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Inhibition of the carotid sinus reflex by the chronic administration of propranolol

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1. The changes in heart rate and arterial pressure produced by the intravenous injection of isoprenaline (0·5 μg/kg), noradrenaline (1·0 μg/kg), phenylethylamine (0·5 mg/kg), amphetamine (0·5 mg/kg) and by bilateral occlusion of the carotid arteries and by stimulation of the central ends of both vagus nerves have been recorded in groups of dogs anaesthetized with pentobarbitone.

2. The acute intravenous injection of propranolol (1 mg/kg) reduced the increases in heart rate produced by the six procedures, the increases in arterial pressure in response to the last five procedures and the decrease in pressure produced by isoprenaline.

3. This decrease produced by propranolol in the pressor responses resulted from a reduction in the increases in cardiac output elicited by the five procedures and has been attributed to blockade of cardiac adrenergic β-receptors.

4. Three groups of dogs were pretreated for 6 weeks by the oral administration of either placebo, propranolol 50 mg/kg daily or propranolol 10 mg/kg twice daily. The responses to the six test procedures were obtained 17–24 hr after the last dose of propranolol, when only minimal blockade of adrenergic β-receptors was present. In the propranolol-treated groups, the pressor response to carotid occlusion but not to the other test procedures was significantly reduced.

5. The pressor response to carotid occlusion was not reduced in a fourth group of dogs given a single dose of propranolol (50 mg/kg) 24 hr before the test procedures.

6. The mechanism of this selective reduction in the pressor response to occlusion of the carotid arteries is not clear. It is suggested that it may contribute to the hypotensive action of propranolol in man during prolonged oral administration.

Several reports have shown that the intravenous injection of propranolol (5–15 mg) under resting conditions in patients with normal or raised arterial pressure

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reduced heart rate and cardiac output (Epstein, Robinson, Kahler & Braunwald, 1965 ; Shinebourne, Fleming & Hamer, 1967 ; Ulrych, Frohlich, Dustan & Page, 1968). A small reduction in arterial pressure was observed by Epstein *et al.* (1965) and by Shinebourne *et al.* (1967), but Ulrych *et al.* (1968) found no change. In all three studies propranolol had no significant effect on calculated systemic peripheral resistance. The increase in arterial pressure during exercise is reduced by the intravenous injection of propranolol through a reduction in cardiac output (Epstein *et al.*, 1965 ; Shinebourne *et al.*, 1968). The oral administration of propranolol for several weeks leads to a gradual and significant reduction in arterial pressure in hypertensive patients (Prichard & Gillam, 1964 ; Patterson & Dollery, 1966 ; Waal, 1966 ; Frohlich, Tarazi, Dustan & Page, 1968). The mechanism of this hypotensive action is not clear but it does not seem to be due to the acute effects of blockade of adrenergic β-receptors, for Frohlich *et al.* (1968) showed that the changes in heart rate and cardiac output produced by propranolol were similar after acute intravenous injection and prolonged oral administration, but a reduction in arterial pressure occurred only after oral administration. This hypotensive action was associated with an unchanged peripheral resistance.

In conscious and in anaesthetized normotensive dogs, the intravenous injection of propranolol (0·2–1 mg/kg) reduces heart rate, cardiac output and arterial pressure, but increases systemic peripheral resistance (Shanks, 1966 ; Bergamaschi & Shanks, unpublished observations). The reduction in arterial pressure is caused by the decrease in cardiac output following the removal by propranolol of resting sympathetic drive to the heart (Shanks, 1966). This effect does not seem to contribute directly to the hypotensive action of propranolol in man following chronic oral administration, so we have made observations in anaesthetized dogs which have been treated with propranolol for 6 weeks to see if changes in cardiovascular reactivity occur after the prolonged administration of the drug.

