

AN OPPOSING ROLE FOR THE ADRENALS IN THE HYPOTENSIVE EFFECTS OF PROPRANOLOL IN THE SPONTANEOUSLY HYPERTENSIVE RAT

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d,l-Propranolol (1 and 5 mg/kg s.c.) did not cause a fall in blood pressure and induced only a limited decrease in heart rate in conscious spontaneously hypertensive rats (SHR). In contrast, after bilateral adrenalectomy, d,l-propranolol induced a rapid and profound decrease in blood pressure and heart rate. Decreases in heart rate and blood pressure in the individual animals were not correlated. The effects were mainly caused by l-propranolol but an additional effect of d-propranolol cannot be excluded. The decrease in blood pressure was not observed after removal of the adrenal medulla. Heart rate decreased only slightly in these animals. After treatment of adrenalectomized SHR with corticosterone (1 mg/kg b.w./h) the decrease in blood pressure due to d,l-propranolol was completely abolished. The fall in heart rate was diminished. Central injection of d,l-propranolol into the lateral brain ventricle of adrenalectomized SHR caused cardiovascular changes which were less pronounced than those following peripheral injection of comparable doses. The inhibitory effects of d,l-propranolol also occurred in adrenalectomized normotensive Wistar Kyoto rats. However, no significant changes in blood pressure and only a limited fall in heart rate were observed in adrenalectomized normotensive and renal hypertensive Wistar rats. It is concluded that the presence of the adrenal cortex, but not of the adrenal medulla prevents acute hypotension and bradycardia after propranolol in the conscious SHR.

Spontaneously hypertensive rat
Corticosteroids

Hypotension and bradycardia

Propranolol

Adrenalectomy

1. Introduction

The anti-hypertensive effect of propranolol in various types of hypertension in man has been well documented (Prichard and Gillam, 1969; Frolich et al., 1968; Bühler et al., 1972; Zacharias et al., 1972). In the rat with experimental hypertension however, the blood pressure lowering effect is less clear (Farmer and Levy, 1968; Menard et al., 1973; Lundgren, 1974; Fernandes et al., 1976; Leenen and Ackerman, 1976). There is some evidence that the spontaneously hypertensive rat (SHR, Wistar Kyoto strain) may be a relatively sensitive laboratory animal for observing the anti-hypertensive effects of β -adrenergic block-

ing drugs (Roba et al., 1972; Vavra et al., 1973; Weiss et al., 1974; Forman and Mulrow, 1974).

The decrease in blood pressure after systemic administration of propranolol in the SHR generally occurs after 2–3 days of treatment (Forman and Mulrow, 1974; Sweet et al., 1977). The mechanism of action has not yet been fully elucidated. Both a peripherally mediated mechanism and a centrally mediated one merit consideration (Tarazi and Dustan, 1972; Bühler et al., 1973; Day and Roach, 1974; Reid et al., 1974; Garvey and Ram, 1975; Ram et al., 1977). Neither of the proposed mechanisms of action however gives a satisfactory explanation for the dif-

ferences in hypotensive activity of propranolol in several types of hypertension. Recently however, Buckenham et al. (1978) reported that adrenal catecholamines in DOCA-saline hypertensive rats moderated the hypotensive effect of high doses of the non-selective β -adrenoceptor blocking drug pindolol.

In the present study we investigated the role of the adrenals in the acute cardiovascular effects of propranolol in SHR.

2. Materials and methods

Male spontaneously hypertensive rats of the Wistar Kyoto strain (SHR/NIH-Cpb) aged 11–15 weeks were used. The blood pressure was recorded in conscious animals from a cannula (PE25 connected to a PE60 cannula) in the caudal artery at the base of the tail, by a Statham transducer (model P23Ac) connected to a Grass polygraph. The heart rate was calculated from the blood pressure tracings. Cannulas were implanted under ether anesthesia 4–5 h before the experiment was started.

Renal hypertension was induced by applying a solid silver clip (internal diameter 0.20 mm) on the left renal artery of male Wistar rats weighing 130–160 g (Leenen and De Jong, 1971). This procedure results in a regular development of hypertension, reaching a plateau 3–4 weeks after the operation. The hypertensive rats were used 3–4 weeks after application of the clip. The body weight range at that time was 180–250 g.

