A STUDY OF THE RELATIONSHIP BETWEEN THE CHEMICAL SENSITIVITY OF SMOOTH MUSCLE AND THE BLOOD PRESSURE OF GENETICALLY HYPERTENSIVE RATS

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A STUDY OF THE RELATIONSHIP BETWEEN THE CHEMICAL SENSITIVITY OF SMOOTH MUSCLE AND THE BLOOD PRESSURE OF GENETICALLY HYPERTENSIVE RATS

BY

© Ismail Laher, M.Sc.

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ABSTRACT

An increased neuronal uptake and postsynaptic sensitivity to noradrenaline in arterial smooth muscle from spontaneously hypertensive rats (SHR) has been reported by numerous laboratories. Also reported are changes in vascular reactivity of perfused arterial beds, and a deficiency in homeostasis of intracellular calcium (Ca^{2+}) in some tissues of SHR. The work presented here studied these changes in SHR and related animals to determine their relationship to the blood pressure. Also, these changes were studied in another model of genetic hypertension, the Dahl model of salt-sensitive (DS) hypertensive and salt-resistant (DR) normotensive rats.

Increased neuronal uptake of noradrenaline in arterial smooth muscle (tail artery) was present from 6-8 week onward in SHR related animals. This became more pronounced at the later age groups studied (12-16 week and > 52 week old). In venous (portal vein) and non-vascular (anococcygeus) smooth muscle increased neuronal uptake of noradrenaline was present in only the very old SHR-related animals. Postsynaptic sensitivity to noradrenaline was increased only in tail arteries from very old SHR. The increased uptake 1 and enhanced postsynaptic sensitivity to noradrenaline were not present in DS and DR rats; in fact there was a trend for reduced uptake 1 activity in tissues from the DS hypertensive rat.

While perfused mesenteric beds isolated from 12-16 week SHR had a greater reactivity and contractility to noradrenaline, no such changes were observed in mesenteric beds from DS and DR using either noradrenaline, phenylephrine or serotonin as the agonist. The results using papaverine-induced relaxations of DS and DR aortae also suggested no aberrations in sequestration of Ca^{2+} in the Dahl rat.

The response to La^{3+}, thought to reflect a more mobile pool of Ca^{2+} in the SHR, correlated with blood pressure in SHR-related animals when the results were expressed as a percentage of the maximal noradrenaline response, but was not correlated when expressed as mg tension per mg tissue weight. This was due to a negative correlation between blood pressure and the maximal response to noradrenaline in these animals.

The results reported in this study suggested that alterations in pharmacological and mechanical properties of vascular smooth muscle observed in SHR were probably unique to that model of genetic hypertension.

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LIST OF ABBREVIATIONS

SHR	Spontaneously hypertensive rat
WKY	Kyoto Wistar rat
DS	Dahl salt-sensitive rat
DOCA	Deoxycorticosterone acetate
DR	Dahl salt-resistant rat

INTRODUCTION

Etiology of Hypertension in Spontaneously Hypertensive Rats

The predominant form of hypertension is of an unknown etiology, and is not mimicked experimentally by producing hypertension in animals through surgical means which invariably reflect secondary forms of the disease. Selection of animals with naturally occurring high blood pressure for inbreeding has led to the production of several strains of hypertensive rats. The first inbred strain of hypertensive rats was reported by Smirk's group (Smirk, 1949; Smirk and Hall, 1958; Phelan, 1968) in New Zealand. This was followed by other strains that all had the characteristics of inherited hypertension with unknown etiology, eg. the spontaneously hypertensive rat (Okamoto and Aoki, 1963), the Dahl strain of salt-sensitive rats (Dahl, Heine and Tassinari, 1962), the Milan strain (Bianchi, 1968) and the Brunus Edwardii strain (Blackmore et al. 1972). The most commonly used of these strains is that introduced by Okamoto, the characteristics of which, while not representative of all types of essential hypertension, is best documented.

The successful isolation of a colony of spontaneously hypertensive rats (SHR) was reported by Okomoto and Aoki in 1963. This was done by selective inbreeding of Wistar rats from the Animal Center Laboratory, Kyoto University, Faculty of Medicine, and normotensive relatives of this strain are

commonly referred to as WKY rats. The SHR were produced by selective inbreeding from a male with hypertension and females with slightly higher blood pressure than the average among WKY. The arguments favouring the use of the SHR as a model for human essential hypertension have been summarised by Trippodo and Frohlich (1981), and an opposing viewpoint has been presented by McGiff and Quilley (1981).

The development of hypertension in the SHR demonstrates a two stage process of initially high cardiac output and normal total peripheral resistance (5 - 12 weeks) which then reverts to normal cardiac output and a raised total peripheral resistance in the established phase (Albrecht, 1974a, b; Preutitt & Dowell, 1979).

The arterial baroreceptors are the only means by which the central nervous system can sense peripheral blood pressure and thus in considering the etiology of hypertension, a question of importance is whether baroreceptor function is normal or abnormal. One point of view is that baroreceptor control is shifted to a new set-point as a result of reduced wall distensibility. Recently, Struyker-Boudier et al. (1982) examined baroreflex sensitivity in relation to development of hypertension in SHR at 4 weeks of age when the SHR and WKY had similar baroreflex sensitivity even though blood pressure in SHR was elevated. During further growth, the SHR pressure rapidly increased with no further changes in baroreflex sensitivity. Corresponding WKY rats had an age related increase in

baroreflex sensitivity. These results do not point to a baroreflex sensitivity decrease in SHR as a consequence of structural vascular changes after hypertension, such as decreased distensibility in aortic receptors. Rather, they could reflect different maturation rates of the two strains of rats. Similar results were reported by Judy et al. (1979).

The mode of inheritance of SHR has been investigated by many laboratories, and it was shown that a polygenic inheritance, without any sex-linkage, existed in these hypertensive rats (Louis et al. 1969; Yamori et al. 1972; Yamori 1977). It is clear that a few major genetic components (2 to 4 genes) act together (Yen et al. 1974; Tanase et al. 1970) in concert with multiple minor genes (Yamori et al. 1972; Tanase et al. 1979). These studies all followed the transmission of the hypertension in progeny from various types of breeding arrangements.

Current knowledge about the mechanisms regulating circulatory physiology is extensive. Numerous control systems exist within the body that specifically are designed to regulate various aspects of circulatory functions such as blood flow and pressure. Hypertensive disease is a failure of circulatory regulation which is determined by an abnormally high resistance to blood flow. Therefore, the basic mechanisms in most forms of hypertension are traced to changes in the regulation, function and structure of blood vessels (Brody & Zimmerman, 1976). The vast majority of

human cases of hypertension are defined as primary or essential hypertension where the disease is of unknown origin (Julius, 1977).

The relationship between the flow of fluid through a cylindrical tube and the pressure gradient across the ends of the tube is described by Poiseuille's equation:

$$Q = \Delta P \times \frac{\pi r^4}{8L} \times \frac{1}{z}$$

This expression states that the rate of flow Q is dependent on various independent variables viz. the effective pressure gradient along the vessel (P), the radius of the vessel (r), its length (L) and the coefficient of viscosity of the fluid (z). Therefore, the flow of fluid through the tube will increase if the pressure gradient or radius is increased, or if the length or viscosity is decreased. When this formula is applied to the circulation, it is assumed that the overall length of the vasculature in an individual remains unchanged.

The resistance to flow (R) can be extracted from this equation, as

$$R = \frac{8 z L}{\pi r^4}$$

Consequently, analogous with Ohm's law, in the cardiovascular system, the relationship $P = QR$ becomes $MAP = CO \times TPR$ where MAP is the mean arterial blood pressure (mmHg), CO is cardiac output (Litres per minute) and TPR is

total peripheral resistance (mmHg per litre per minute). Clearly MAP can be modified by factors influencing either CO or TPR (or both).

The factors that elevate CO are i) enhanced cardiac contractility; ii) increased blood volume in relation to venous capacity and iii) disturbances in electrolyte composition. The factors that elevate TPR have received considerably more attention, and have recently been summarized by Webb & Bohr (1981) and Folkow (1982). Briefly, elevated TPR can result from structural or functional changes in blood vessels. Before discussing the pharmacological evidence for these various changes, a definition of the following terms will be necessary:-

contractility: force-generating ability of the muscle when it is maximally activated.

reactivity: the ease of activation of a perfused vascular bed measured by its threshold (or ED_{50}) for an agonist.

sensitivity: the ease of activation of an isolated vascular strip measured by its threshold or ED_{50} for an agonist.

A) Structural Adaptations

Two types of structural modifications have been described, 1) changes in the vascular media and 2) rarefaction of resistance vessels.

1) Changes in the vascular media. This aspect of a contributing factor to the elevation of total peripheral resistance has drawn much interest since its initial statement in 1956 by Folkow. We know that resistance to flow is greatly dependent on vessel size ($R \alpha \frac{1}{r^4}$); consequently minute changes in vessel radius will profoundly alter resistance to flow. Hemodynamic evidence for increases in wall-to-lumen ratio of resistance vessels in hypertensive subjects comes from three types of observations i) maximal vasodilation is impaired in many vascular beds (Conway, 1963); ii) the slope of the dose-response curve to vasoconstrictor agents is steeper (Silvertsson, 1970; Folkow et al. 1970); iii) the magnitude of the maximal vasoconstrictor response is increased (Folkow et al. 1970; Mulvany et al. 1978).

Folkow has suggested that in some forms of essential hypertension (including SHR) the elevated resting tone of the blood vessels can be explained entirely by structural modification of the vessels (Folkow et al. 1978). If this were the case, then two predictions can be made: a) the dose-response curve to all vasoconstrictors should be altered to the same extent (with respect to threshold, slope and maxima) and b) structural changes should be absent in vascular tissues not exposed to elevated distending pressures.