The tests for cardiovascular reactivity are in general similar to those described by Stone, Ross, Wenger, Ludden, Blessing, Totaro & Porter (1962). These authors studied the effects of drugs on the increases in heart rate and arterial pressure produced by (i) noradrenaline, which acts directly on adrenergic receptors, (ii) phenylethylamine and amphetamine which act indirectly by releasing noradrenaline from its stores and (iii) bilateral occlusion of the carotid arteries and stimulation of the central ends of the vagus nerves which reflexly affect the heart and circulation. The responses to isoprenaline were obtained for assessment of the presence of blockade of adrenergic β-receptors. In the present experiments inhibitory reflex activity on the heart following changes in arterial pressure—for example, after noradrenaline administration—were reduced by the presence of bilateral vagotomy and pentobarbitone anaesthesia (Shanks, 1966).

Methods

Beagles of both sexes weighing 10–15 kg were anaesthetized by the intravenous injection of pentobarbitone ('Nembutal'; Abbott Laboratories) 30 mg/kg. A cuffed endotracheal tube was inserted and the animals ventilated with room air delivered by a Starling Ideal pump. A polythene catheter was inserted into the right jugular vein for the administration of drugs. Both carotid arteries were isolated and carotid sinus hypotension produced by tightening snares placed around the vessels. The vagus nerves were isolated in the neck and divided between

ligatures. Bipolar shielded electrodes were applied to the central end of each vagus nerve. The nerves were stimulated simultaneously by rectangular pulses of 5 m-sec duration applied at a frequency of 30/sec at an intensity of 8 V. Arterial pressure was measured by inserting a cannula into the right femoral artery. The cannula was attached to an inductive-type differential pressure transducer (New Electronic Products Limited), the output of which was connected to a carrier amplifier (S.E. Laboratories). Pressure was recorded on an ink-writing Mingograph (Elema-Schonander). Heart rate was read directly from a cardiotachometer (Horsfall, 1965) triggered by the QRS complex of the electrocardiogram obtained by means of fine needle electrodes inserted into the skin.

The changes in heart rate and mean blood pressure produced by the intravenous injection of (±)-isoprenaline sulphate (Burroughs Wellcome), 0·5 μg/kg ; (−)- noradrenaline bitartrate (Winthrop), 1·0 μg/kg ; (±)-phenylethylamine hydrochloride, 0·5 mg/kg ; (±)-amphetamine sulphate (May & Baker) 0·5 mg/kg, and by occlusion of the carotid arteries for 45 sec and by stimulation of the central ends of both vagus nerves for 45 sec, were recorded in all experiments. All doses are expressed in terms of the salt. The order followed in each dog was stimulation of the vagi, occlusion of the carotid arteries and the intravenous injection of phenylethylamine, noradrenaline, isoprenaline and amphetamine. All procedures produced a rapid change in arterial pressure and heart rate (Fig. 1). The responses, with the exception of those to amphetamine, were of short duration and baseline values were regained in less than 4 min (Fig. 1). The responses to amphetamine were of longer duration and baseline levels were not reached within 20 min.

The test procedures for vascular reactivity were carried out on groups of dogs which were pretreated as follows:

(*A*) Oral administration of an inert placebo, 50 mg/kg, at 10 a.m. daily for 6 weeks.

(*B*) Oral administration of propranolol hydrochloride, 50 mg/kg, at 10 a.m. daily for 6 weeks.

(*C*) Oral administration of propranolol hydrochloride, 50 mg/kg, one dose only at 10 a.m.

(*D*) Oral administration of propranolol hydrochloride, 10 mg/kg, at 8 a.m. and 5 p.m. daily for 6 weeks.

Propranolol ('Inderal,' Imperial Chemical Industries, Ltd.) was given as tablets in gelatine capsules. The dogs in groups *A*, *B* and *C* were anaesthetized 24 hr after their last dose and those in group *D* 17 hours after their last dose.