Effects of propranolol in normotensive Wistar Kyoto and Wistar rats were assessed in groups age-matched with the hypertensive animals.

Injections into the central nervous system were given into the lateral ventricle via a permanently implanted cannula as described by Hayden et al. (1966).

Bilateral adrenalectomy or nephrectomy was carried out under ether anesthesia 4–5 h before the experiment was started. Removal of the adrenal medulla was done under ether

anesthesia 2 days before the experiment by making a small incision in the adrenal and softly pushing out the medulla.

d,l-Propranolol (propranolol hydrochloride, ICI), d-propranolol (ICI), l-propranolol (ICI) or vehicle (0.9% NaCl) were injected subcutaneously in a volume of 1 ml/kg body weight or dissolved in a volume of 2 μ l saline for CNS injection. Substitution therapy was carried out with corticosterone (25 mg/ml in ethanol diluted with saline).

Results are expressed as means \pm standard of the mean (SEM). The significance of the difference between values for the control and treated groups was determined with Student's *t*-test. *P* values less than 0.05 were considered significant.

3. Results

Two different doses of d,l-propranolol (1 and 5 mg/kg s.c.) failed to decrease blood pressure during the 2 h of measurement in intact SHR (table 1). A small increase was observed 5 min after the administration and for the lowest dose this was followed by a small decrease after 120 min. With the highest dose, the heart rate decreased significantly by a maximum of 50 ± 6 bpm.

Administration of d,l-propranolol to animals bilaterally adrenalectomized 4–5 h previously however induced a profound decrease in blood pressure and heart rate (fig. 1). Maximal effects were observed 30 min after the injection (-34 ± 6 mm Hg and -140 ± 8 bpm respectively after 5 mg/kg). After 120 min both parameters in both groups of rats were still significantly different from their respective control values. The individual values for decrease in blood pressure and heart rate 30 min after propranolol (5 mg/kg) were not correlated ($r = 0.25$).

In the adrenalectomized rats receiving d,l-propranolol there was a marked fluctuation of the blood pressure when it was maximally decreased (fig. 2). No simultaneous changes in heart rate occurred however.

TABLE 1

Effect of various doses of d,l-propranolol (s.c.) on mean blood pressure and heart rate of conscious spontaneously hypertensive rats.

Treatment	Dose (mg/kg)	Basal values	Time after injection (min)								
			5	15	30	45	60	75	90	105	120
Δ Blood pressure											
Saline	—	142	0	3	6	—3	—1	1	—1	4	0
		± 3 (6) ¹	± 1	± 3	± 5	± 2	± 5	± 5	± 7	± 4	± 3
Propranolol	1	141	12	6	—2	—9	—11	—8	—8	—6	—13
		± 9 (6)	± 5 ²	± 6	± 3	± 4	± 5	± 4	± 5	± 6	± 5 ²
Propranolol	5	131	10	1	5	—2	—1	1	—1	2	1
		± 5 (6)	± 4 ²	± 3	± 3	± 4	± 5	± 5	± 3	± 3	± 1
Δ Heart rate											
Saline	—	324	11	22	32	10	27	17	13	—5	12
		± 9	± 15	± 18	± 10	± 12	± 19	± 14	± 16	± 12	± 6
Propranolol	1	320	22	8	32	2	5	17	—13	—16	—22
		± 18	± 20	± 21	± 10	± 14	± 14	± 14	± 14	± 10	± 9 ²
Propranolol	5	354	—27	—34	—39	—50	—36	—36	—38	—38	—37
		± 21	± 10	± 5 ²	± 10 ²	± 6 ²	± 11 ²	± 11 ²	± 7 ²	± 9 ²	± 10 ²

¹ Number of animals is given in parentheses.

² $P < 0.05$, compared to corresponding control value (saline treatment).

In order to investigate the effect of the isomers on blood pressure and heart rate d- and l-propranolol (2.5 and 5 mg/kg) were administered to different groups of adrenalectomized SHR. The maximal responses 15–30 min after administration of l- and d-propranolol are depicted in fig. 3. A dose-dependent fall in heart rate was observed after l-propranolol. The hypotension and bradycardia after d-propranolol were much less pronounced. After the highest dose responses were less than half those observed after 5 mg/kg l-propranolol.