In a study of perfused mesenteric beds from SHR rats, Hamilton (1975) demonstrated that the change in perfusion

pressure produced by noradrenaline differed both quantitatively and qualitatively from that produced by serotonin. Similar results were obtained by Cheng & Shibata (1980) using a perfused hindquarter preparation from SHR. These authors reported a larger difference in the responsiveness to serotonin in tissues from normotensive and hypertensive rats as compared to responsiveness to noradrenaline or potassium. Likewise, Eikenberg et al. (1981) demonstrated differential sensitivity changes to noradrenaline, vasopressin and barium chloride in isolated perfused mesenteric beds from SHR. Finch & Haeusler (1974) using a variety of perfused preparations showed that while the responsiveness to noradrenaline was elevated in hypertension, the response to calcium in depolarized mesenteric artery preparations was not altered. These studies point out that while structural adaptation could explain some of the characteristics of dose-response curves in perfusion studies from hypertensive rats, there clearly do exist alterations in excitation-contraction coupling. These would be changes intrinsic to the properties of the vessels from hypertensive animals.

In a study of SHR and experimentally induced hypertensive rats (DOCA/NaCl and renal), Finch and Haeusler (1974) recorded a reduced threshold dose for the constrictor effects of noradrenaline in the perfused hindquarters and mesentery from the DOCA/NaCl and renal hypertensive, but not from the spontaneously hypertensive rat. In all three

hypertensive rats, the vascular resistance measured at maximal vasodilation was elevated. In earlier studies by Haeusler and Finch (1971, 1972) and later confirmed by Armstrong (1972), a reduced threshold dose for serotonin was also observed in SHR, renal and DOCA/NaCl hypertensive rats. Finch and Haeusler (1974) favoured the view of a specific alteration in the adrenergic (α) and serotonin receptor (5HT) as a primary aberration in vascular smooth muscle from hypertensive rats, since they were able to demonstrate reduced threshold values for noradrenaline and serotonin with no indications of changes in the dose-response curve for calcium (in potassium-depolarized mesenteric preparations). However, in studies also performed in perfused mesenteric beds from SHR and DOCA/NaCl hypertensive rats (Ekas and Lokhandwala, 1980; 1981) nonspecific increases in reactivity were reported. These authors demonstrated greater reactivity and contractility for barium, vasopressin and noradrenaline in perfused mesenteric beds from hypertensive rats but no attempt was made to distinquish between changes due to purely structural adaptations and those due to intrinsic properties of hypertensive vessels.

Utilising cultured aortic smooth muscle cells, Yamori et al. (1981) reported on the basic mechanisms underlying structural vascular changes occurring in hypertension by studying growth rate and protein-synthesis-indicators. These authors clearly demonstrated a pressure-independent,

genetically determined difference in the characteristic patterns of growth in smooth muscle cells from hypertensive animals.

Obviously thickening of resistance vessels in hypertension could result from a contribution (whole or in combination) of an increase in cell number (hyperplasia) or cell size (hypertrophy). It is generally agreed that smooth muscle cell hypertrophy alone accounts for the increased wall thickening in vessels from hypertensives (Owens et al. 1981; Olivetti et al. 1982). In addition to changes in cell size, Owens et al. (1981) have determined changes in nuclear ploidy in cells from SHR. As pointed out by these authors, these nuclear changes in DNA are irreversible, such that chronic treatment with antihypertensive agents would not be effective in reverting the structural components of increased TPR. These findings would partially explain the results of Mulvany et al. (1981b) if we assume that smooth muscle hypertrophy (and its accompanying nuclear response) are genetically determined characteristics in the SHR, unrelated to chronic distensions of arterial beds (Yamori et al. 1981). Mulvany et al. (1981b), who after chemical sympathectomy of SHR at birth, reported that while the blood pressure of SHR was reduced to normotensive levels, the morphological and pharmacological properties of vessels from SHR remained distinctly different from those of normotensive animals.

Clearly, medial thickening in arterial beds of SHR does

occur; however, its primary role in the disease process cannot be conclusively demonstrated. Furthermore, Folkow's hypothesis (1956) has not been shown to be generalised in other models of genetic hypertension.

Tension generation of smooth muscle from SHR

Another functional consequence of smooth muscle cell hypertrophy is its effect on the ability of the tissues to develop tension. Hypertrophic intestinal smooth muscle cells have been shown to develop decreased contractile force per unit cross-sectional area (Gabella, 1979). In hypertensive vessels, there is an increased concentration of collagen fibrils and ground substance within the muscle layers, and this has the net effect of reducing the force-generating ability of the contractile mass in hypertension. Numerous studies have shown that vascular tissues from SHR have a decreased maximum force output (Spector et al. 1969; Bandick & Sparks, 1970; Clineschmidt et al. 1970; Hansen et al. 1974; Hansen & Bohr, 1975; Janis & Triggle, 1972; Field et al. 1972; Antonaccio et al. 1980; Webb and Bohr, 1981). These authors utilized analyses of pharmacological data, such as maximum force developed per smooth muscle area or weight, to arrive at the observation regarding depressed force generating ability of SHR vasculature. In contrast to these findings, others (Hallback et al. 1971; Mulvany et al. 1978; Whall et al. 1980; Arner & Hellstrand, 1981; Arner & Uvelius, 1982) have found an unaltered, or increased force-

producing ability of SHR vessels. The reasons for these discrepant results on the basic properties of SHR vessels is not clear. In a study by Seidel (Seidel et al. 1980) it was shown that while the content of actomyosin (per mg aortic total protein) was not different between SHR and the normotensive WKY, the ability of SHR aorta to develop tension for a given amount of actomyosin was much lower than for WKY.

Reduced force development in SHR (Bandick & Sparks, 1970; Field et al. 1972; Hansen & Bohr, 1975; Shibata et al. 1973; Webb and Bohr 1981) was not apparent in small arteries which were maintained in their cylindrical form (Mulvany & Halpern, 1977; Warshaw et al. 1977; Whall et al. 1980). One explanation for this difference in results comes from the findings of Cox (1977, 1979), who used a device to inflate intact carotid arteries isolated from SHR, DOCA/NaCl and renal hypertensive rats. Using this method, Cox (1977) was able to show that maximum active force per cross-sectional area in SHR exceeded the WKY, and that carotid arteries from SHR were able to shorten to a greater extent against distending pressures. Similar results were recorded when carotids from DOCA/NaCl and renal hypertensive rats were compared to their respective controls. Cox (1977, 1979) proposed that the increased leakiness to ions of vascular smooth muscle in hypertension makes the arteries more susceptible to damage from the dissection required to prepare helical strips.

2) Rarefaction of resistance vessels

Rarefaction of blood vessels has been reported for the SHR cremaster muscle (Hutchins & Darnell, 1974), mesentery (Henrich et al. 1978) and skin (Haack et al. 1980) as well as for human conjunctiva (Harper et al. 1978). The group led by Hutchins (Hutchins et al. 1977; Hutchins, 1979) later realized that rarefaction in adult SHR could be due to a combination of both the number of open arterioles (functional rarefaction) and a decreased total number of arterioles (structural rarefaction). Haack et al. (1980) studied rarefaction of the first four branches of an arcade supplying cutaneous tissue in SHR, WKY and Wistar rats. The differences observed between cutaneous vessels from WKY and Wistar were as great as those for similar vessels from SHR and WKY. This could reflect genetically determined alterations in architecture unrelated to the blood pressure of the animal (Haak et al. (1980)).

B) Functional Alterations

It is clear that blood vessels modify their structure when chronically exposed to elevated blood pressure. Since structural adaptations occur as a response to elevated blood pressures (Folkow 1978; 1982) other mechanisms must exist to initiate a raising of TPR. A summary of some of the functional alterations in hypertensive vessels has recently been presented by Webb & Bohr (1981).

Neurogenic influences in SHR

Brody & Zimmerman (1976) reviewed the literature concerning neurogenic factors in the development of essential hypertension in SHR, where regional vascular resistance reportedly is decreased (Nosaka et al. 1972) or unaffected (Lais et al. 1974) by nerve section.

The cardiovascular system of the SHR is influenced by environmental stresses; for instance graded alerting stimuli (Hallback & Folkow, 1974), immobilization (Kvetnancky et al. 1979) and elevated temperatures (Yen et al. 1978) all produce exaggerated blood pressure changes in the SHR. Likewise, deprivation of sensory stimuli (Lais et al. 1974) by placing newborn SHR in a quite dark room retards the development of hypertension. Some indication for an exaggerated central sympathetic drive in SHR comes from evidence indicating that sympathetic activity in the splanchnic nerve appears elevated (Okamoto et al. 1967). Sectioning of the splanchnic nerve produced a greater fall in blood pressure in SHR than in normotensive WKY (Iruchijima, 1973). Selective destruction of adrenergic fibres in the central nervous system in newborn SHR prevents the development of hypertension (Haeusler et al. 1972), thereby confirming that an intact sympathetic nervous system is required for the initiation of hypertension. As Zimmerman & Brody (1974) point out, such experiments do not demonstrate that activation of the sympathetic nervous system initiates the hypertensive process; it may only have

a passive role in the process of initiation and/or maintenance of the disease process by acting in conjunction with other changes.

The contribution of the sympathetic nervous system to vascular resistance changes in SHR was investigated by Touw et al. (1980) and Mulvany et al. (1981b). Interruption of sympathetic nerve transmission with ganglionic blockade or chemical sympathectomy produced equivalent percentage reductions in blood pressure in SHR and WKY. Following these treatments the blood pressure in the SHR still exceeded that of WKY but the changes in arterial pressure and regional vascular resistance (renal, mesenteric and hindquarter) were equivalent in SHR and WKY (Touw et al. 1980). These results are in agreement with a previous report by Kubo (1979), who also found similar blood pressure decreases due to ganglionic blockade in SHR and WKY.

Isolated tissue studies

Folkow (1978, 1982) has argued that in intact preparations (perfused) the influence of structural adaptations should be minimized at the threshold of the dose-response curve. However, in isolated rings or strips of vascular smooth muscle, we can discount the influence of vessel structure on the characteristics of dose-response curves (Bohr, 1964, 1974a). Therefore, if structural changes alone caused an elevated resistance to flow, then in isolated tissue studies there should be minimal differences

in threshold or sensitivity to vasoconstrictors when tissues from SHR and WKY are compared.

Apart from using isolated tissue preparations to dissociate structural and functional characteristics in the development of hypertension in SHR, another approach would be the use of genetically inbred "normotensive"-SHR and the study of dose-response characteristics in tissues isolated from these animals. This approach was taken by Bhattacharya et al. (1977), who were successful in isolating and inbreeding "normotensive" SHR. These workers found that the characteristic increased slope and maxima of SHR compared to WKY were maintained when tissues from "normotensive" SHR were used. Clearly, this points to the presence of factors other than structural elements that are genetically determined characteristics in tissues from SHR. Furthermore, Haeusler & Finch 1972) showed a reduced threshold dose for serotonin in the perfused mesenteric bed from three types of hypertensive rats (renal, DOCA/NaCl and SHR) compared to normotensive WKY rats.

