheses) groups:- *$P<0.05$; **$P<0.025$; ***$P<0.01$; †$P<0.001$; ††$P<0.0005$

within each group and as an unpaired test for differences between experimental and control groups. Since the observations were often repeated twice or thrice in individual rats, the analysis was applied separately to experiments and to individual rats, the mean of the observations being used in an individual. Little essential difference emerged in the analysis whether applied to experiments or to individual rats and mainly the comparisons between individual rats have been presented.

Results

Haemodynamic observations

The responses of cardiac output, heart rate and mean arterial blood pressure to acute propranolol are shown in Table 1. Both heart rate and cardiac output fell significantly (8.9% and 30.5% respectively) while blood pressure rose significantly (12.9%). Stroke volume was derived in 12 experiments and showed a fall of 21.3% which was significant ($P<0.025$) compared to 5 controls. Derived total peripheral resistance rose by 69%.

Oxygen uptake

The effect of propranolol on oxygen uptake is shown in Table 2. A mean fall of 12.2% in 15 rats was significant when compared to 8 controls.

Oxygen carriage

The effect of propranolol on mixed venous and arterial haemoglobin, oxygen saturation, oxygen content and on $^{\Delta}(A-V)O_2$ is shown in Table 3. Arterial and mixed venous haemoglobin rose significantly by 6.3% and 4.9% respectively. There was no significant change in arterial or mixed venous oxygen saturation. Arterial oxygen content rose significantly by 9.1% but there was no change in mixed venous content. The rise in $^{\Delta}(A-V)O_2$ of 31.5% was due primarily to the rise in arterial oxygen content. The controls showed no significant changes except that a rise in $^{\Delta}(A-V)O_2$ by 7.3% achieved borderline significance.

Venous pressure

The action of propranolol on venous pressure is

Table 2 The acute effect of propranolol on O_2 uptake.

	No. of rats	*Initial* ($ml\ min^{-1}$	*uptake* $200\ g^{-1}$)	*Final* ($ml\ min^{-1}$	*uptake* $200\ g^{-1}$)	*Mean change*	*Mean % change*
Propranolol-treated rats	15	4.01	(0.6)	3.47	(0.5)	−0.54†† (***)	−12.17†† (***)
Controls	8	4.19	(0.6)	4.17	(0.6)	−0.04	−0.6

Standard deviations are in parentheses.
Significance within and between (in parentheses) groups:- ***$P<0.01$; ††$P<0.0005$.

Table 3 The acute effect of propranolol on Hb, O_2 sat and O_2 content on R.V. and aortic blood.

			No. of rats	*Initial (s.d.)*		*Final (s.d.)*		*Mean change*	*Mean % change*
Haemoglobin (g%)	RV	Propranolol	10	12.5	(0.8)	13.11	(1.0)	+0.61†† (***)	+4.9†† (***)
		Control	7	10.67	(1.3)	10.66	(1.4)	−0.02	−0.3
	Aortic	Propranolol	10	12.11	(0.9)	12.85	(0.9)	+0.75†† (**)	+6.3†† (**)
		Control	7	10.9	(1.5)	11.0	(1.6)	+0.16	+1.4
O_2 saturation (%)	RV	Propranolol	10	59.3	(7.3)	56.7	(5.4)	−2.6	−3.3
		Control	7	54.9	(6.4)	52.6	(9.5)	−2.2	−4.1
	Aortic	Propranolol	10	95.7	(3.9)	97.1	(3.1)	+1.3	+1.5
		Control	7	97.5	(2.7)	97.1	(2.9)	−0.4	−0.4
O_2 content (ml dl^{-1})	RV	Propranolol	10	10.3	(0.7)	10.3	(1.2)	−0.04	−0.02
		Control	7	8.2	(1.7)	7.8	(2.0)	−0.4	−4.7
	Aortic	Propranolol	10	16.0	(1.2)	17.5	(1.5)	+1.5†† (***)	+9.1†† (***)
		Control	7	14.7	(2.2)	14.8	(2.2)	+0.1	−0.6
(A − V) O_2 (ml dl^{-1})		Propranolol	10	5.7	(1.4)	7.2	(1.0)	+1.5*** (**)	+31.5*** (**)
		Control	7	6.6	(1.3)	7.1	(1.1)	+0.4*	+7.3*

Significance within and between (in parentheses) groups:- *$P<0.05$; **$P<0.025$; ***$P<0.01$; †$P<0.001$; ††$P<0.0005$.

shown in Table 4. The individual rat data showed a rise, significant on a paired *t* test but not significant when compared to the control rats by an unpaired *t* test. The data from total observations showed a rise in venous pressure which achieved borderline significance compared to the controls.