To investigate whether the adrenal cortex or the adrenal medulla was responsible for the influence of the adrenals, d,l-propranolol was administered to demedullated animals. In these rats d,l-propranolol (5 mg/kg) caused no significant decrease of blood pressure. The heart rate showed only a limited decrease from 15–60 min after the d,l-propranolol injection (fig. 4). After treatment of adrenalectomized animals with corticosterone (1 mg/kg b.w./h s.c.) the decrease in heart rate

and blood pressure due to d,l-propranolol was nearly abolished. The heart rate showed only a small decrease after 30 and 45 min (fig. 5). Substitution with 0.3 mg/kg b.w./h s.c. corticosterone did not prevent the hypotensive action and bradycardia (fig. 5).

Central injection of d,l-propranolol into a lateral brain ventricle of adrenalectomized rats (0.5 and 1.5 mg/kg) caused cardiovascular changes which were less pronounced than those following the peripheral injection of comparable doses (table 2). Significant changes in blood pressure and heart rate were only observed with the highest dose of d,l-propranolol. The maximal responses occurred after the same time interval as after peripheral injection of d,l-propranolol.

Parasympathetic activation did not seem to be an important factor in causing the bradycardia or hypotension since bilateral vagotomy and pretreatment with atropine (5 mg/kg) did not prevent the cardiovascular effects of d,l-propranolol in adrenalectomized SHR. Maximal decreases in blood pressure and heart

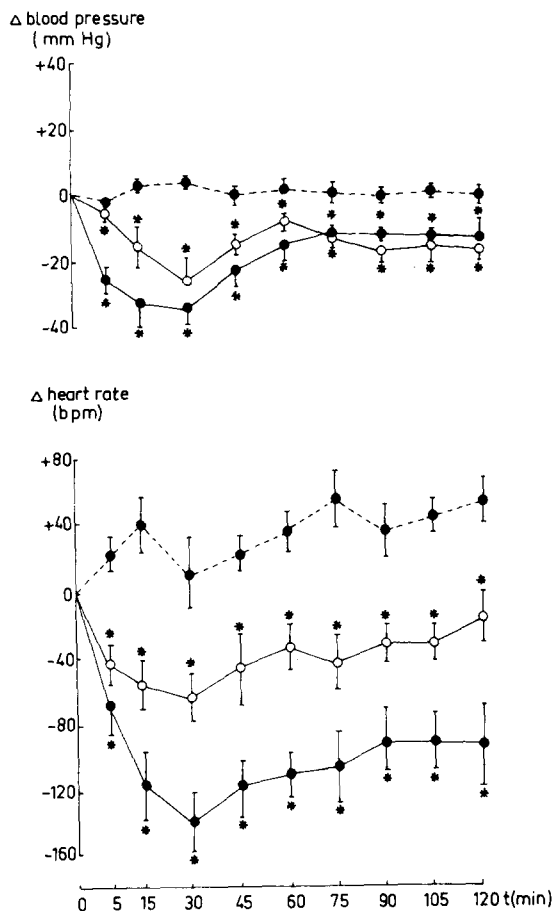


Fig. 1. Effect of various doses of d,l-propranolol on mean blood pressure and heart rate of adrenalectomized conscious spontaneously hypertensive rats. ●-----● saline (basal values: 128 \pm 5 mm Hg and 348 \pm 13 bpm, n = 8). ○-----○ 1 mg/kg s.c. propranolol (basal values: 128 \pm 5 mm Hg and 349 \pm 14 bpm, n = 6). ●-----● 5 mg/kg s.c. propranolol (basal values: 134 \pm 5 mm Hg and 396 \pm 20 bpm, n = 7). * P < 0.05.

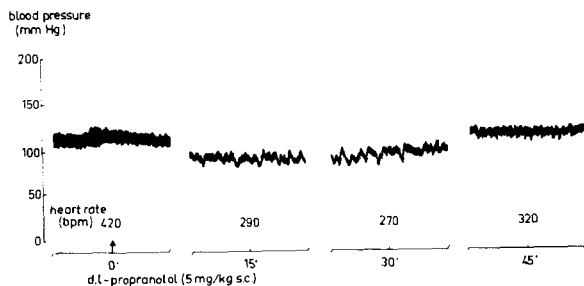


Fig. 2. Blood pressure recording depicting the response to d,l-propranolol (5 mg/kg s.c.) in an adrenalectomized conscious spontaneously hypertensive rat.