Observations were also made in five dogs which were not pretreated before anaesthesia was induced with pentobarbitone. The chest was opened through the fourth left interspace and the ascending aorta dissected free from surrounding tissues. A snugly fitting probe for an electromagnetic flowmeter (Medicon, K-2000 ; Statham Instruments) was placed round the ascending aorta to measure stroke volume less coronary blood flow. Femoral arterial pressure and heart rate were also measured and recorded with blood flow through the ascending aorta on a tape-recorder (Ampex, SP300) and displayed on a 4 channel oscilloscope (Airmec Ltd.). The tape-recorder was run continuously throughout the experiment and on completion of the experiment was re-run and the output fed into an ink-writing Mingo-

graph recorder (Elema-Schonander). Total peripheral resistance was expressed in arbitrary units and obtained by dividing mean arterial pressure (mm Hg) by cardiac output (ml./min). The changes in cardiac output, mean arterial pressure, heart rate and total peripheral resistance were recorded in response to the test procedures before and after the intravenous injection of propranolol, 1 mg/kg.

Observations were made in six conscious dogs in which heart rate was measured by a cardiotachometer using fine needle electrodes inserted into the skin. Isoprenaline was injected through a fine catheter inserted into an ear vein. The increases in heart rate in response to isoprenaline were determined before and at regular intervals after the oral administration of propranolol hydrochloride.

Results

Effect of pretreatment on heart rate and arterial pressure

Thirty minutes after completion of surgery, heart rate and arterial pressure were recorded in each dog. The average values for each in the different groups of dogs are given in Table 1. There were no significant differences in resting heart rate

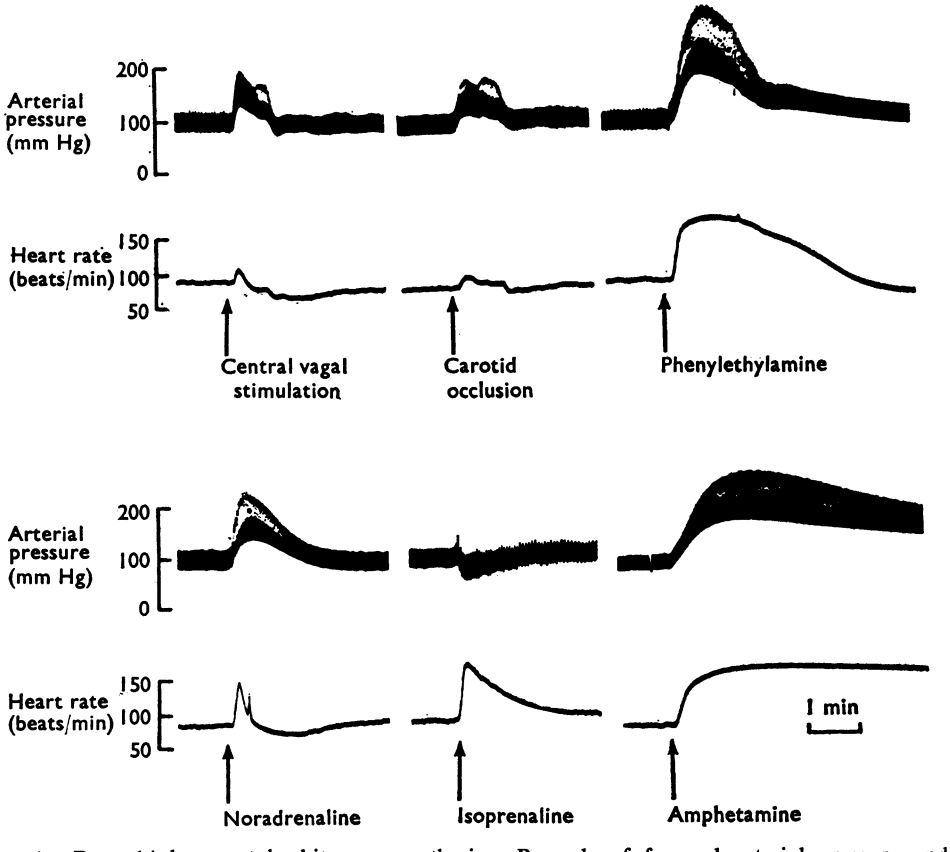

FIG. 1. Dog, 14 kg, pentobarbitone anaesthesia. Records of femoral arterial pressure and heart rate. Responses to the six test procedures described in the text.

and arterial pressure between the control (placebo-treated) and propranolol-treated groups of dogs except that heart rate was significantly less ($P<0.05$) in group *C* which received a single dose of propranolol.

