hormone, (ii) the association of an increase in angiotensin receptors and a shift to the left of the dose-response curve implies the existence of limiting factor(s) distal to the receptor, (iii) the consequence of the existence of this limiting factor is that after nephrectomy, some receptors behave as 'spare receptors', (iv) no evidence for the existence of spare receptors could be demonstrated in normal uteri.

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Evolution of aortic and cardiac cyclic AMP phosphodiesterase during the onset of mineralocorticoid hypertension in the rat

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Amer (1975) suggested that increased activity of cyclic AMP phosphodiesterase (PDE) in heart and aorta may play a part in the onset of hypertension in the rat. The present investigation was undertaken to determine whether the increase of PDE activity precedes or follows the rise of BP during mineralocorticoid hypertension in the rat. Male Sprague Dawley rats were implanted with 100 mg desoxycorticosterone acetate in 4 pellets and subsequently were given *ad libitum* a 9% w/v NaCl solution. The rats were killed by decapitation. The heart and the aorta (freed from adventitia layer) were rapidly removed and homogenized as described previously (Lugnier & Stoclet, 1974). PDE activity was determined in crude homogenates using a method modified from Thompson & Appleman (1971). The modification consisted of measuring the yield of the separation of the reaction products from residual ^{3}H-cyclic AMP by adding [^{14}C]-adenosine to each tube and of using a different resin for the separation (QAE Sephadex A25). Protein was measured according to Lowry, Rosenbrough, Farr & Randall (1951).

Table 1 shows that cardiac PDE measured at both substrate concentrations increased with age in control but not in hypertensive rats, where it was already maximal after 2 weeks of treatment. In the aorta the only observed modification was an increase of PDE measured at low substrate concentration in hypertensive rats, after 2 weeks of treatment.

The data show that modifications of cardiac and aortic PDE specific activity occur during the onset of mineralocorticoid hypertension but are no more apparent during the chronic phase of hypertension.

Table 1 Variations of the specific activity of cyclic AMP phosphodiesterase (PDE) with age and hypertension, in heart and aorta from control and mineralocorticoid hypertensive rats

	Systolic BP	*PDE (pmol . min^{-1} . mg protein^{-1}) (2)*			
		Heart		*Aorta*	
	(mmHg) (1)	*1×10^{-4} M (3)*	*1×10^{-6} M (3)*	*1×10^{-4} M (3)*	*1×10^{-6} M (3)*
		8 weeks old (after 2 weeks of treatment)			
Control	115 ± 2	474.7 ± 12.6	74.5 ± 1.0	1143.2 ± 157.8	174.0 ± 10.7
Hypertensive	163 ± 2†	1447.0 ± 80.0†	165.0 ± 3.0†	1385.4 ± 124.0	246.0 ± 4.5†
		16 weeks old (after 10 weeks of treatment)			
Control	146 ± 3*	1188.6 ± 43.9*	164.1 ± 4.2*	1575.8 ± 185.0	186.2 ± 7.5
Hypertensive	184 ± 9†	1274.2 ± 55.0	163.8 ± 1.6	1595.4 ± 135.0	192.5 ± 6.9

(1) Mean of 10 rats ± s.e. mean.
(2) Mean of 4 determinations on pools 10 organs, ± s.e. mean.
(3) Substrate concentration.
Student's *t* tests: † $P < 0.001$ compared with controls.
* $P < 0.001$ compared with 8 weeks old rats.

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Evidence of central cardiovascular effects of intracerebroventricular isoprenaline in anaesthetized rat

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Isoprenaline (1, 2 and 4 μg) injected intracerebroventricularly in urethane anaesthetized rat produced a long lasting hypotension and tachycardia. It is unlikely that these effects are related to leakage in peripheral circulation of the amine because: (1) After intraventricular injection, [^{3}H]-isoprenaline diffused partially out of the central nervous system, but maximal blood and heart levels measured 5 min after administration were about 2 ng/g. These concentrations were unable to induce cardiovascular effects when injected intravenously. (2) In rats cephalic cross-circulation experiments indicated that intraventricular injection of 8 μg isoprenaline to the rat donor produced tachycardia which was not observed in the second animal.

The present study showed that isoprenaline had mainly central cardiovascular effects after intracerebroventricular injection.

Characteristics and altered sensitivity of cerebral β-adrenoceptors assessed by [^{3}H]-propranolol binding

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Studies on the nature and characteristics of the β-adrenoceptor have been greatly assisted by the observation that in many tissues this receptor is closely associated with the enzyme adenylate cyclase (Robison, Butcher & Sutherland, 1971). We have previously utilized this approach in assessing catecholamine-induced cyclic AMP formation in chick cerebral hemispheres and have provided evidence that these effects are mediated by a βadrenoceptor (Nahorski, Rogers, Smith & Anson, 1975). In the present study we have extended our experiments on the characterization of this receptor by examining the binding of ^{3}H propranolol, a specific ligand for the β-adrenoceptor (Nahorski, 1976), to chick cerebral membranes.

Experiments were performed on 1–6 day old male Ranger chicks. Cyclic AMP formation was determined in 0.37 mm incubated slices of the cerebral hemispheres by a protein binding assay. [^{3}H] (±)-propranolol binding was examined in a crude synaptic membrane fraction prepared by differential centrifugation (Nahorski, 1976). The order of potency of the catecholamines to stimulate cyclic AMP formation, isoprenaline > adrenaline > noradrenaline, was also observed in the ability of these compounds to displace [^{3}H]-propranolol from membrane binding sites. Salbutamol, although only a partial agonist, had a similar potency to adrenaline in both of these systems and dopamine was inactive at concentrations up to 100 μM.

(–)-Propranolol was a potent antagonist of isoprenaline (1 μM)-stimulated cyclic AMP formation ($IC_{50} = 7 \times 10^{-8}$ M) and [^{3}H]-propranolol binding ($IC_{50} = 1 \times 10^{-8}$M). (+)-Propranolol was about 100-fold less potent in both systems. H35/25(1-(*p*-tolyl)-2-isopropylamino-1-propanol), a relatively specific β_2-