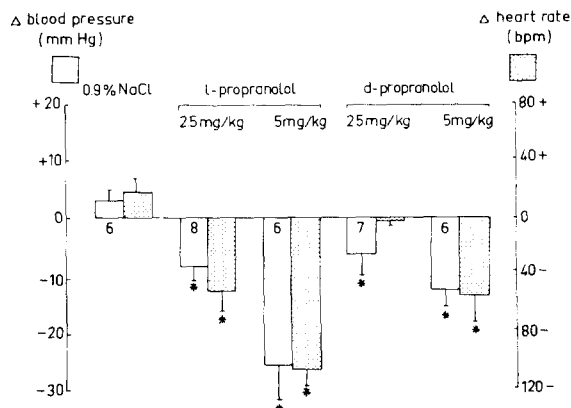


Fig. 3. Maximal decreases in mean blood pressure and heart rate, 15-30 min after administration of different doses of d- and l-propranolol to adrenalectomized conscious spontaneously hypertensive rats. Basal values did not differ significantly from those depicted in fig. 1. * P < 0.05.

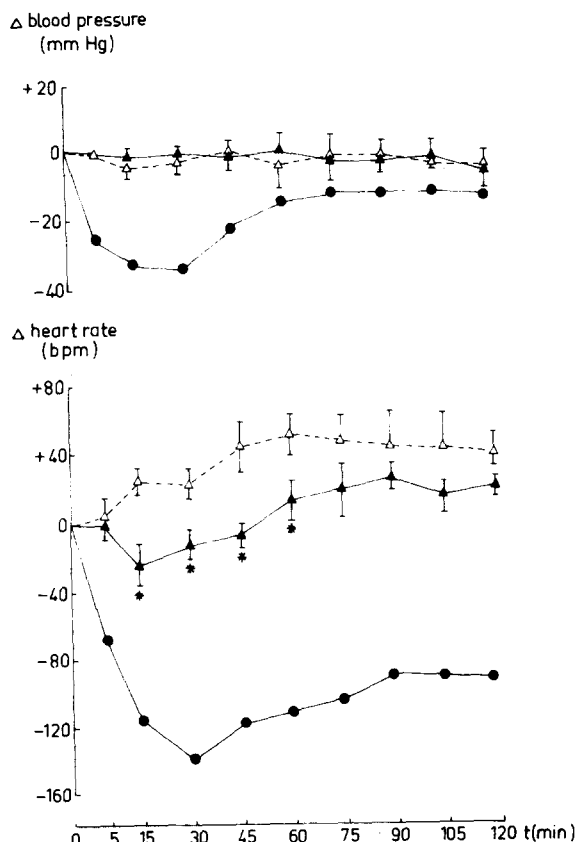


Fig. 4. Effect of d,l-propranolol (5 mg/kg s.c.) on mean blood pressure and heart rate of adrenal demedullated conscious spontaneously hypertensive rats. ▲-----▲ propranolol after demedullation (basal values: 128 \pm 7 mm Hg and 313 \pm 11 bpm, n = 6). △-----△ saline after demedullation (basal values: 145 \pm 3 mm Hg and 328 \pm 6 bpm, n = 5). The group of adrenalectomized rats treated with propranolol alone (●-----●) is taken from fig. 1. * P < 0.05.

TABLE 2

Effect of central (i.c.v.) administration of various doses of d,l-propranolol on mean blood pressure and heart rate of adrenalectomized conscious spontaneously hypertensive rats.

Treatment	Dose (mg/kg)	Basal values	Time after injection (min)								
			5	15	30	45	60	75	90	105	120
Δ Blood pressure											
Saline	—	152	0	−1	−4	−8	−9	−9	−11	−12	−12
		± 4 (9) ¹	± 1	± 2	± 3	± 3	± 2	± 3	± 3	± 3	± 3
Propranolol	0.5	143	−3	1	−2	−3	−7	−13	−15	−15	−13
		± 6 (7)	± 2	± 1	± 3	± 3	± 4	± 7	± 8	± 9	± 8
Propranolol	1.5	151	−8	−15	−7	−8	−8	−11	−13	−16	−14
		± 2 (7)	± 3 ²	± 4 ²	± 2	± 2	± 1	± 4	± 4	± 4	± 4
Δ Heart rate											
Saline	—	422	−2	9	8	−1	−1	−8	−4	−9	7
		± 14	± 12	± 7	± 9	± 9	± 9	± 12	± 11	± 8	± 10
Propranolol	0.5	354	10	−13	11	18	19	34	29	27	22
		± 13	± 10	± 13	± 17	± 13	± 17	± 13 ²	± 15	± 18	± 18
Propranolol	1.5	401	−19	−24	−34	−9	−5	−3	5	10	8
		± 18	± 18	± 10 ²	± 10 ²	± 18	± 12	± 21	± 18	± 15	± 23