When Cheng & Shibata (1980) compared vascular responsiveness to serotonin and noradrenaline in isolated perfused rat hindquarters, they reported that by protecting the preparation from elevated pressures (by aortic occlusion) the enhanced contractility to serotonin was reversed more than with noradrenaline. In addition, in hindquarters from renal hypertensive rats, the enhanced contractility was greater for serotonin than for

noradrenaline. These results provide additional support for alterations intrinsic to the properties of vascular smooth muscle in hypertension.

Hansen & Bohr (1975) utilized an experimental model in which rat hindlegs were protected regionally from increased wall stress by tying off one external iliac artery. The arteries from both the 'high' and 'low' pressure legs were compared in matched WKY, SHR and DOCA/NaCl hypertensive rats. Maximum active tension (contractility) was depressed in tissues from both legs of the hypertensive rats; moreover, when the sensitivity of the iliac arteries to KCl was examined, the excitability of tissues from both 'low pressure' and 'high pressure' zones of hypertensive rats was increased. These authors recorded a leftward shift and decreased threshold-dose for KCl in iliac arteries from hypertensive rats. A similar increased sensitivity (reduced ED_{50} value) for KCl was reported for iliac artery strips from SHR by Swamy & Triggle (1980). Lais and Brody (1975) studied the threshold vasoconstrictor doses for noradrenaline, angiotensin and barium in isolated perfused hindlimb preparations from SHR. These studies, carried out in adult animals, suggested a specific reduction in the threshold dose for noradrenaline. Collis & Alps (1975) demonstrated a similar decrease in the concentration of noradrenaline which elicited a threshold constrictor response in the early phases of experimental renal hypertension. Later Lais & Brody (1978) re-examined their

earlier finding of a specific reduction in threshold dose of noradrenaline in SHR using isolated perfused hindlimbs of three-week old animals. This group had shown that at this age, SHR had no detectable elevated blood pressures (Lais et al. 1977); however, the threshold dose for noradrenaline (but not barium) was already sigificantly reduced (Lais and Brody, 1978). In fact their results show that as the animal matures, the initially lowered threshold for vasoconstrictor doses of noradrenaline relative to the control animal may become less evident as the blood pressure increases. At both age groups used by Lais & Brody (1975, 1978), there was no difference in the reactivity to barium (similar ED_{50} values in SHR, WKY), but there were clear differences in contractility elicited by barium (perfusion pressure elicited by maximal doses of barium). This suggested the possibility of mechanisms (other than structural changes) in the regulation of vascular reactivity in SHR eg., interaction of calcium with contractile proteins and the availability of calcium ions (Johansen, 1974).

Specific changes in membrane properties of SHR

Using the recently developed myograph method for studying the properties of isolated segments (100 to 200 µm) of vessels, Mulvany and Nyborg (1980) compared mesenteric vessels from young (4 week) and adult (4 month) SHR and WKY. While Lais and Brody (1975, 1978) reported differences in blood pressure of young SHR and WKY, the rats used by Mulvany and Nyborg (1980) had similar pressures at 4 weeks

of age. The mesenteric arteries (from SHR and WKY at both ages) were maximally stimulated by noradrenaline in a calcium-free incubation medium; when calcium dose-response curves were performed, the tissues from SHR were twice as sensitive as tissues from WKY. When potassium was used to activate the tissues, the calcium dose-response curves (in age matched tissues) did not differ for SHR and WKY. These results indicate that there are inherent differences in the properties of the vasculature from the SHR and that the potential-dependent (potassium activated) calcium permeability of the SHR smooth muscle is normal, whereas the receptor-activated (noradrenaline stimulated) calcium permeability is abnormally high. These effects were later shown to be present even in SHR treated from birth with antihypertensive therapy (Mulvany et al. 1981a). Therefore, it could be concluded that the increased calcium-sensitivity of SHR is not a consequence of increased blood pressure. Consistent with this conclusion is the observation that hypertension induced by the 2-kidney Goldblatt procedure showed no such alterations in noradrenaline-activated calcium semitivity (Mulvany et al. 1981a).

Lin et al. (1982) compared the characteristics of α-adrenoceptors in aortic tissues from normotensive and renal hypertensive rats. These authors reported several unique findings - notably that the threshold and ED_{50} for noradrenaline was reduced in tissues from renal hypertensive rats. Another interesting finding was that the K_a value

(the dissociation constant) for noradrenaline was also lower in aortic rings from renal hypertensive rats.

The results of studies performed in isolated perfused vascular beds from hypertensive rats are summarized in Table A (page 20). It is clear from a glance at the literature that in these studies the two parameters most often inspected were the slopes of the dose-response curves and the alterations in the maxima.

TABLE A: Summary of results from studies comparing responses to various agents in perfused vascular beds from numerous experimental models of hypertension. Threshold(t), reactivity(r) and contractility(c) have previously been defined on page 5.

Stimumus	Preparation	Animal Model	Threshold (t) Reactivity (r) Contractility (c)	Reference
Serotonin	McGregor (Isolated perfused mesenteric arcade)	SHR	+c	McGregor and Smirk (1970)
			+c	Hamilton (1975)
			+c	Finch (1974, 1975)
			+c	Haeusler and Finch (1972)
		renal	+c	McGregor and Smirk (1970)
			+c	Cheng and Shibata (1980)
			+r +t	Haeusler and Finch (1972)
		DOCA/NaCl	+c	Finch (1974, 1975)
			+r +c +t	Haeusler and Finch (1972)
	perfused hindquarter	SHR	+c	Cheng and Shibata (1980)
		SHR and renal	+c	Haeusler and Finch (1972)
	pithed rat	SHR and renal	+c	Kubo (1978)

TABLE A (cont'd)

Stimulus	Preparation	Animal Model	Threshold(t) Reactivity(r) Contractility(c)	Reference
Noradrenaline	McGregor	SHR	+c	McGregor and Smirk (1970)
			+r +c +t	Collis and Alps (1975)
			+r +c +t	Bhattacharya et al (1977)
			+c	Kawasaki et al (1982)
			+c	Ekas and Lokhandwala (1981)
			+r +c	Haeusler and Haefely (1970)
			+r +c	Finch (1974, 1975)
		DOCA/NaCl	+r +c +t	Haeusler and Finch (1972)
			+r +c	Finch (1971, 1975)
		renal	+r +c +t	Haeusler and Finch (1972)
			+r +c +t	Finch (1971)
			+c	Haeusler and Haeply (1970)
			+r +c +t	Collis and Alps (1976)
			+c	McGregor and Smirk (1970)
			+c	Cheng and Shibata (1980)
			+c	Eikenburg et al (1981)

TABLE A (cont'd)

Stimulus	Preparation	Animal Model	Threshold(t) Reactivity(r) Contractility(c)	Reference
	perfused hindquarter	SHR	↑c	Bhattacharya et al (1977)
			↑c	Cheng and Shibata (1980)
		renal	↑c ↓t	Kubo (1978)
				Finch and Haeusler (1974)
		SHR and DOCA/NaCl	↑c	Finch and Haeusler (1974)
		SHR	↑c ↓t	Lais and Brody (1978)
Nerve Stimulation	McGregor	SHR	↑c	Kamikawa et al (1980)
			↑c	Kawasaki et al (1982)
			↑c	Ekas and Lokhandwala (1981)

Dose-response characteristics in tissues from hypertensive animals

The simplest means of analysing alterations in reactivity uncomplicated by structural adaptations is to record the sensitivity of isolated muscle (vascular and nonvascular) (Bohr, 1964; 1974). Here any alterations in the position in the dose-response curve (under controlled conditions) can only be due to changes in properties intrinsic to the muscle. In other words, unlike total peripheral resistance, vascular sensitivity is an intrinsic property of smooth muscle.

In studies of renal hypertensive rats, Bandick and Sparks (1970) noted a reduced threshold for noradrenaline as well as an increased sensitivity. These results were later confirmed by Bohr and Sitrin (1970) using femoral arteries from DOCA/NaCl rats. Bohr and Sitrin (1970) showed that the lowered threshold was present in hypertensive vessels for a variety of agonists (adrenaline, potassium, calcium). A slight increase in the response to low doses of noradrenaline was observed in aortae from renal hypertensive rats and SHR (Field et al. 1972). These are uncommon findings; the vast body of evidence regarding noradrenaline sensitivity in SHR isolated smooth muscle preparations has not been conclusive. Certainly part of the reason for this has been the different strains (of hypertensive and normotensive animals) and the time course of hypertension, as well as the choice of agonist, tissue and techniques

(Winquist et al. 1982). For instance, the maximal response to noradrenaline in aortic strips from SHR has been reported as unchanged (Clineschmidt et al. 1970; Strecker et al. 1975; Hallback et al. 1971) increased (Cohen and Berkowitz, 1974) or decreased (Shibata et al. 1973). There is also a report of increased tension at low and reduced tension at higher doses of noradrenaline in aortic rings from renal hypertensive rats (Field et al. 1972). In strips of tail artery, Webb has consistently shown (Webb and Vanhoutte, 1979; Webb et al. 1981) no difference in noradrenaline sensitivity between SHR and WKY under control conditions, while in iliac arterial strips, Swamy and Triggle (1980) reported a higher ED_{50} (lower sensitivity) for noradrenaline in SHR vs WKY. A similar increased ED_{50} for noradrenaline was reported by Halloway and Bohr (1973) and Hansen and Bohr (1975).