Duration of action of propranolol

The increases in heart rate produced by the intravenous injection of isoprenaline 0·4 μg/kg were recorded before and at intervals after the oral administration of propranolol 10 mg/kg in two conscious dogs. The averaged results are given in Fig. 2a. Propranolol reduced the isoprenaline tachycardia ; the reduction was still marked 10 hr after its administration.

In four dogs, the responses to isoprenaline were obtained before and at intervals after the oral administration of propranolol 50 mg/kg. Observations were made on all four dogs for 7 hr and on two for a further 5 hr. The averaged results are given in Fig. 2b. As the response to 0·4 μg/kg isoprenaline was completely blocked

TABLE 1. *Mean values* (±S.E.) *for heart rate and mean arterial pressure in the four groups of dogs.*

Group	Drug	Dose (mg/kg)	No. of days	No. of dogs	Heart rate (beats/min)	Arterial pressure (mm Hg)
A	Placebo	50	42	11	136±4·9	144±5·9
B	Propranolol	50	42	12	135±5·2	134±6·2
C	Propranolol	50	1	7	*119±6·2	124±7·5
D	Propranolol	10×2	42	8	135±5·8	140±6·9

* $P<0.05$

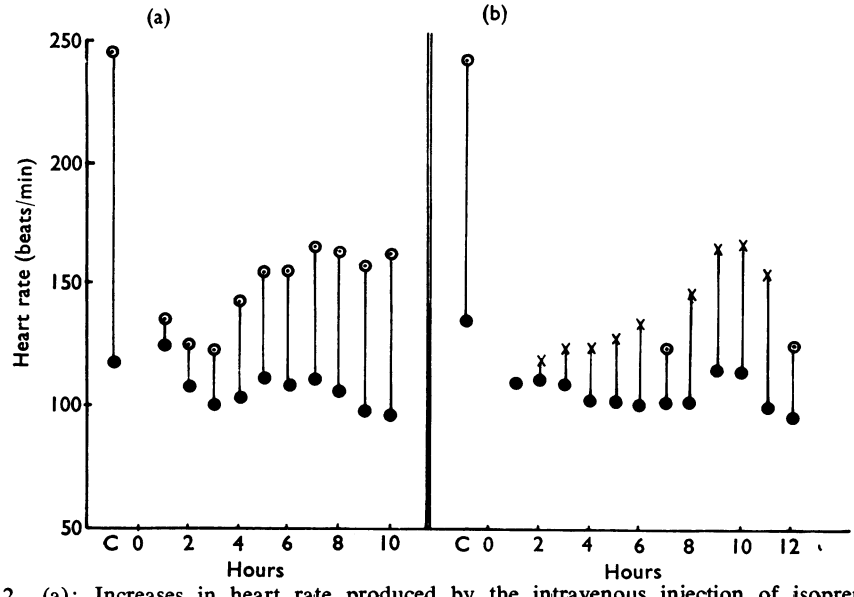

FIG. 2. (a): Increases in heart rate produced by the intravenous injection of isoprenaline 0·4 μg/kg before (C) and at intervals after the oral administration of propranolol 10 mg/kg at time 0. Mean of observations in two conscious dogs. ●, Resting heart rate ; ⊙, maximum response to isoprenaline. (b): Similar observations in conscious dogs given propranolol 50 mg/kg orally. Mean of observations in four dogs for first 7 hr and in two dogs from 8 to 12 hr. ●, Resting heart rate ; ⊙, maximum response to isoprenaline 0·4 μg/kg ; ×, maximum response to isoprenaline 2·0 μg/kg.

1 hr after the administration of propranolol, the dose of isoprenaline was subsequently increased to 2·0 μg/kg except for the tests 7 and 12 hr after propranolol. The effect of propranolol on the isoprenaline tachycardia declined with time ; after 11 hr the response to isoprenaline 2·0 μg/kg was only 50% of the control response to 0·4 μg/kg and at 12 hr the response to the latter dose was still reduced by 73%. These results indicate that in the dogs pretreated with propranolol there was marked blockade of adrenergic β receptors in the heart during the greater part of each 24 hr period.