Correlations

Linear regression analysis was applied to the data from propranol-treated animals. There was a significant correlation between percentage fall in heart rate and percentage fall in oxygen uptake (Figure 2). No significant correlation was found between percentage falls in oxygen uptake and cardiac output ($r=0.41$; $P<0.15$), percentage falls in heart rate and cardiac output ($r=0.09$; $P<0.4$) or between percentage rise in blood pressure and percentage fall in oxygen uptake ($r=0.36$; $P<0.1$). A plot of percentage fall in cardiac output against increase in arterial oxygen content gave a correlation of probable significance, using total observations ($r=0.5$; $P<0.025$) but not when individual data were plotted.

Table 4 The acute effect of propranolol on venous pressure

	No. of rats	*Initial venous pressure* (mmHg)		*Final venous pressure* (mmHg)		*Change*	*% change*
Propranolol (individual rats)	10	2.83	(1.00)	3.11	(0.81)	+0.28**	+15.9**
Controls	5	2.80	(0.58)	2.86	(0.62)	+0.06	+2.1 (*)
Propranolol (total experiments)	14	3.08	(1.12)	3.34	(0.78)	+0.26**	+13.1**

Standard deviations are in parentheses.
Significance within and between (in parentheses) groups:- *$P<0.05$; **$P<0.025$.

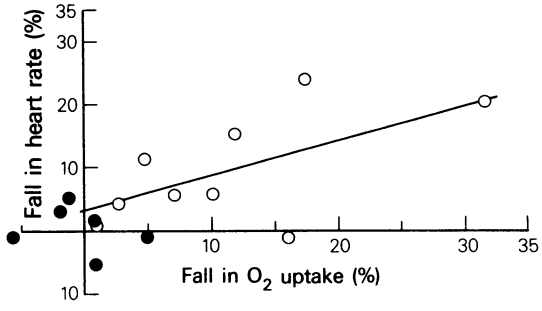

Figure 2 Correlation between the changes in heart rate and O_2 uptake in propranolol-treated (○) and control (●) rats. Regression line shown for propranolol-treated group ($r = 0.62$; $P < 0.025$).

Discussion

The acute responses to an oral dose of propranolol which are described here for the first time in conscious rats, include declines in heart rate, cardiac output and derived stroke volume as have been previously reported in man (Ulrych *et al.*, 1968; Brundin *et al.*, 1976). There have been no previous reports on the correlations of variables as presented here. Blood pressure rose very significantly in contrast to findings in man (Ulrych *et al.*, 1968; Hansson *et al.*, 1974; Brundin *et al.*, 1976) but in agreement with reports in rats (Struyker-Boudier *et al.*, 1979; Coleman, Smith, Smits & Struyker-Boudier, 1980). The significant fall of 12.2% in oxygen uptake is in agreement with the findings of Brundin *et al.* (1976) in which oxygen uptake fell acutely by 6% in man.

The fall in oxygen uptake could have been due to a primary action of propranolol or to a reduction in tissue perfusion directly depressing metabolic rate. Denervation of the gracilis muscle causes an elevation in blood flow; this is associated with an increased oxygen consumption in rat preparations but that of dogs remains constant (Honig, Frierson & Nelson, 1971). In the present experiments, the correlation between the falls in cardiac output and oxygen uptake were not significant but it is not possible to exclude the possibility that the latter was dependent on the former. On average, a reduction of 30.5% in cardiac output was associated with a 12.2% reduction in oxygen uptake. The fall in oxygen delivery, calculated as the reduction in the product of cardiac output and arterial oxygen content, was 26%: thus the ratio of the reduction of oxygen uptake to reduction in oxygen delivery was 0.47. To test this hypothesis, a group of four unanaesthetized rats were subjected to withdrawal of between 2.5 and 3 ml of blood and the change in oxygen delivery and uptake measured before and after blood loss. Oxygen delivery fell by an average of 38% and oxygen uptake by 17%, the ratio between the falls being 0.44. These observations strongly suggest that, at least in small animals such as the rat, the fall in oxygen uptake, induced by propranol, may be purely secondary to the fall in cardiac output and oxygen delivery. This may not apply to larger animals or man.