Sympathetic neuronal influence on contractile agents

In studies on the isolated perfused kidneys from 6-8 week old animals, Collis and Vanhoutte (1978) reported a greater response to nerve stimulation in kidneys from SHR, although both groups responded similarly to noradrenaline, angiotensin II and barium. Later, it was shown that the increased contractile responses to nerve stimulation resulted from a greater release of endogenous noradrenaline (Collis et al. 1979), and that the difference between the WKY and SHR responses to nerve stimulation could not be

abolished by inhibition of transmitter disposition mechanisms (neuronal and extraneuronal uptake, monoamine oxidase, catechol-o-methyltransferase). These experiments were then performed in kidneys from 4-6 month old rats, when it was observed that in the adult SHR the renal vasoconstrictor response to sympathetic nerve stimulation was comparable to that observed in WKY kidneys, while at the same time an exaggerated response to exogenous noradrenaline was observed only in SHR kidneys. In addition, cocaine potentiated the response to renal nerve stimulation more in SHR kidneys than in WKY kidneys. These observations led to the hypothesis that in the young SHR, more noradrenaline is released from the sympathetic nerves, and that as the SHR matured, it compensated for this by increasing the neuronal uptake of noradrenaline at a time when the postsynaptic sensitivity to noradrenaline was increased. Thus an enhanced uptake 1 would mask the underlying increase in the sensitivity to noradrenaline by effectively decreasing the concentration of noradrenaline in vascular smooth muscle of SHR. Since this increased noradrenaline sensitivity was absent in young SHR, Collis *et al.* (1978) suggested that it was a consequence of the high blood pressure.

In a study from the same laboratory, Webb and Vanhoutte (1979) reported that tail artery strips from 4-6 month old SHR and WKY had a similar sensitivity to exogenous noradrenaline and neurally released noradrenaline. When the tail artery strips were denervated, a significant leftward

shift in the noradrenaline dose-response curve was observed only in SHR arterial strips. This again indicated that, at least in 4-6 month old animals, there is a greater than normal neuronal uptake of noradrenaline such that in innervated tissues, the noradrenaline response was similar in SHR and WKY. In the absence of uptake 1, the SHR had a higher sensitivity to noradrenaline (Webb and Vanhoutte, 1979).

Another attempt to examine the modulatory role of the adrenergic nerve ending in regulation of smooth muscle sensitivity was reported by Halpern et al. (1980). In isolated mesenteric arteries from 5 month old animals, the sensitivity to noradrenaline was similar in innervated tissues from SHR and WKY. In denervated tissues, there was a greater increase in noradrenaline sensitivity in tissues from SHR than WKY; i.e. denervation produced a greater leftward shift in the dose-response curve to noradrenaline in tissues from SHR than WKY. The enhanced uptake$_1$ activity was confirmed in SHR vessels using direct measurements of radiolabelled noradrenaline (Halpern et al. 1980). These authors envisioned a situation where the cells of the SHR were twice as sensitive to noradrenaline and developed far more noradrenaline-induced wall tension changes; the increased uptake$_1$ activity would then act in vivo to minimise these effects (Halpern et al. 1980). More detailed results were provided later (Whall et al. 1980) when it was reported that, following adrenergic denervation, the

noradrenaline sensitivity of mesenteric resistance arteries from 5 month old SHR was increased nine times, while the WKY age matched controls showed only a fourfold left shift in the dose-response curve. Again, the total rate of uptake of radiolabelled noradrenaline was significantly higher in tissues from SHR. Had the extent of neuronal accumulation of radiolabelled noradrenaline been the same in SHR and WKY, then denervation would have shifted the dose response curves to the same extent. Bearing in mind that in the absence of neuronal influences the ED_{50} for noradrenaline was considerably lower in vessels from SHR, we can conclude the following based on the results of Whall et al. (1980) and Halpern et al. (1980):- Vasculature from SHR show an increase in vitro sensitivity to noradrenaline; however, this underlying sensitivity change is masked by an increased neuronal uptake of noradrenaline. On the other hand, the in vivo reactivity of SHR vascular beds to noradrenaline is almost always enhanced. This is because when the sympathetic nerve-endings in SHR vascular beds are depolarised during tonic sympathetic activity, uptake of noradrenaline is simultaneously inhibited (Bonaclorsi et al. 1977; Webb et al. 1981), thereby increasing junctional noradrenaline concentration. Thus in vitro, this action of the uptake mechanisms would then result in an overestimation of the true ED_{50} for noradrenaline responses in smooth muscle from SHR (Whall et al. 1980).

An attempt to examine the age related changes in

sensitivity and neuronal uptake of noradrenaline was made by the group led by Mulvany (Mulvany et al. 1980b). They examined arteries from the mesenteric bed of 6, 12 and 24 week old SHR using the myograph technique. Several parameters were investigated; regarding noradrenaline sensitivity, the ED_{50} was not different for tissues obtained from SHR and WKY at any age, i.e. no age or strain differences reported. In the presence of cocaine (in innervated tissues), the leftward shift in the noradrenaline dose-response curve was greatest in tissues from SHR at all age groups. Analysis of variance indicated that the noradrenaline ED_{50} in the absence of cocaine was not strain or age related while in the presence of cocaine, the noradrenaline sensitivity was both age and strain related - sensitivity increased with age and blood pressure. Closer examination of the data (Mulvany et al. 1980) indicates that the ratio of noradrenaline ED_{50} (before/after cocaine) was not diffent for SHR (or WKY) at the various ages, i.e. it is unlikely that the total uptake of noradrenaline was age dependent. In the study by Mulvany et al. (1980), the vascular sensitivity changes were apparent at all ages (6, 12 and 24 week old SHR), while the blood pressure profile showed that at six weeks of age, the mean arterial pressure of SHR and WKY animals were not different. Futhermore, medial hypertrophy of SHR mesenteric arterioles occurred only in 12 and 24 week old tissues, suggesting that while medial hypertrophy was always present in the later phases of

hypertension, the vascular sensitivity changes preceded it (Mulvany et al. 1980). While the results of Collis et al. (1979) and of Webb et al. (1981) suggest that the adaptive changes in uptake$_1$ and noradrenaline ED_{50} are a response to the elevated blood pressure, the findings of Mulvany et al. (1980) would suggest that these changes occur prior to the onset of hypertension.

It is difficult to determine if the increased rate of neuronal uptake is due to an increased rate or to an increase in the number of varicosities since a combination of these effects could cause an increase in stimulated release of noradrenaline in tissues from SHR (Whall et al. 1980; Zsoter et al. 1982). An attempt to resolve this issue was made by Rho et al. (1981a) who examined the uptake of radiolabelled noradrenaline into various fractions of mesenteric artery preparations of SHR and WKY. In agreement with the findings of Whall et al. (1980) the total uptake of noradrenaline in arteries from SHR exceeded that of WKY arteries. As was pointed out by Rho et al. (1980a), total uptake includes both cytoplasmic and vesicular uptake. When these authors excluded the cytoplasm from the pellet that contained structures usually associated with noradrenaline vesicles, it was found that SHR arteries contained a larger amount of neurotransmitter vesicles (Rho et al. 1981a). An abnormal regulation of noradrenaline release due to alterations in presynaptic α-adrenoceptors seems unlikely based on the findings of Ekas et al. (1981) and Eikenberg et

al. (1981) who used fourteen week old SHR and WKY. The possible role of an altered function of presynaptic α_2-adrenoceptors in the SHR was studied by Galloway & Westfall (1982); these authors concluded that presynaptic modulation was similar in pre- and young hypertensive and normotensive animals (6 and 10 week old), but was significantly reduced in tail arteries from chronically hypertensive adult SHR rats (six months old). These authors suggested a desensitisation of prejunctional α_2-adrenoceptors during the course of hypertension (Galloway & Westfall, 1982).

The alteration in enhanced noradrenaline sensitivity in SHR tail artery and mesenteric arteries, and the presence of an increased neuronal uptake of noradrenaline in these tissues has received considerable attention (Whall et al. 1980; Vanhoutte et al. 1980; Webb et al. 1981; Mulvany et al. 1980). No difference in noradrenaline ED_{50} was found when Mulvany et al. (1980c) compared portal veins from 3-4 month old SHR and WKY. These findings are in contrast with the earlier findings of Greenberg & Bohr (1975) and Sutter & Ljung (1977) who reported a greater sensitivity of SHR portal veins to noradrenaline when the Wistar rat was used as a normotensive control rat. Clearly, these are strain-related effects due to the choice of Kyoto-Wistar rats by Mulvany et al. (1980) and Wistar rats by Greenberg & Bohr (1975) and Sutter & Ljung (1977). Using a similar age of SHR and WKY rats as Mulvany et al. used (1980c), Rho et al. (1981b) reported no difference in uptake of radiolabelled

noradrenaline in synaptosmal fractions of SHR and WKY portal veins.

A summary of the review of adrenergic mechanisms of hypertension by Vanhoutte *et al.* (1980) is presented in Table B.

TABLE B: Adrenergic Mechanisms in Hypertension

Synthesis	i) activity of rate limiting enzyme (tyrosine hydroxylase) is increased at early age; normal or reduced in adult SHR (Tarver et al. 1971).
	ii) activity of dopamine-β-hydroxylase increased in young, but normal or reduced in adult SHR (Trajkov et al. 1974).
	Synthesis of noradrenaline is augmented in blood vessels of young SHR, but is normal/reduced in adult animals (Berkowitz et al. 1980).
Neuronal Uptake	i) normal uptake 1 activity in young SHR (Collis et al. 1979) in DOCA/NaCl hypertensive rats (De Champlain, 1977) and in rabbits made hypertensive by coarctation of the aorta (Bevan et al. 1975).
	ii) elevated uptake 1 activity in young SHR (Mulvany et al. 1980).
	iii) elevated uptake 1 activity in adult SHR arterial vessels (Collis et al. 1980; Mulvany et al. 1980).
	iv) normal uptake 1 in portal veins from adult SHR (Mulvany et al. 1980c).

Storage

i) normal noradrenaline content in adult SHR tail artery (Webb and Vanhoutte, 1979).

Release

i) increased exocytotic release in young SHR (Collis et al. 1979).

ii) normal, or reduced release in adult SHR, renal or DOCA/NaCl hypertension (Collis and Vanhoutte, 1977, 1978, 1980; Collis et al. 1979; Webb and Vanhoutte, 1979; Webb et al. 1981).

Postjunctional Sensitivity to Noradrenaline

i) endogenous noradrenaline-sensitivity increased in young, and normal in adult SHR (Collis et al. 1979; Webb et al. 1981).

ii) exogenous noradrenaline-sensitivity increased in young (Mulvany et al. 1980) or normal in young (Collis et al. 1979) prehypertensive SHR.

iii) exogenous noradrenaline-sensitivity increased in adult SHR arterial smooth muscle (when uptake 1 is inhibited) (Mulvany et al. 1980; Webb et al. 1981; Abel and Hermsmeyer, 1981).

iv) unaltered sensitivity in adult SHR portal veins (Mulvany et al. 1980c).