Acute effects of propranolol

The responses to the test procedures were obtained before and after the intravenous injection of propranolol 1 mg/kg in the eleven dogs which were pretreated with placebo (group *A*). The averaged results are given in Table 2. Propranolol reduced significantly the increases in heart rate and the changes in mean arterial pressure produced by all the test procedures. Further studies were made in five dogs. The results of these experiments are given in Table 3. The effects of propranolol on the changes in heart rate and arterial pressure produced by the test procedures were similar to those described above. Cardiac output was increased by the six procedures ; the increases were smaller after propranolol. The reduction in peripheral resistance produced by isoprenaline was significantly less after the administration of propranolol. The other five procedures increased peripheral resistance before and after propranolol. The effect of noradrenaline was increased significantly after propranolol. The increases in peripheral resistance produced by phenylethylamine and amphetamine were significantly less after propranolol. There was no significant change in the increases in resistance produced by carotid occlusion and central vagal stimulation.

Effect of pre-treatment with propranolol on responses to test procedures

Responses to isoprenaline

The intravenous injection of isoprenaline produced an increase in heart rate in the four groups. The increase was significantly less in group *C* than in group *A* (Table 4). Isoprenaline produced a significant fall in arterial pressure in groups *A* and *D* only (Table 4). These results show that at the time of eliciting the test procedures there was blockade of adrenergic β receptors in the peripheral vessels in groups *B* and *C* and of the chronotropic receptors in group *C*.

Responses to noradrenaline

The intravenous injection of noradrenaline increased arterial pressure in the four groups ; there was no significant difference between the responses (Table 4). Heart rate was increased by noradrenaline in all groups ; the increase was significantly less in group *B* than in group *A* (Table 4).

Responses to phenylethylamine

The intravenous injection of phenylethylamine increased arterial pressure to the same extent in all four groups (Table 4). Heart rate was increased in the four groups but the increase was significantly less in groups *B*, *C* and *D* than in group *A* (Table 4).

TABLE 2. *Effect of propranolol, 1 mg/kg by intravenous injection, on the changes in heart rate and mean arterial pressure produced by the test procedures.*

	Heart rate (beats/min)				Arterial pressure (mm Hg)			
	Control		Propranolol		Control		Propranolol	
Test procedures	Initial value	Response	Initial value	Response	Initial value	Response	Initial value	Response
Isoprenaline	149 ±6·3	72 ±6·6	126 ±7·0	*7 ±2·0	127 ±5·1	−36 ±5·8	128 ±10·2	*2 ±3·6
Noradrenaline	147 ±6·5	58 ±11·1	127 ±6·3	*7 ±1·9	130 ±6·3	91 ±12·5	136 ±10·1	*52 ±11·6
Phenylethylamine	137 ±6·2	134 ±8·6	123 ±6·2	*13 ±2·6	140 ±5·7	172 ±9·9	121 ±10·9	*54 ±6·4
Amphetamine	154 ±7·6	110 ±7·5	143 ±6·5	*21 ±2·8	112 ±6·6	147 ±11·7	132 ±11·9	*41 ±3·5
Carotid occlusion	133 ±6·7	32 ±4·1	123 ±6·1	*1 ±0·8	142 ±5·9	65 ±6·8	127 ±9·8	*13 ±4·3
Central vagal stimulation	136 ±4·9	36 ±10·0	125 ±6·0	*1 ±0·3	144 ±5·9	67 ±15·0	130 ±11·3	*26 ±10·8

Average results from eleven dogs except for amphetamine (6 dogs). Standard errors of each mean value are included.

* $P<0·001$.