Increased extraction of oxygen by the tissues was evident, with $^{\Delta}(A-V)O_2$ increasing by 31.5%. Mechanisms which could facilitate this include the slower rate of tissue perfusion and possibly, changes in haemoglobin-oxygen affinity (Oski, Miller, Delivoria-Papadopoulos, Manchester & Shelbourne, 1972; Agostoni, Berfasconi, Gerli, Luzzana & Rossi-Bernardi, 1973) and capillary diffusing capacity. These possibilities are currently under study. The increase in $^{\Delta}(A-V)O_2$ was mainly due to the rise in arterial haemoglobin concentration. This was more likely to have been due to a fall in plasma volume than to an increase in circulating red cell mass. Other workers have found an acute fall in plasma volume after propranolol in man (Julius, Pascual, Abbrecht & London, 1972). The pressure gradient from capillaries to central veins would be reduced by the fall in cardiac output (30.5%) but increased if the post-capillary resistance rose in parallel with the arterial resistance (69%). It is possible that such a rise in pressure gradient, together with a rise in venous pressure, would cause ultrafiltration and haemoconcentration. A rise in venous pressure, which achieved borderline significance in the present studies has not been reported by other investigators of β-blockade. The presence of venodilator β-adrenoceptors has, however, been reported (Sutter, 1965; Sicuteri, Fanciullacci & Del Bianco, 1966; Zsoter & Tom, 1977) and blockade of these may bring about venoconstriction. However, the rise in venous pressure may have been brought about by the reduction in cardiac output due to the inotropic and chronotropic actions of propranolol. The data on cardiac output and venous pressure were derived from separate experiments and the possibility of a significant correlation could not be tested.

Derived total peripheral resistance rose by 69% in the present studies but this did not correlate with heart rate ($P < 0.35$) or with oxygen uptake ($P < 0.35$). It is unlikely that flow was autoregulated to meet a lowered demand for oxygen since the fall in cardiac output was much greater than that in oxygen uptake. Lundvall & Jarhult (1976) maintained that stimulation of the regional sympathetic fibres in the vascular bed of skeletal muscle caused α-adrenergic constriction in the muscle vasculature, which was normally modified by simultaneous β-adrenergic dilatation; they found propranolol increased vascular tone in these circumstances. If rats have a high sympathetic outflow, then propranolol may increase vas-

cular tone by inhibition of vasodilator activity. The effect of propranolol on the baroreceptors has not been determined; Simon, Kiowski & Julius (1977) found no change in sensitivity of the baroreceptors acutely whereas others have reported an increase (Pickering, Gribbin, Strange-Petersen, Cunningham & Sleight, 1972); Hansson *et al.* (1974) demonstrated an increase in sensitivity but only in the long term. There has been no evidence to suggest that propranolol resets the baroreceptors to a higher level and inhibition of vasodilator activity seems the most likely cause of the blood pressure rise. However, cardio-selective β-blockers (β_1) raise total peripheral resistance as well as non-selective (β_1 and β_2) blockers (Frohlich & Bhatia, 1971) such as propranolol and evidence suggests that vasodilatation in muscle is mediated by a β_2-receptor (Dunlop & Shanks, 1967). An alternative suggestion has been made by Struyker-Boudier *et al.* (1979) that the blood pressure rise may be due to the baroreflex response to the acute reduction in cardiac output, persisting even when blood pressure returns to normal or above.

It is not likely that the reduction in heart rate was due to a baroreceptor response to the elevated blood pressure because of the poor correlation between these two changes ($P<0.1$) and because the chronotropic effect of propranolol is well established (Levy & Richards, 1965; Warltier, Gross & Hardman, 1976). The good correlation between changes in heart rate and O_2 uptake might indicate that these were two independent actions of propranolol whose magnitude of response varied together, being dependent on the sensitivity of the animal and on the metabolism of the orally administered drug. Alternatively, changes in oxygen uptake and heart rate may be causally related, in which case they would probably be linked by cardiac output changes, but the latter did not correlate with either of the two former. A multiple linear regression analysis was applied to data on oxygen uptake, arterial oxygen content and cardiac output in an attempt to define cardiac output in terms of oxygen requirement and arterial oxygen carriage; this gave no significant correlation. However, the correlation between cardiac output and arterial oxygen content changes in total observations did achieve borderline significance.

It is concluded that it is only possible to postulate one clear primary site of action of propranolol from the results of these experiments, the well known negative inotropic and chronotropic effect on the heart, to account for the fall in heart rate and cardiac output, associated with a rise in venous pressure. Although it is possible that the rise in arterial pressure may have been secondary to a further action of the drug in blocking the adrenergic vasodilator system, the possibility that arterial resistance and blood pressure rose due to a baroreceptor response to the acute reduction in cardiac output cannot be excluded. The fall in plasma volume could have occurred due to haemoconcentration if post-capillary resistance rose in parallel with arterial resistance. Lastly, the clear fall in oxygen uptake is thought unlikely to have been due to a primary action of propranolol in depressing metabolic rate but is more probably a consequence of the dependence of oxygen uptake on tissue perfusion observed in small animals.

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References

AGOSTONI, A., BERFASCONI, C., GERLI, G.C., LUZZANA, M. & ROSSI-BERNARDI, L. (1973). Oxygen affinity and electrolyte distribution of human blood: changes induced by propranolol. *Science*, **182**, 300–301.