Disposition	i) Uptake 2 normal in blood vessels of young SHR (Collis et al. 1979).
(extraneuronal)	ii) likely to be increased in adult SHR (Webb and Vanhoutte, 1979).
	iii) in adult SHR, catechol-o-methyltransferase, but not monoamine oxidase activity, is increased in vascular tissues. (Trajkov et al. 1974)

Vascular smooth muscle sensitivity and blood pressure

Three approaches have been tried in order to determine whether the vascular smooth muscle sensitivity changes noted by many (Webb and Bohr, 1981 for references) were the secondary results of hypertension or the primary causes of hypertension. Briefly, these methods are: (1) the use of non-arterial or non-vascular smooth muscle to determine if the changes observed in SHR were generalized membrane alterations; (2) comparing certain vascular beds that were "protected" from high blood pressure (e.g., using aortic occlusion or femoral artery ligation) with paired control vessels; (3) by producing "normotensive" SHR (by selective breeding or treating with antihypertensive therapy from birth) and testing pharmacological properties of vascular and non-vascular smooth muscle, or by contrasting properties of young, prehypertensive SHR smooth muscle with those of adult rats.

Studies with non-arterial smooth muscle

Several attempts have been reported where the generalization of the membrane alterations in SHR have been studied by the use of portal vein and other venous tissues (Sutter and Ljung, 1977; Greenberg and Bohr, 1975; Greenberg et al. 1978; Pang and Sutter, 1980a, b; Greenberg, 1981). According to Greenberg (1980) veins provide a model for the study of changes in the vasculature of the hypertensive animal, uncomplicated by the effects of an increased venous

pressure. An early report by Bevan et al. (1975) did demonstrate a slightly enhanced sensitivity to noradrenaline in venous smooth muscle from rabbits made hypertensive by aortic coarctation. In the same year, Greenberg and Bohr (1975) demonstrated that in the absence of increased venous pressure, pulmonary arteries, inferior venae cavae and portal veins of SHR had a hypertrophied media. In isolated tissue bath studies, portal veins from SHR had an increased frequency and amplitude of spontaneous contractions, and a reduced threshold for PGA_2 and PGB_2 and an unaltered threshold for noradrenaline, adrenaline, potassium, barium and strontium. While the sensitivity was only altered for the prostaglandins, the contractility to all agents was increased in portal veins from SHR (Greenberg and Bohr, 1975). Using Wistar rats as controls, Sutter and Ljung (1977) also reported an increased contractility in portal veins of SHR to noradrenaline and acetylcholine at both prehypertensive (6 week old) and established hypertensive phases (6 month). This was later confirmed by Pang and Sutter (1980b) when they compared portal vein contractility from WKY and SHR. Furthermore, Sutter and Ljung (1977) demonstrated significantly lower ED_{50} values for SHR portal veins when noradrenaline and acetylcholine were used to construct dose-response curves.

Greenberg (1981) examined venous hypertrophy and extensibility under numerous experimental conditions. Since hypertrophy and reduced extensibility was present in portal

and femoral veins from WKY made hypertensive (by the Goldblatt method) as well as in veins from SHR, it was suggested that altered venous mechanical properties were not genetically determined events. Because venous pressures in these areas were not elevated in hypertensive animals, Greenberg concluded that hypertrophy and extensibility were unrelated to distending pressures. In this study on the properties of veins in hypertension, Greenberg also subjected animals to antihypertensive therapy with clonidine or alpha-methyldopa. Antihypertensive therapy decreased the biochemical indicies of hypertrophy and improved extensibility in portal and femoral veins from hypertensive rats without concomitant alteration in intravascular pressure. Because α-adrenoceptor blockade (phentolamine, phenoxybenzamine) did not affect the effects of the antihypertensive therapy on venous hypertrophy and extensibility, it seemed unlikely that the beneficial effects of antihypertensive therapy on venous hypertrophy was due to stimulation of smooth muscle α-adrenoceptors or reduction in tone (Greenberg, 1981). Hollander et al. (1968), as well as Nakada and Lovenberg (1978) had previously suggested that vascular hypertrophy in hypertension was due to chronic stimulation of α-adrenoceptors (which in turn mediated the accumulation of precursors of cellular proteins and lipids). Based on these, and later findings, Greenberg concluded that the antihypertensive agents acted by inhibiting the release

(and/or synthesis) of a circulating trophic or humoral factor (Greenberg et al. 1981).

The pressure-independent hypertrophy of veins initially investigated by Greenberg et al. (1978) was confirmed by Johansson and Nordborg (1978). In contrast, Hallback et al. (1971) were not able to demonstrate any pressure-independent changes in the portal vein from SHR.

Other studies in non-arterial smooth muscle from SHR have also suggested the possibility of a general alteration in the sensitivity of smooth muscle; for instance, Altman et al. (1977) studied the contractile response of visceral smooth muscle (fundus strips) to various stimulants. Clear reductions in the ED_{50} value for barium, strontium and calcium were evident in fundus strips from SHR, suggesting an alteration in excitation-contraction coupling in extravascular smooth muscle of SHR. In vasa deferentia from SHR, Corbett et al. (1980) demonstrated a lower threshold for potassium when compared to age-matched WKY rats.

Low-pressure arterial beds in hypertensive rats

In studies performed on blood-perfused isolated hindlimb preparations from DOCA-hypertensive pigs, Berecek and Bohr (1977) confirmed a lower threshold and increased reactivity to constrictor agents. When the hindlimb in these hypertensive pigs was protected from increased arterial pressure by ligation of the iliac artery, the procedure prevented the development of structurally based

changes in resistance and reactivity. However, the threshold dose of noradrenaline was lower in both protected and non-protected hindlimbs from the hypertensive pigs. Thus while contrattility and reactivity in the DOCA-hypertensive pig may be pressure related adaptations, altered postsynaptic sensitivity may be a property of hypertensive vessels.

Another technique used to study vascular reactivity in beds not exposed to high systemic pressures in hypertensive animals is by coarctation of the aorta. In such a preparation, vascular beds below the coarctation are not exposed to elevated levels of pressure, and abnormalities here would not be secondary to increased intravascular pressure (Bell and Overbeck, 1979). An early report by Nolla-Panades (1963) showed an elevated basal resistance to flow and reactivity to noradrenaline in the normotensive hindquarters of coarcted rats. Bell and Overbeck (1979) confirmed these findings. It was shown that elevated vascular resistance in the normotensive hindquarters persisted at maximum vasodilation, indicating that structural changes may have occurred in both normotensive and hypertensive beds of coarcted rats. Furthermore, a greater fall in hindlimb resistance occurred in coarcted rats than in sham operated rats when these beds were acutely denervated. Therefore, in coarcted rats with hypertension, vascular (structural and functional) and neurogenic changes occur even in low pressure beds.

Normotensive SHR and antihypertensive therapy in SHR

Normotensive SHR are produced by treatment of SHR with antihypertensive therapy, and in order to remove any effects secondary to the blood pressure changes, therapy is usually initiated as early as possible (Goldberg and Triggle, 1978). Another method is to in-breed "low-pressure" SHR, as was done by Bhattacharya et al. (1977).

Doyle and Fraser (1961) studied the vascular reactivity in the forearm of the normotensive offspring of hypertensive parents. They were able to demonstrate a greater vasoconstrictor response to noradrenaline in these subjects. In isolated perfused hindquarters of young SHR (3 to 5 week old) Dietz et al. (1978) and Lais and Brody (1978) were able to demonstrate significant alterations in the responsiveness to noradrenaline and barium, as well as in the characteristics of pressure-flow curves. Finch (1975) found that rendering DOCA/NaCl rats normotensive by anti-hypertensive therapy failed to alter the elevated vascular reactivity and contractility. Unfortunately, in both these studies antihypertensive therapy was commenced after the hypertension had become established and irreversible structural changes may have occurred. Similarly, Burkaw and Leach (1981) were able to normalise the blood pressure of adult SHR by eight weeks of daily injections of propranolol, and not detect any changes in the slope or maxima of the perfused mesenteric bed to serotonin and noradrenaline. The problem of antihypertensive therapy commencement at

different ages of SHR was more thoroughly investigated by Antonaccio et al. (1980). These authors concluded that the efficacy of therapy depended on the duration of hypertension, and not on the severity of the pressures. It was argued that at later stages of the hypertensive process in SHR, antihypertensive therapy would produce little change in blood vessel wall properties because of substantial collagen growth that would make these vessels stiffer (Antonaccio et al. 1980).

Goldberg and Triggle (1978) treated SHR in utero, and from weaning, with timolol orally to produce normotensive SHR that maintained the vascular characteristics of untreated, age-matched SHR. In addition, Bhattacharya et al. (1977) reported similar vascular responsiveness of isolated perfused mesenteric beds in both inbred "normotensive" SHR and the hypertensive control SHR.

A number of reports have suggested an alteration in the membrane properties of vascular smooth muscle from SHR. It has been repeatedly shown that microsomes prepared from SHR aorta (Hoki et al., 1976; Bhala et al. 1978, 1980; Webb et al. 1976 and Wei et al. 1976) have a reduced Ca^{2+}-sequestering ability. These findings have been confirmed in mesenteric artery microsomes from DOCA/NaCl and SHR (Kwan et al. 1979; 1980). It has been pointed out by Daniel and Kwan (1981) that the reduced ability to maintain Ca^{2+} gradients in plasma membranes could be due to a combination of a defect in Ca^{2+}-stimulated ATPase transport or in the

permeablity of the microsomal membranes. An increased permeability to calcium ion may account for the increased myogenic activity observed in large (Fitzpatrick and Szentivanyi, 1980; Goldberg and Triggle, 1978; Noon et al. 1978; Suzuki et al. 1979) and small-resistance arteries from hypertensive animals (Bran et al. 1980). Kwan et al. (1980) also have presented data to indicate that decreased Ca^{2+} transport in the plasma membrane of SHR vasculature was present prior to the onset of hypertension. Altered membrane properties are further indicated by the ability of La^{3+} to induce a contraction in arteries from SHR but not in controls (Bohr, 1974b; Goldberg and Triggle, 1977, 1978; Hansen and Hohr, 1975 and Shibata et al. 1973). It has been hypothesised that these contractions result from intracellular displacement of calcium which is loosely bound to plasma membrane (Webb and Bohr, 1981).