TABLE 3. *Changes in heart rate, mean arterial pressure, cardiac output and peripheral resistance produced by the test procedures before (a) and after the intravenous injection of propranolol, 1 mg/kg (b). Mean of observations in five dogs.*

		Heart rate (beats/min.)		Arterial pressure (mm/Hg)		Cardiac output (ml./min)		Peripheral resistance	
Test procedure		Initial	Response	Initial	Response	Initial	Response	Initial	Response
Isoprenaline	*a*	158·4	76·0	114·8	−32·6	1276	953	0·0894	−0·0401
0·5 μg/kg	*b*	125·4	5·6*	125·4	+0·6*	905	118*	0·1439	−0·0073*
Noradrenaline	*a*	161	48·4	121·8	75·8	1451	754	0·0851	0·0191
1·0 μg/kg	*b*	124·8	−6·2*	116·4	68·4	895	−63*	0·1389	0·1441*
Phenylethylamine	*a*	162·2	79·4	120	144·8	1488	335	0·0839	0·0705
0·5 mg/kg	*b*	125	6·2*	119·8	36·2*	949	163	0·1280	0·0233*
Amphetamine	*a*	156	68·4	123	112·6	1205	356	0·1180	0·0568
0·5 mg/kg	*b*	128·6	1·4*	115·8	18·4*	930	122*	0·1325	0·0043*
Carotid occlusion	*a*	156	15·8	119·6	87·6	1214	408	0·0671	0·0797
	b	127·4	3·2*	118·8	36·2	970	46*	0·1293	0·0536
Central vagal stimulation	*a*	161·6	15	118	113	1364	498	0·0864	0·0652
	b	127·8	6·2*	121·6	55·6	1061	−117*	0·1140	0·0827

* $P<0·05$

TABLE 4. *The changes in mean arterial pressure and heart rate (±S.E.) produced by the test procedures in the four groups of dogs.*

Group	Drug	Daily dose (mg/kg)	Duration (days)	Number of dogs	Mean arterial pressure (mm Hg) Initial value	Response	*P*	Heart rate (beats/min) Initial value	Response	*P*
					Isoprenaline 0·5 μg/kg					
A	Placebo	50	42	11	127±5·1	−36±5·8		149±6·3	72±6·6	
B	Propranolol	50	42	12	131±4·9	−0±5·5	<0·0005	139±6·0	64±6·4	N.S.
C	Propranolol	50	1	7	104±6·5	−6±7·2	<0·0025	123±7·9	47±8·3	<0·025
D	Propranolol	10×2	42	8	130±6·0	−30±6·8	N.S.	134±7·4	86±7·8	N.S.
					Noradrenaline 1·0 μg/kg					
A	Placebo	50	42	10	130±6·3	91±12·5		147±6·5	58±11·1	
B	Propranolol	50	42	12	131±5·7	81±11·4	N.S.	140±5·9	29±10·0	<0·05
C	Propranolol	50	1	7	104±7·5	105±14·9	N.S.	123±7·8	54±13·3	N.S.
D	Propranolol	10×2	42	8	129±7·0	124±14·0	N.S.	140±7·3	59±12·4	N.S.
					Phenylethylamine 0·5 mg/kg					
A	Placebo	50	42	11	140±5·7	172±9·9		137±6·2	134±8·6	
B	Propranolol	50	42	12	131±5·4	145±9·5	N.S.	135±5·8	95±8·3	<0·0025
C	Propranolol	50	1	7	113±7·2	164±12·4	N.S.	120±7·7	102±10·8	<0·025
D	Propranolol	10×2	42	8	132±6·7	181±11·7	N.S.	138±7·2	109±10·1	<0·05
					Amphetamine 0·5 mg/kg					
A	Placebo	50	42	6	112±6·6	147±11·7		154±7·6	110±7·5	
B	Propranolol	50	42	5	114±9·3	109±12·8	N.S.	146±8·3	80±8·2	<0·0125
D	Propranolol	10×2	42	8	131±7·3	146±10·0	N.S.	142±6·5	98±6·5	N.S.
					Bilateral carotid occlusion					
A	Placebo	50	42	11	142±5·9	65±6·8		133±6·7	32±4·1	
B	Propranolol	50	42	12	133±5·7	37±6·5	<0·005	137±6·4	7±3·9	<0·0005
C	Propranolol	50	1	7	121±7·5	60±8·6	N.S.	120±8·4	15±5·1	<0·0125
D	Propranolol	10×2	42	8	139±7·0	44±8·0	<0·05	133±7·9	17±4·8	<0·025
					Central vagal stimulation					
A	Placebo	50	42	11	144±5·9	67±15·0		136±4·9	36±10·0	
B	Propranolol	50	42	10	134±6·2	61±15·7	N.S.	135±5·2	22±11·9	N.S.
C	Propranolol	50	1	7	124±7·5	86±18·7	N.S.	119±6·2	39±10·6	N.S.
D	Propranolol	10×2	42	8	140±6·9	54±17·5	N.S.	135±5·8	19±12·7	N.S.

