considering the natural evolution of hypertension in Okamoto rats which is milder in female SHR.

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Molecular mechanism of post-nephrectomy uterine supersensitivity to angiotensin

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Bilateral nephrectomy has been shown to induce a specific supersensitivity of the response of isolated rat uteri to angiotensin II which is expressed by a shift to the left of the dose-response curve. This phenomenon could not be explained by a simple freeing of receptor sites secondary to the disappearance of endogenous angiotensin. The pA_2 values of two competitive antagonists of angiotensin II were not modified by nephrectomy suggesting that supersensitivity was related neither to a change in the affinity of receptors nor to a variation of a possible equilibrium existing between active and inactive receptor conformations (Meyer, Papadimitriou & Worcel, 1974). If angiotensin receptor affinity is unchanged after nephrectomy, two hypotheses may explain the supersensitivity to angiotensin, both based on the obligatory assumption that a limiting factor of the angiotensin effect after nephrectomy exists beyond the receptor site (i) *increase in the number of receptors.* If the limiting factor is distal to the receptor site, an increase in the number of receptors would be responsible for the supersensitivity, and maximal contraction would be obtained at an angiotensin concentration lower than in control experiments, (ii) *no variation in the number of receptors but an increase in the 'efficiency' of the limiting factor distal to receptors.* In this case, an increased response would result from the same number of hormone-receptor interactions.

In order to test these hypotheses, we have studied the specific binding of a [^{3}H]-angiotensin II with high specific activity and intact biological activity to membranes of uteri isolated from normal and nephrectomized rats. In normal rats, the specific binding of [^{3}H]-angiotensin II to uterine membranes was half saturated and saturated at angiotensin concentrations of 2×10^{-8} M and 10^{-7} M respectively. The similarity of these values to the ED_{50} value and to the angiotensin concentration inducing maximal contraction suggests that in normal rats a linear relation exists between angiotensin receptor occupancy and contraction.

Bilateral nephrectomy produces, after 18–20 h, a 70% increase in the total number of binding sites (control 0.7 pmol mg^{-1}; nephrectomized 1.2 pmol mg^{-1} protein) which cannot be accounted for by variations in the occupancy of receptor sites, and no significant variation in the apparent dissociation constant (Chevillotte, Rouzaire-Dubois, Devynck & Meyer, 1974). It has also been demonstrated that the variations in angiotensin receptor number was directly related to plasma angiotensin levels.

These pharmacological and biochemical results allow the following conclusions which will be analysed in this communication: (i) Supersensitivity of uterine muscle to angiotensin observed after nephrectomy is secondary to a true increase in angiotensin receptors without significant variation in their affinity for the

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.