Abnormal Ca^{2+} permeability of the rat aorta from SHR was first suggested by Noon et al. (1978) who observed that aortic strips from SHR, but not WKY, relaxed in Ca^{2+}-free Krebs solution. When Ca^{2+} was reintroduced in a non-depolarized preparation, only tissues from SHR contracted. This finding was confirmed by Goldberg and Triggle (1978), who were able to repeat these observations in aortic rings isolated from normotensive SHR (treated from birth with timolol).

La^{3+} response in SHR tissues

Shibata and Kurahashi (1972) and Shibata et al. (1978) described a response to manganese, cobalt and lanthanum that was present in only aortic strips from SHR, and not from Wistar or Sprague-Dawley normotensive rats. The response to these ions was present in aortae from prehypertensive 30 day SHR (Shibata and Kurahashi, 1972). It is surprising that La^{3+} was able to produce a contraction in the aortic strips from SHR, since it was shown by Shibata and Kurahashi (1972) to behave as an antagonist for the tonic phase of a noradrenaline-induced contraction. Lettvin et al. (1964) had previously predicted that La^{3+}, by virtue of its similar ionic radius and higher valence would bind at superficial Ca^{2+} sites with a slower dissociation rate than Ca^{2+}.

Since the group of Shibata (Shibata and Kurahashi, 1972; Shibata et al. 1973) used only single concentrations of the ions, Bohr (1974) repeated the study with some modifications. Again, Sprague-Dawley rats served as the control strain for both SHR and DOCA/NaCl hypertensive rats. With La^{3+} as an agonist, dose-response curves indicated that carotid artery strips from SHR only were able to contract, with tissues from DOCA/NaCl or control Spague-Dawley rats showing minimal responses (Bohr 1974). While changes in tension due to La^{3+} were large in aortic strips (Shibata et al. 1973), those in carotid artery strips from SHR were only small in comparison (Bohr, 1974). Hermsmeyer and Walton (1977) were unable to demonstrate any La^{3+}-induced tension

increases in strips of tail artery from adult SHR. In the experiments of Hansen and Bohr (1975) where one hindlimb of SHR and DOCA/NaCl hypertensive rats was protected from high pressures by tying of the external iliac artery, La^{3+} caused a contractile response in femoral artery strips from both high and low pressure areas of SHR rats only.

The nature of the La^{3+} response in the thoracic aorta from SHR was most thoroughly investigated by Goldberg and Triggle (1977, 1978). Their results can be summarised thus:-

a) a major component of the La^{3+} response results from a change in pH caused by La^{3+} precipitating the phosphate and bicarbonate in physiological bathing solutions. The La^{3+} response could be reproduced by decreasing the pH of the medium directly with H^{+}.

b) both the H^{+} and La^{3+} responses were in part dependent upon the extracellular Ca^{2+} concentration, since high concentrations of D-600 inhibited a portion of the responses.

c) there was a direct pH independent effect of La^{3+} which could be due to a intracellular site of action of La^{3+} in SHR.

d) SHR maintained normotensive with timolol from conception showed a La^{3+} response not different from untreated SHR.

These data are supportive of a defect of the SHR smooth

muscle membrane that could be related to an elevated permeability to ions such as Na^+, K^+, Ca^{2+} (Jones, 1982). Hinke (1966) reported that perfused tail arteries from DOCA/NaCl hypertensive rats contract at lower concentrations of Ca^{2+} when depolarized by potassium. Shibata et al. (1973) found it easier to reverse potassium induced contractures in a calcium-free medium when aortae from SHR were used. Evidence for a role of Ca^{2+} in altered membrane permeability in hypertension comes from the observations of Bohr (1963), Holloway et al. (1972) and Hansen and Bohr (1975). It was initially shown by Bohr (1963) that the response to adrenaline or potassium in isolated blood vessels increased with the concentration of calcium up to 2mM Ca^{2+} (physiological levels); thereafter calcium has a depressant action on tension developments. This was thought to be due to the membrane stabilizing effects of high doses of calcium (Bohr, 1963). Holloway et al. (1975) extended this observation by comparing vascular smooth muscle from hypertensive and normotensive rats and found that greater concentrations of calcium were required for optimal tension development in SHR. These authors concluded that either less calcium was bound to the membrane, or that once bound, it was less effective in stabilizing the membrane of hypertensive vessels (Hansen et al. 1975).

Dahl (salt-dependent) hypertensive rat

The SHR rat was isolated by Okamoto and Aoki in 1963;

after the F_3 generation, this Japanese strain of rats were invariably hypertensive (Okamoto and Aoki, 1963). In contrast to the SHR, other strains of rats require a prolonged period of growth or salt loading to maintain a high blood pressure (Bianchi and Baer, 1976; Dahl et al. 1962). The SHR has received the most research investigation primarily due to the donation of breeding stock (F_{22} generation) to the National Institute of Health, U.S.A. Because of the wide distribution of the SHR, variations in breeding methods, and possibly other unknown local factors, has resulted in substrains of SHR having different profiles of blood pressure (Geller, 1979). On the other hand, local breeding of the Dahl strain of rats is not allowed by the distributers and therefore a homogeneous population of rats can be assumed.

A strain of genetically hypertensive rat developed by Dahl et al. (1962) has drawn considerable interest because of the operation of factors in these rats that are thought to be of importance in the pathogenesis of human hypertension. Selye (1942) determined that addition of NaCl to the drinking water of baby chicks treated with DOCA greatly enhanced the severity of the hypertension induced by DOCA alone. Dahl (1972) measured the blood pressure response to salt in unselected rats, and found a variety of responses from none (25% of the rats) to gradually increased pressures with varied severity (72%) to fulminant hypertension in a few animals. The unequal responses among

normal Sprague-Dawley rats suggested to Dahl and his group at Brookhaven laboratory that variations in genetic complement were modifying blood pressure responses to salt. Dahl et al. (1962, 1972) succeeded in isolating two strains of rats (Sprague-Dawley derived) that differed in their response to dietary sodium intake; the sensitive strain (DS) developed an elevated blood pressure dependent on the concentration of sodium ingested, while the resistant strain (DR) showed only modest, age-related changes in blood pressure. It required seven generations of breeding (about 32,000 animals) before the DS and DR rats were established (Dahl et al. 1972). The epidemiological evidence relating dietary sodium intake with human hypertension is considerable; indeed there exists a host of reviews on this subject, e.g. those by Dahl (1977), Tobian (1977, 1979), Battarbee and Meneely (1978), Freis (1976), Tudge (1981), and Swales (1980), Weiner (1976). Some of the pitfalls in the evidence relating dietary sodium intake with human hypertension have been reviewed by Simpson (1979, 1982) and Pickering (1980). The usefulness of the Dahl strain of rats as a model of human essential hypertension has been reviewed by Tobian (1979) and Rapp (1982b).

Renal mechanisms in Dahl rats

There is a considerable amount of evidence to indicate a primary defect in renal function in DS rats as a cause of hypertension. Tobian et al. (1966) were the first to show

that a genetic fault in the kidneys of the DS rat caused hypertension. This work was confirmed by Dahl, Heine and Thompson (1972, 1974). Essentially, these workers found that when kidneys are transplanted from one strain to the other (DS to DR, and vice versa), the influence on blood pressure arrives with the kidney. Therefore, a kidney from a DS rat will, when transplanted, elevate the blood pressure of a DR rat. The same applied to kidney transplants in the opposite direction, where transplanted DR kidneys can reduce the blood pressure of DS rats fed high salt (Tobian et al. 1966; Dahl et al. 1972, 1974). These transplantion experiments suggested some type of baroceptor resetting within the kidneys, that by itself was able to regulate blood pressure. This hypothesis was tested by Tobian et al. (1978).

The results of Tobian et al. (1978) using blood perfused kidneys isolated from DS and DR rats (fed 0.06% NaCl) clearly indicated that DS rat kidneys excreted only half as much sodium when perfused at similar inflow pressures as kidneys from DR rats. In other words, the pressure-natriuresis curve for kidneys from DS were shifted to the right, so that for equal excretions of sodium the DS kidney would require much higher perfusion pressures (Tobian et al. 1978). In either strain of rats fed low concentrations of dietary sodium, the in vivo difference in renal perfusion pressures would cause little difference in renal sodium handling. If there was a resetting of the

pressure natriuresis curve in the *in vivo* DS rats, these rats would become hypertensive when fed high sodium. The experiments of Iwai *et al.* (1977) provided some evidence for an *in vivo* difference in pressure natriuresis curves between DS and DR kidneys. When DS and DR rats were fed a high NaCl intake, co-administration of chlorothiazide in the diet significantly increased urinary sodium excretion in only DS rats. If the chlorothiazide was later withdrawn, the daily sodium excretion of DS rats dropped significantly (Iwai *et al.* 1977). These results were interpreted as evidence that the *in vivo* resetting of DS kidneys favoured a slower rate of natriuresis and addition of chlorothiazide shifted the pressure-natriuresis curve to the left.

When perfused at low inflow pressures, kidneys from DS rats show virtually no renin release (Tobian *et al.* 1978; Iwai *et al.* 1973) even when fed low dietary sodium. The kidneys from DS rats on a low salt diet have no obvious pathological disturbances (Tobian *et al.* 1966; 1978). To test if sodium itself was a stimulus for the rightward shift in the pressure-natriuresis curve, Tobian *et al.* (1979) allowed adult DS and DR rats a diet of 8% NaCl, with or without thiazide therapy. In this group of rats, only the DS rats without thiazide were hypertensive at all stages. When kidneys from normal Sprague-Dawley rats were perfused with blood from DR rats, the excretion pattern at different input pressures were similar to results obtained with perfusion using normal Sprague-Dawley rats; however,

perfusion with blood from pre-hypertensive or hypertensive DS rats halved the excretion of sodium at all inflow pressures. This suggested and confimed earlier reports by Dahl et al. (1967) and Knudsen et al. (1969) indicating a role for a humoral agent present in DS blood (Tobian et al. 1979). Later, Tobian (1979b) suggested that DS rats had a greater humoral antinatriuretic factor, or a reduced natriuretic factor, when compared to normal Sprague-Dawley or DR rats. It is not clear what relationship the factor described by Tobian (1979b) has with the natriuretic factors described by Dahl et al. (1967), and Knudsen et al. (1969) or reviewed by de Wardner and Clarkson (1982) and Haddy (1982).