Responses to amphetamine

The responses to the intravenous injection of amphetamine were determined in groups *A*, *B* and *D*. Amphetamine increased arterial pressure in the three groups to the same extent (Table 4). An increase in heart rate occurred in the three groups but was significantly less in group *B* than *A* (Table 4).

Responses to bilateral carotid occlusion

Occlusion of the carotid arteries increased arterial pressure and heart rate in all groups. The increase in pressure was significantly less in groups *B* and *D* than in group *A* (Table 4). The increase in heart rate was significantly less in groups *B*, *C* and *D* (Table 4).

Responses to central vagal stimulation

Arterial pressure and heart rate were increased in the four groups by stimulation of the central ends of the vagi. There was no significant difference between the responses in group *A* and in the other groups (Table 4).

Discussion

The intravenous injection of noradrenaline, phenylethylamine and amphetamine, bilateral occlusion of the carotid arteries and stimulation of the central ends of the vagi raised mean arterial pressure through increases in cardiac output and in peripheral resistance. The acute administration of propranolol reduced the pressor responses to all these procedures. In the case of noradrenaline and central vagal stimulation, this resulted only from a reduction in the increase in cardiac output, as after propranolol, there was a greater increase in peripheral resistance. This potentiation of the vasoconstrictor action of noradrenaline may be attributed to propranolol blocking its peripheral vasodilator action which is mediated through adrenergic β-receptors (McNay & Goldberg, 1966 ; Brick, Hutchison & Roddie, 1967). The smaller increases in arterial pressure produced by amphetamine, phenylethylamine and bilateral carotid occlusion after propranolol resulted from a reduction in the increases which they caused in both cardiac output and peripheral resistance. The reduction produced by propranolol in the cardiac output responses to the five procedures can be attributed to blockade of adrenergic β-receptors in the heart (Shanks, 1966). The reduction in the peripheral vasoconstriction in response to amphetamine and phenylethylamine was unexpected and cannot at present be explained.

The object of the present experiments was to study the effects of prolonged adrenergic β-receptor blockade on the responses to the test procedures apart from those produced by acute blockade. Thus observations were made in the dogs at a time when it was hoped that propranolol was not producing blockade of β-receptors. The administration of propranolol 50 mg/kg orally produced marked inhibition of an isoprenaline tachycardia for more than 12 hr in the conscious dogs. The presence or absence of blockade of β-receptors at the time the test procedures were performed is shown by comparison of the effects of isoprenaline on heart rate and arterial pressure in the different groups of dogs. The isoprenaline tachycardia was not reduced in the dogs which received propranolol 50 mg/kg daily or 10 mg/kg

twice per day, but was slightly reduced in the group given a single dose of 50 mg/kg; the reduction was much less than that produced by the intravenous administration of propranolol 1 mg/kg. In the two groups given propranolol 50 mg/kg daily there was a reduction in the isoprenaline depressor response as compared with the placebo group, indicating blockade of adrenergic β-receptors in the peripheral blood vessels. Thus, cardiac β-receptor blockade was absent or minimal at the time observations were made in all three groups of dogs pretreated with propranolol. This was confirmed by the absence of a difference in the pressor responses produced by noradrenaline in the four groups.

The most striking finding in these experiments was the significant reduction in the pressor response to bilateral carotid occlusion in the two groups of dogs which received propranolol for six weeks. The pressor responses to the other test procedures were not reduced in these groups. The same differences were not clearly seen in the heart rate responses.