BRUNDIN, T., EDHAG, O. & LUNDMAN, T. (1976). Effects remaining after withdrawal of long-term beta-receptor blockade. Reduced heart rate and altered haemodynamic response to acute propranolol administration. *Br. heart J.*, **38**, 1065–1072.

COLEMAN, T.G., SMITH, T.L., SMITS, J.F.M. & STRUYKER-BOUDIER, H.A.J. (1980). Acute haemodynamic effects of propranolol in the conscious spontaneously hypertensive rat (S.H.R.). *Br. J. Pharmac.*, **68**, 110P.

DUNLOP, D. & SHANKS, R.G. (1967). Selective blockade of adrenoceptive beta receptors in the heart. *Br. J. Pharmac.*, **32**, 201–218.

FROHLICH, E.D. & BHATIA, S. (1971). Haemodynamic effects of propranolol practolol and sotalol in hypertensive patients. *Clin. Pharmac. Ther.*, **13**, 138–144.

HANSSON, L., ZWEIFLER, A.J., JULIUS, S. & HUNYOR, S.N. (1974). Haemodynamic effects of acute and prolonged beta-adrenergic blockade in essential hypertension. *Acta med. scand.*, **196**, 27–34.

HONIG, C.R., FRIERSON, J.L. & NELSON, C.N. (1971). O_2 transport and VO_2 in resting muscle: significance for tissue-capillary exchange. *Am. J. Physiol.* **220**, 357–363.

JULIUS, S., PASCUAL, A.V., ABBRECHT, P.H. & LONDON, R. (1972). Effect of beta-adrenergic blockade on plasma volume in human subjects. *Proc. Soc. exp. Biol. Med.*, **140**, 982–985.

LEVY, J.V. & RICHARDS, V. (1965). Inotropic and metabolic effects of three beta-adrenergic receptor blocking drugs on isolated rabbit left atria. *J. Pharmac. exp. Ther.*, **150**, 361–369.

LUNDVALL, J. & JARHULT, J. (1976). Beta-adrenergic dilator component of the sympathetic vascular response in skeletal muscle. Influence on the microcirculation and

on transcapillary exchange. *Acta physiol. scand.*, **96,** 180–192.

OSKI, F.A., MILLER, L.D., DELIVORIA-PAPADOPOULOS, M., MANCHESTER, J.H. & SHELBOURNE, J.C. (1972). Oxygen affinity in red cells: changes induced by propranolol. *Science*, **175,** 1372–1373.

PICKERING, T.G.B., GRIBBIN, B., STRANGE-PETERSEN, E., CUNNINGHAM, J.C. & SLEIGHT, P. (1972). Effects of autonomic blockade on the baroreflex in man at rest and during exercise. *Circulation Res.*, **30,** 177–185.

POPOVIC, V., KENT, K.M. & POPOVIC, P. (1963). Technique of permanent cannulation of the right ventricle in rats and ground squirrels. *Proc. Soc. exp. Biol. Med.*, **113,** 599–605.

SICUTERI, F., FANCIULLACCI, M. & DEL BIANCO, P.L. (1966). Alpha and beta adrenergic receptors in human veins. *Med. Pharmac. Exp.*, **15,** 73–80.

SIMON, G., KIOWSKI, W. & JULIUS, S. (1977). Effect of β-adrenoreceptor antagonist on baroreceptor reflex sensitivity in hypertension. *Clin. Pharmac. Ther.*, **22,** 293–298.

STRUYKER-BOUDIER, H.A.J., SMITS, J.F. & VAN ESSEN, H. (1979). The role of the baroreceptor reflex in the cardiovascular effects of propranolol in the conscious spontaneously hypertensive rat. *Clin. Sci.*, **56,** 163–167.

SUTTER, M.C. (1965). The pharmacology of isolated veins. *Br. J. Pharmac. Chemother.*, **24,** 742–750.

ULRYCH, M., FROHLICH, E.D., DUSTAN, H.P. & PAGE, I.H. (1968). Immediate haemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive man. *Circulation*, **37,** 411–416.

WARLTIER, D.C., GROSS, G.J. & HARDMAN, H.F. (1976). Effect of propranolol on regional myocardial blood flow and oxygen consumption. *J. Pharmac. exp. Ther.*, **198,** 435–443.

WEEKS, J.R. & JONES, J.A. (1960). Routine direct measurements of arterial pressure in unanaesthetized rats. *Proc. Soc. exp. Biol. Med.*, **104,** 646–650.

ZSOTER, T. & TOM, H. (1967). Adrenoceptive sites in the veins. *Br. J. Pharmac. Chemother.*, **31,** 407–414.

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