¹ Number of animals is given in parentheses.

² $P < 0.05$, compared to corresponding control value (saline treatment).

TABLE 3

Effect of d,l-propranolol (5 mg/kg s.c.) on mean blood pressure and heart rate of adrenalectomized conscious normotensive and hypertensive rats.

	Basal values	Time after injection (min)									
		5	15	30	45	60	75	90	105	120	
Δ Blood pressure											
Wistar	97	-2	-5	-7	-6	-4	-4	-5	-6	-5	
	\pm 2 (10) ¹	\pm 1	\pm 2	\pm 2	\pm 3	\pm 2	\pm 2	\pm 2	\pm 2	\pm 2	
Renal hypertensive (Wistar)	151	0	-2	6	0	0	8	-3	-8	-7	
	\pm 4 (7)	\pm 5	\pm 8	\pm 7	\pm 3	\pm 10	\pm 3	\pm 6	\pm 1	\pm 3	
Wistar Kyoto	114	-8	-25	-26	-20	-18	-24	-22	-22	-18	
	\pm 5 (6)	\pm 4	\pm 8	\pm 6	\pm 7	\pm 6	\pm 8	\pm 6	\pm 6	\pm 7	
Spontaneously hypertensive	134	-26	-33	-34	-23	-15	-12	-13	-13	-14	
	\pm 5 (7)	\pm 4	\pm 7	\pm 6	\pm 4	\pm 5	\pm 2	\pm 2	\pm 2	\pm 6	
Δ Heart rate											
Wistar	356	-9	-36	-47	-30	-24	-27	-22	-2	-7	
	\pm 12	\pm 9	\pm 12	\pm 15	\pm 10	\pm 14	\pm 14	\pm 13	\pm 15	\pm 15	
Renal hypertensive (Wistar)	372	-41	-56	-58	-57	-48	-52	-48	-56	-51	
	\pm 16	\pm 8	\pm 15	\pm 13	\pm 10	\pm 10	\pm 5	\pm 11	\pm 7	\pm 8	
Wistar Kyoto	371	-55	-107	-108	-93	-81	-77	-84	-75	-49	
	\pm 15	\pm 26	\pm 17	\pm 30	\pm 24	\pm 16	\pm 16	\pm 19	\pm 15	\pm 25	
Spontaneously hypertensive	396	-68	-118	-140	-119	-112	-106	-91	-92	-92	
	\pm 20	\pm 21	\pm 22	\pm 18	\pm 16	\pm 13	\pm 21	\pm 19	\pm 19	\pm 29	

¹ Number of animals is given in parentheses.