This reduction in the pressor response to carotid occlusion did not result from blockade of adrenergic β-receptors in the heart for the reasons discussed above. The reduction must be the consequence of the prolonged administration of propranolol because the response was not reduced in the group which received the single dose of propranolol.

During occlusion of the carotid arteries, pressure in the carotid sinuses is reduced (Corcondilas, Donald & Shepherd, 1964). This leads to a reflex increase in sympathetic nervous activity increasing heart rate, cardiac output and peripheral resistance (Polosa & Rossi, 1961 ; Corcondilas *et al.*, 1964). Many drugs with different modes of action can reduce the pressor response to carotid occlusion. These include ganglion blocking agents (Prochnik, Maison & Stutzman, 1950) and reserpine and guanethidine which block sympathetic nerve transmission at a post-ganglionic site through depletion of tissue stores of noradrenaline, or interference with transmission in the nerve fibre (Green, 1962 ; Stone *et al.*, 1962). The reduction in the pressor response to carotid occlusion in the present experiments did not result from depletion of the tissue stores of noradrenaline, as the responses to amphetamine and phenylethylamine were not reduced or from interference with transmission through the sympathetic ganglia or post-ganglionic sympathetic fibres, as the response to central vagal stimulation was not reduced. Thus it would appear that the response to carotid occlusion was reduced by interference with the afferent side of the reflex.

The present experiments did not elucidate the mechanism by which propranolol interfered with the carotid occlusion reflex. The effect may be due to a direct action of propranolol unrelated to blockade of adrenergic β-receptors. Propranolol has local anaesthetic properties which have been demonstrated in the skin of the guinea-pig (Morales-Aguilerá & Vaughan Williams, 1965) and in the isolated sciatic nerve of the frog (Dunlop & Shanks, 1968). The local anaesthetic action occurs with concentrations of propranolol greater than those required to block adrenergic β-receptors in the heart (Black, Duncan & Shanks, 1965). It is not known if the concentrations of propranolol in the blood after the oral administration of the doses used in the present experiments are sufficient to interfere with nerve function. Biscoe (1965) has shown in the isolated superfused carotid body that pronethalol reduced chemoreceptor activity and suggested that this did not result from its local anaesthetic activity. The effects of propranolol on this preparation have not been studied, but if it possessed a similar action and if, in addition, both drugs affected

the carotid sinus in the same way as the carotid body, propranolol would reduce responses elicited by changing pressure in the sinuses. There is no apparent explanation for the delay in the onset of action of propranolol on the reflex.

On the other hand, the reduction in the carotid occlusion reflex may be the indirect result of blockade of adrenergic β-receptors in the heart. Propranolol reduces the increases in cardiac output which occur during exercise (Donald & Samueloff, 1966) and excitement (Bergamaschi & Shanks, unpublished observations) in conscious dogs. As a result of the reduction in stimulation of the carotid sinus baroreceptors, these may become reset at a different level. Prichard (1966) has suggested that this is the mechanism by which the prolonged oral administration of propranolol reduces arterial pressure in patients with hypertension (Prichard & Gillam, 1964 ; Frohlich *et al.*, 1968). As the latter found that the acute intravenous injection of 10 mg propranolol in hypertensive patients did not reduce arterial pressure, it would appear that the hypotensive action in man is not due to the acute effects of blocking adrenergic β-receptors. Prichard (1966) has suggested that there is a gradual resetting of the arterial baroreceptors to regulate arterial pressure at a lower level following dampening down of pressor responses by blockade of their cardiac component. At present there is no evidence to indicate if the findings in the present experiments are related to the hypotensive action of propranolol in man, although they may both be a manifestation of the same basic action or the effect in hypertensive patients may result from a re-setting of the baroreceptors and from interference with the carotid sinus reflex as found in the present experiments.

The prolonged administration of propranolol did not reduce arterial pressure in the present experiments ; Farmer & Levy (1968) have found that it did not reduce arterial pressure in normotensive or hypertensive rats or dogs. These observations do not exclude a relationship between the present experiments and the hypotensive action of propranolol in man.

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