



**THE RELATIONSHIP BETWEEN VASCULAR  
STRUCTURE, CONTRACTILE PROTEINS, VASCULAR  
REACTIVITY AND BLOOD PRESSURE IN ANIMAL  
MODELS OF HYPERTENSION**

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by

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## ABSTRACT

The principal aim of the studies presented in this thesis was to examine the relationship between vascular reactivity, contractile proteins and blood pressure development in the spontaneously hypertensive rat (SHR). In addition, the influence of angiotensin II on blood pressure and vascular structure and function was investigated.

In initial experiments hypertension was induced in the normotensive Wistar Kyoto rat (WKY), the most appropriate control for the SHR. Mineralocorticoid therapy (DOCA-salt) produced an increase and sustained elevation in systolic blood pressure in the normotensive WKY rat. The elevated blood pressure was associated with a marked increase in total 3-methylhistidine (a marker for contractile proteins), DNA and protein content. In contrast to the marked increase in contractile proteins, contractile responses of the perfused mesenteric preparation to vasoactive agents were similar in preparations from control WKY and hypertensive WKY rats. Moreover, the elevated blood pressure and increases in the total 3-methylhistidine, DNA and protein content were insensitive to angiotensin converting enzyme inhibitor (quinapril) treatment,  $\alpha_1$ -adrenoceptor antagonist (doxazosin) treatment and calcium channel blockade (diltiazem). The data suggest that the elevation in blood pressure in the H-WKY does not mimic the characteristics of hypertension seen in the SHR in which vascular reactivity is augmented and sensitive to pharmacological treatments.

The perfused mesenteric preparations from SHRs demonstrated augmented reactivity to vasoactive agents when compared with preparations from WKY rats. However, the enhanced reactivity was not associated with increased total 3-methylhistidine, DNA and protein content in the mesenteric vasculature. ACE



inhibitor treatment of the SHR from 5 to 18 weeks of age prevented the development of hypertension and normalised contractile responses. Moreover, ACE inhibitor treatment reduced the total content of 3-methylhistidine, DNA and protein in the mesenteric vasculature. Both  $\alpha_1$ -antagonist treatment and calcium blockade, although maintaining systolic blood pressure approximately 20 mmHg below that of untreated SHRs, were without influence on contractility and the biochemical parameters.

Cessation of ACE inhibitor therapy after 13 weeks of treatment for a period of 4 weeks resulted in both systolic blood pressure and vascular reactivity increasing but remaining lower than in untreated SHRs. In contrast, 3-methylhistidine, DNA and protein content of the mesenteric vasculature reverted to levels seen in vessels from untreated SHRs. In addition, co-administration of the  $\alpha_1$ -adrenoceptor antagonist doxazosin with the ACE inhibitor and continuation of the  $\alpha_1$ -adrenoceptor antagonist after withdrawal of the ACE inhibitor, prevented to a certain degree, the increases in 3-methylhistidine, DNA and protein content in the mesenteric vasculature observed after withdrawal of the ACE inhibitor, without preventing the increase in systolic blood pressure and augmented contractile responses. Although the data raise the possibility that inhibition of angiotensin II may influence growth of the mesenteric vasculature in this model the results also suggest that other process(es) involving angiotensin II, may influence structure and thereby contractility.