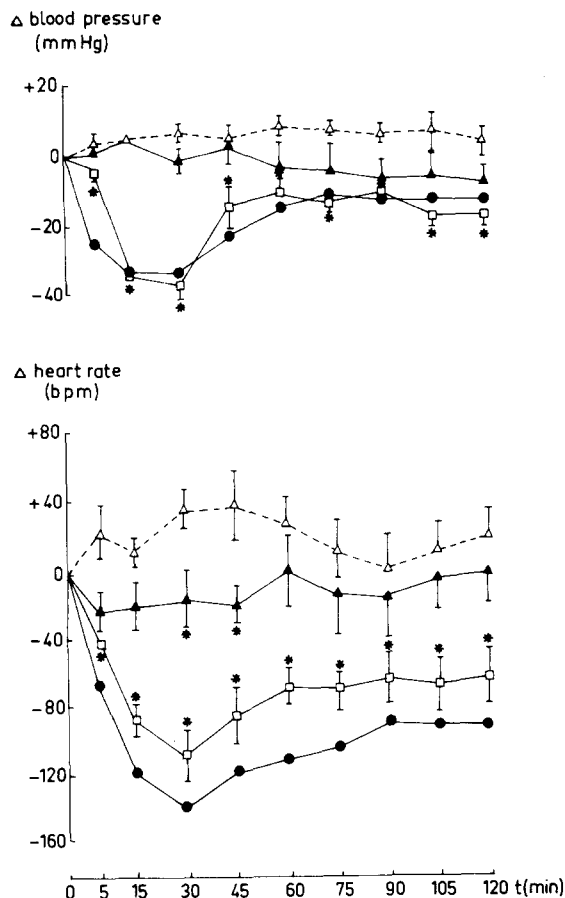


Fig. 5. Effect of d,l-propranolol (5 mg/kg s.c.) on mean blood pressure and heart rate of adrenalectomized conscious spontaneously hypertensive rats receiving corticosterone as replacement therapy. \square — \square propranolol + 30 μ g/100 g b.w./h corticosterone (basal values: 128 ± 4 mm Hg and 387 ± 2 bpm, $n = 10$), \blacktriangle — \blacktriangle propranolol + 100 μ g/100 g b.w./h corticosterone basal values: 129 ± 3 mm Hg and 357 ± 20 bpm, $n = 5$), \triangle — \triangle saline + 100 μ g/100 g b.w./h corticosterone (basal values: 121 ± 11 mm Hg and 342 ± 20 bpm, $n = 5$). The group of rats treated with propranolol alone (\bullet — \bullet) is taken from fig. 1. * $P < 0.05$.

rate were -40 ± 5 mm Hg and -140 ± 3 bpm respectively ($n = 4$, $P < 0.05$ for both parameters).

In order to study the role of the kidneys and of renin, d,l-propranolol (5 mg/kg) was administered to adrenalectomized rats which

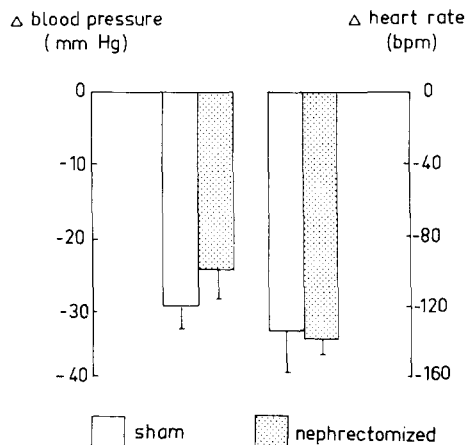


Fig. 6. Effect of d,l-propranolol (5 mg/kg s.c.) on mean blood pressure and heart rate of nephrectomized-adrenalectomized conscious spontaneously hypertensive rats. Basal values for the nephrectomized group were 121 ± 5 mm Hg and 409 ± 9 bpm ($n = 7$) and for the control group 130 ± 5 mm Hg and 340 ± 20 bpm ($n = 6$).

had also been nephrectomized. There was no significant inhibition of the hypotensive action or of the bradycardia (fig. 6).

The inhibitory effects of d,l-propranolol were not restricted to the SHR, since similar effects were observed in the adrenalectomized normotensive Wistar Kyoto rat (table 3). The responses were different in the Wistar strain. d,l-Propranolol did not lower the blood pressure significantly during the 2 h observation period in either the adrenalectomized normotensive Wistar rat or the adrenalectomized renal hypertensive Wistar rat. The heart rate decreased but the response was less than half that of the Wistar Kyoto and SHR.

4. Discussion

The present experiments aimed to study the role of the adrenals in the effects of propranolol on blood pressure and heart rate of the SHR. Although no substantial blood pressure lowering effect of propranolol occurred in the intact conscious SHR,

we observed a profound acute hypotension and bradycardia after adrenalectomy. The failure of propranolol to decrease blood pressure in rats with established hypertension has been previously noted (Lundgren, 1974; Fernandes et al., 1977; Pak et al., 1977). Several reports indicate that propranolol can even induce a pressor response which might be due to the release of catecholamines from the adrenal medulla (Yamamoto and Sekiya, 1972; Brunner and Hedwall, 1970; Grewal and Kaul, 1970; Regoli, 1970). Such a release of catecholamines may have contributed to the failure to decrease blood pressure by β -blockers. In our experiments however the acute decrease in blood pressure after propranolol in the adrenalectomized SHR did not depend on the absence of the adrenal medulla, since no substantial decreases in blood pressure or heart rate occurred in demedullated animals. In contrast the adrenal cortex seems to be important, since replacement therapy of adrenalectomized SHR with doses of corticosterone resulting in a near control level of corticosterone (25 μ g/100 ml plasma; unpublished observation) prevented the hypotension and bradycardia after propranolol. Adrenal corticosteroids therefore seem to be responsible for the absence of inhibitory effects of propranolol on the cardiovascular system of SHR.