Neurogenic mechanisms in Dahl rats

The mechanism leading to this sodium induced rise in systemic pressure of Dahl rats is poorly understood. Approximately fifty percent of the increased peripheral resistance in DS rats is thought to be due to the sympathetic nervous system (Takeshita and Mark, 1978). Neurogenic mechanisms in the Dahl rat were initially investigated by Dahl et al. (1968) who tested the response of DS rats to repeated episodes of electroshocks and conditioning signals for six months; no blood pressure responses to this "emotional stress" could be detected even when the rats were fed sodium rich diets. Under the same conditions, SHR had a stress-induced rise in blood pressure

(Dahl et al. 1968). The presence of a circulating humoral agent in DS rats was described by Tobian et al. (1979b). DS and DR rats were fed 8% NaCl for four weeks, and these rats connected artery-to-artery and vein-to-vein via constant flow pumps to a hindquarter preparation isolated from DR and DS rats. When isolated DR hindquarters were perfused by DS rats, a 17% rise in vascular resistance occurred. It was unlikely to be renin or angiotensin II in the circulation that was responsible for this vasoconstriction, since DS plasma contained 40% less renin than DR plasma when assayed (Tobian et al. 1979b). Blood perfusion of isolated DS hindquarters by DS rats produced no change in vasoconstriction (Tobian et al. 1979b). This circulating humoral agent was further investigated by Tobian's laboratory, and preliminary results were reported recently (Tobian et al. 1982). It was shown that when all renal tissue was removed from salt fed DS rats, these rats were not different from sham-operated DR when bioassayed on the isolated DR hindquarter. Total nephrectomy also reduced significantly the increases in vascular resistance produced by sympathetic nerve stimulation or injections of noradrenaline (Tobian et al. 1982). This is further evidence for a key role for the kidney in the pathogenesis of hypertension in DS rats. This vascular "sensitizing" factor need not necessarily issue from the DS kidney; it could be that DS kidneys influence the release of other agents from elsewhere in the body (Tobian et al. 1982).

Evidence for the participation of the nervous system of DS rats in salt-induced hypertension is also available. Ganguli et al. (1976) had reported that kidneys from DS rats failed to exhibit increased medullary blood flow when placed on a high salt diet, therefore DS rats appear to lack the ability to decrease renal vascular resistance in response to chronic sodium intake. This was shown not to be due to an excessive sympathetic renal drive, since renal vascular resistance changes to denervation or renal nerve stimulation were identical in DS and DR (Fink et al. 1980). Furthermore, renal vascular resistance changes in response to angiotensin II and noradrenaline was similar in DS and DR in a high salt diet. By measuring vascular responses to maximal vasodilation (with acetylcholine) no evidence for altered structural changes were found in renal arteries from DS and DR on low or high salt intake (Fink et al. 1980).

Neurogenic mechanisms in DS rats were investigated by Takeshita and Mark (1978) who studied the control of vascular resistance in hindquarters in anesthesised rats. The role of neurogenic mechanisms in effecting vasconstriction in the DS and DR rat were determined by comparing vascular resistance before and after acute denervation (by cutting the lumbar sympathetic chain). Denervation significantly decreased vascular resistance only in DS rats fed 8.0% NaCl; under these conditions elevated neurogenic tone accounted for about half of the salt-induced increase in hindquarter vascular resistance in DS rats.

(Takeshita and Mark, 1978). Qualitatively similar results were obtained when DS and DR rats (8.0%) were examined for blood pressure measurements before and after infusion of a ganglionic blocking drug (Gordon et al. 1981). When Dahl rats were chemically sympathectomised (6-hydroxydopamine) before being subjected to a high salt diet, no rise in blood pressure was recorded (Takeshita et al. 1979), thus indicating a role for the intact sympathetic nervous system in the development of hypertension in Dahl rats. In both the Takeshita and Mark study (1978) and that by Fink et al. (1980) no evidence for structural changes in blood vessels in high salt DS rats could be determined in hindquarter or renal vessels. Yet, neurogenic mechanisms operate to increase tone in the hindquarter, and not renal vascular bed. Regarding postsynaptic sensitivity changes in vascular smooth muscle as an additional cause of the increased TPR in DS rats, it has been shown in several studies by Hermsmeyers group (Hermsmeyer et al. 1982; Hermsmeyer, 1981 and Abel et al. 1981) that the noradrenaline sensitivity (ED50) either in the absence or presence of neuronal uptake was identical when isolated tail artery strips from salt-fed DS and DR were compared.

Gordon et al. (1981) found that DS rats failed to adequately buffer increases in arterial pressure produced by high salt diets. Even in DS rats on low salt diets (with blood pressures not different from DR rats) an abnormal baroreflex control of heart rate was present, indicating

that DS rats have an inherent resetting of baroreflexes (Gordon et al., 1981). These authors concluded that in intact DS rats, the elevated pressor responses to phenylephrine were due to a reduced baroreceptor buffering reflex since in the presence of ganglion blockade, the DS and DR responded identically to vasoconstrictors (Gordon et al. 1981).

In studies of the central nervous system of DS rats, Ikeda et al. (1978) found an elevated sensitivity to the pressor effects of hypertonic saline and angiotensin II injections into the lateral brain ventricle. Later, Tobian et al. (1980) and Goto et al. 1981 demonstrated that this hypersensitivity to the central effects of angiotensin II and hypertonic saline could be antagonised by adding 2% KCl to the drinking water of DS rats. When the anteroventral third ventricle region (AV3V) in DS rats was sectioned in DS rats, ten weeks of high salt diet (8% NaCl) had only 40% of the blood pressure increment which occurred in sham-operated DS rats (Goto et al. 1982). The AV3V region has been identified as a site containing angiotensin receptors involved in dipsogenic responses (Brody et al. 1980). The enhanced pressor responses to centrally injected angiotensin and hypertonic saline can be reduced, but not reversed, by treating DS rats with thiazides (Ikeda et al., 1978).

OBJECTIVES

The preceeding literature survey indicates general agreement on the following differences between SHR and WKY:-

i) an increased medial thickness of blood vessels, thereby allowing a greater contractility of perfused beds from SHR.

ii) a greater than normal neuronal accumulation of noradrenaline (uptake 1) in arterial smooth muscle from SHR.

iii) an anomalous response of aorta from SHR to the non-physiological ion, La^{3+}.

The overall objectives of the thesis were to a) compare these observations in two models of genetic hypertension, the spontaneously hypertensive rat and the Dahl strain of salt sensitive rat and b) to elaborate on aspects of the above noted differences between SHR and WKY. Experiments were designed to answer the following questions:

A) Is the altered neuronal uptake of noradrenaline and postsynaptic sensitivity to noradrenaline related to the age of the animal?

It is clear that in blood vessels from SHR (compared to WKY) a greater total accumulation of noradrenaline occurs (e.g. Collis and Vanhoutte, 1978; Mulvany, 1979; Whall et al. 1980; Mulvany et al. 1980a; Webb et al. 1981; Rho et al. 1981a). It has been suggested that this elevated neuronal

uptake of noradrenaline occurs in response to an increased postsynaptic sensitivity to noradrenaline in SHR blood vessels. Therefore, the postsynaptic sensitivity to noradrenaline will have a greater ED_{50} value in the absence of neuronal uptake inhibition (Vanhoutte, 1980; Vanhoutte et al.1980).

It is not certain at what stage of the disease this excessive neuronal accumulation of noradrenaline occurs. Whall et al. (1980) and Webb et al. (1980; 1981) suggest that this change occurs in arterial smooth muscle of older SHR only (14 to 20 weeks). At this stage of the disease, the postsynaptic noradrenaline sensitivity is elevated in SHR arterial strips. When 7 week and 16-20 week old SHR and WKY were compared, Collis and Vanhoutte (1978) and Collis, DeMey and Vanhoutte (1980) also concluded that enhanced neuronal activity occurred in the older SHR only (i.e. 16-20 week old animals). However, when Mulvany et al. (1979; 1980a) compared these changes in neuronal uptake of arterial smooth muscle of SHR and WKY at 6, 12 and 24 weeks of age, they reported an increased uptake of noradrenaline, as well as elevated postsynaptic noradrenaline sensitivity, in arterial tissues from all SHR regardless of age (6 to 24 weeks).

Experiments were designed to examine the effect of age on the neuronal uptake of noradrenaline by studying rats at the following age groups: 6-8 weeks (prehypertensive), 16-20 weeks (established hypertension) and > 52 weeks (mature established hypertension). Neuronal uptake activity was

assessed by measuring the susceptibility of noradrenaline dose-response curves to cocaine - simply put, by measuring the ED_{50} value for noradrenaline before and after cocaine such that a ratio of these values would represent the shift in the dose-response curve. This is a commonly applied method in such studies (e.g. Collis and Vanhoutte, 1978; Mulvany et al. 1980a, b; Whall et al. 1980; Webb et al. 1981).

In this part of the study, the influence of other factors (e.g. extraneuronal uptake, β-adrenoceptor activation) on the postsynaptic sensitivity to noradrenaline was also assessed with the use of appropriate antagonists.

B) Is the altered neuronal uptake of noradrenaline and postsynatic sensitivity to noradrenaline restricted to arterial smooth muscle?

The influence of neuronal uptake of noradrenaline on postsynaptic sensitivity to noradrenaline has been most widely studied in arterial smooth muscle. Exceptions to this generalization is the study by Mulvany et al. (1980b) who found no changes in either neuronal uptake or postsynaptic sensitivity in portal vein preparations from 16 week SHR, and a reduced uptake of radio-labelled noradrenaline in membrane preparations of portal veins from 16 week SHR (Rho et al. 1981b).

Therefore, neuronal uptake of noradrenaline and postsynaptic sensitivity to noradrenaline were measured in

the following representative tissues: tail artery (muscular, arterial smooth muscle), aorta (non-innervated), elastic arterial anococcygeus (non-vascular smooth muscle). The tail artery, portal vein and anococcygeus all receive a dense adrenergic innervation.