It is not clear in which way corticosterone interferes with the hypotension and bradycardia due to propranolol. There have been reports relating to the action of glucocorticoids in inhibiting the extraneuronal as well as the neuronal uptake of catecholamines (Iversen and Salt, 1970; Nicol and Rae, 1972; Bassett and Cairncross, 1976). β -Blockers have been shown to reduce noradrenaline release during adrenergic nerve stimulation in studies carried out both in vivo (Dahlöf et al., 1975; Yamaguchi et al., 1977) and in vitro (Adler-Graschinsky and Langer 1975; Dahlöf et al., 1978). These effects seem to be mediated by a presynaptic β -adrenoceptor mediating a positive feed-back regulation of noradrenaline release from sympathetic

nerve terminals (see Langer, 1977). An effect of β -blockers on presynaptic mechanisms has been suggested to account for the hypotensive action of propranolol (see De Champlain, 1978). It is possible that in the presence of the corticosteroids the inhibition of the uptake mechanisms might therefore potentiate the effect of endogenous neurotransmitters compensating for the diminished release and thereby antagonizing the cardiovascular effect of propranolol.

Several investigators point to an involvement of the central nervous system (Day and Roach, 1974; Reid et al., 1974; Myers et al., 1975; Garvey and Ram, 1975). In our experiments, however, the central injection of propranolol induced a hypotension which was less profound than that following the peripheral administration of comparable doses. A central site of action therefore does not seem likely. However since propranolol diffuses quickly across the blood-brain barrier, a central site of action cannot be excluded.

Which cardiovascular parameters do mediate the anti-hypertensive action of propranolol under our conditions remains to be elucidated. Suppression of renin release by propranolol is suggested to account for the anti-hypertensive effect in patients with high plasma renin activity (Bühler et al., 1972). In our experiments however, renal renin did not play a major role since in adrenalectomized-nephrectomized SHR there was no significant inhibition of the blood pressure lowering effect of propranolol. A lowering in cardiac output (Prichard and Gillam, 1969; Tarazi and Dustan, 1972) is not unlikely. However, under the experimental conditions used no correlation could be established between the negative chronotropic and the anti-hypertensive effect of propranolol. Whether peripheral vasodilatation contributed to the anti-hypertensive effect of propranolol remains a matter of speculation until cardiac output is measured and total peripheral resistance is calculated in the adrenalectomized SHR.

In addition to its β -adrenergic blocking capacity, d,l-propranolol possesses local anes-

thetic activity (Morales-Aguilera and Vaughan Williams, 1965). This unspecific effect might have contributed to the strong bradycardia in addition to the β -adrenergic blocking activity. The β -antagonistic property of d,l-propranolol, however, is due mainly to the l-isomer, while the d-isomer of propranolol has only weak β -antagonist activity, and both exhibit equivalent local anesthetic activity (Howe and Shanks, 1966; Barrett and Cullum, 1968).

The present results with adrenalectomized SHR suggest that the cardiovascular effects of d,l-propranolol are mainly ascribable to the β -adrenergic capacity of the drug. However, because a higher dose of l-propranolol was necessary to induce a fall in blood pressure comparable to that expected from the dose of d,l-propranolol used, we cannot exclude an additional effect of d-propranolol.

The cardiovascular effects of propranolol were only observed to a statistically significant extent in the Wistar Kyoto strain. Genetically determined differences may explain the observed differences. Despite the difference in blood pressure levels, the normotensive Wistar Kyoto strain and the SHR have many characteristics in common, e.g., comparable levels of salivary gland renin-like enzyme which are higher than those of several other rat strains (De Jong et al., 1972), as well as comparable levels of brain-stem dopa decarboxylase activity which were reported to be lower than that of the Wistar strain (Yamabe et al., 1973).

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