C. Is the altered neuronal uptake and postsynaptic sensitivity to noradrenaline related to the blood pressure of the rat?

Mulvany et al. (1979; 1980a, b) were able to demonstrate alterations in both of the above parameters in 6 week old SHR, when the blood pressure was still at normotensive levels. However, others (reviewed by Vanhoutte, 1980 and Vanhoutte et al. 1980) have detected elevated neuronal uptake of noradrenaline, and an increased postsynaptic noradrenaline sensitivity, only in SHR with established hypertension. Studies of this type have simply compared results from the SHR with those from the control normotensive WKY; it is assumed that the differences between the two groups must reflect changes related (primary or secondary) to the etiology of hypertension in the SHR. Such a protocol may be quite inadequate because it does not take into account the question of simple strain differences between the SHR and WKY that may be totally unrelated to hypertension.

To determine if these changes were related to the blood pressure of the rat, a breeding program was initiated such

that rats with a range of blood pressures, intermediate between SHR and WKY, were produced. With the availability of such animals, it was possible to test the hypothesis that functional changes which are related to the development of hypertension in the cross-bred rats were correlated with the blood pressure. If the differences between the standard SHR and WKY animals were not related to the hypertensive disease process, then there would be no correlation with blood pressure of the cross-bred rat.

Pharmacological studies on the neuronal uptake of noradrenaline, and of its postsynaptic sensitivity, were performed in various tissues taken from these rats at 12-16 weeks and >52 weeks of age.

D. Is the altered noradrenaline uptake and postsynaptic sensitivity due to tonic sympathetic discharge in SHR?

To test this hypothesis, breeding pairs of rats, as well as the litter, received antihypertensive treatment with α-methyldopa. This drug was chosen because its antihypertensive effect is thought to result from a reduction in sympathetic tone. Pharmacological studies in tissues from age-matched treated and untreated rats were compared. Using the results from such experiments with normotensive SHR it was considered possible to determine if the alterations in uptake of noradrenaline and its postsynpatic sensitivity was essential to the development of hypertension, or perhaps a secondary effect of the disease.

E. Are alterations in neuronal uptake activity and postsynaptic sensitivity to noradrenaline restricted to the SHR model? (i.e. are they model dependent?)

The effect of altered neuronal uptake in regulating noradrenaline postsynaptic sensitivity in arterial smooth muscle sensitivity has been extensively studied in SHR. To determine if these changes are restricted to this model of hypertension, another model of hypertension was chosen for study. Neuronal uptake and noradrenaline sensitivity was therefore assessed in tissues from the Dahl strain of hypertensive rats. It should be pointed out that the only study of these parameters has been for the tail artery, performed by Hermsmeyer's group (Hermsmeyer and Walton, 1977; Hermsmeyer, 1981; Hermsmeyer et al. 1982; Abel et al. 1981). Also since the reactivity and contractility of isolated perfused vascular beds from this strain of hypertensive rats has not been reported, studies were performed to determine these parameters and compare them to similar studies performed in SHR and WKY.

F. Is the La^{3+} induced mechanical response related to blood pressure?

The paradoxical La^{3+}-response is thought to reflect alterations in Ca^{2+} homeostasis in hypertensive vessels (Goldberg and Triggle, 1977). To determine if this paradoxical La^{3+}-response is related to blood pressure, it was studied in tissues from (i) two ages of SHR and related

rats (ii) normotensive SHR (drug treated) (iii) Dahl rats (normotensive and hypertensive salt-sensitive DS rats) (iv) different strains of normotensive rats, genetically related or unrelated to SHR.

Results from such experiments would be expected to indicate the effects of both genetic and blood pressure influences on the La^{3+}-response. Studies were also designed to determine if the La^{3+} response (in SHR) was sex-linked.

METHODS

A. ANIMALS

Spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY), of breeding age, were purchased from Charles River Canada, Inc. (St. Constant, Quebec). Five week old Sprague-Dawley and Wistar rats were also purchased from the same supplier. Male Dahl salt-sensitive (DS) and salt-resistant (DR) strains of rats were purchased from Brookhaven National Laboratories (Upton, New York, USA) and were received when five weeks old. The SHR and WKY rats are derived from the original NIH stock obtained from the Japanese breeders at Kyoto University (Okamoto and Aoki, 1963), while the DS and DR rats are direct descendents of the stock of animals described by Louis Dahl at the Brookhaven Laboratories (Dahl et al, 1962; 1967).

All animals were housed under minimal disease conditions, five to a cage except for breeding pairs and lactating mothers. The animals were housed in the animal quarters of the Faculty of Medicine, Memorial University of Newfoundland under a 12 hours light/12 hours dark light-cycle with controlled humidity and temperature. Litters were weaned at five weeks of age.

The SHR were bred for high blood pressure profiles by monitoring the blood pressure of the breeding pairs indirectly (using the tail-cuff method) prior to mating. Similarly, WKY rats were bred for low blood pressure

profiles. Rats related to SHR and WKY were also produced by breeding the following pairs:-

Offspring	Parents
F_1	♂SHR x ♀WKY ♀SHR x ♂WKY
F_2	♀F_1 x ♂F_1
BC_1(W)	♂F_1 x ♀WKY ♀F_1 x ♂WKY
BC_1(S)	♂F_1 x ♀SHR ♀F_1 x ♂SHR

B. RAT FOOD AND WATER

At all times, rats had free excess to food and water. The SHR, WKY, F_1, F_2, BC(W), BC(S) rats were always fed Purina rat chow (0.36% NaCl), and rats not treated with antihypertensive drugs received tap water. For the Dahl DS and DR rats, specially formulated diets containing known amount of sodium (0.4%, 4.0%, 8.0% by weight) was purchased from ICN Nutritional Chemical Company (Cleveland, Ohio, U.S.A.). The potassium content in the Purina rat chow was 1.08%, while the ICN diet contained 1.06% .

C. DRUG THERAPY OF THE SHR, WKY, F_1

Half of the breeding pairs were selected for antihypertensive therapy with α-methyldopa, which was very generously made available by Dr. W. D. Dorian at Merck, Sharp and Dohme Canada (Kirkland, Quebec). Prior to mating, all breeding pairs were checked for high (SHR) and low (WKY)

blood pressures with the tail-cuff method. After setting up the SHR, WKY and F_1 breeding pairs, female rats received 100 mg/kg (i.p.) ∝-methyldopa and 50 mg/kg (i.p.) carbidopa on alternate days (The carbidopa was also donated by Merck, Sharp and Dohme Canada, Kirkland, Quebec). The breeding pairs and ultimately the offspring, received ∝-methyldopa plus carbidopa, in the drinking water. The ∝-methyldopa dosage was increased, as necessitated to maintain a reduced blood pressure, from an initial 75 mg/kg/day to a maximum of 150 mg/kg/day in the drinking water. On alternate days all lactating mothers continued to receive 100 mg/kg (i.p.) ∝-methyldopa and 50 mg/kg (i.p.) carbidopa. The same dosage regimen was used to treat the litter (from 3 to 13 weeks of age), but later increased to 150 mg/kg ∝-methyldopa (13 to 16 weeks of age). Control rats for these experiments received vehicle injections and ascorbic acid and EGTA in the drinking water.

The ∝-methyldopa in the drinking water was stabilized with ascorbic acid (0.5 g/l) and EGTA (0.5 g/l), and since the pH of the final solution varied from five to six, 2% glucose was added to improve palatability of the mixture. Drug concentrations in the drinking water were based on the daily monitoring of fluid intake. This part of the study was terminated when the rats were sacrificed at 16 weeks of age.

D. DRUG THERAPY OF DAHL RATS

The daily fluid intake of four groups of DS and DR rats (DS 0.3% and 8.0% and DR 0.3% and 8.0% NaCl) was monitored. These rats were then subdivided so that one-third of each group received, via the drinking water, either the converting enzyme inhibitor MK421 (also donated by Merck, Sharpe and Dohme) or hydrochlorothiazide (donated by Dr. E. Vos of Ciba-Geigy, Mississauga, Ontario).

Initially, dosages were 15 mg/kg/day and 60 mg/kg/day of MK421 and hydrochlorothiazide respectively. These doses were increased at weekly intervals to maintain the blood pressure of DS within a normotensive range; the final drug dosages at the time of sacrifice were for MK421 100 *mg/kg/day, and for hydrochlorothiazide 400 mg/kg/day.* Unless otherwise stated, all DS and DR rats were sacrificed at 15-16 weeks of age.

E. BLOOD PRESSURE MONITORING

The blood pressures of breeding pairs and drug-treated rats were monitored using the indirect tail-cuff method in awake rats by modifying the procedure described by Friedman and Freed (1949). In this method, systolic rather than diastolic pressures are used since the former is measured with greater accuracy.

Unanesthetised rats were placed (for 15 min.) in cages pre-warmed to approximately 30^{o} - 32^{o}C. The rats were placed in restraining holders and a tail-cuff and microphone

placed over the tail. The microphone was placed over the ventral surface, over the area covering the tail atery. The blood flow was occluded by inflating the cuff to approximately 200 mmHg for about 30 seconds. Thereafter, the cuff was gently deflated at a constant rate and the pressure pulse sounds recorded via the microphone on a pre-calibrated recorder. The mean of four consecutive systolic blood pressures were recorded for each animal.

The inflatable tail-cuff (model 2257), electrosphygmograph (model 2192) and biograph (model 2120) were all purchased from Harvard Apparatus.

Direct blood pressure measurements of all rats were made by femoral artery cannulations of rats just prior to sacrifice. Rats were anaesthetised with sodium pentobarbital (somnotol®) at a dose of 35 mg/kg (i.p.). Anaesthetised rats were placed on a heating pad, and the femoral artery exposed and cannulated using polyethylyne tubing (PE50). The systolic and diastolic pressures were recorded on a Beckman polygraph (Model 1R411) via a pressure transducer (Statham model P23AA).

F. TISSUE PREPARATION

The anaesthetised rats were sacrificed by cervical dislocation. The thoracic aorta, portal vein, tail artery and anococcygeus were exposed, removed and placed in warm oxygenated physiological buffer.

The aorta was then cut into helical strips (2-4 mm wide, 15 mm long) or rings (3-4 mm long) as described by Goldberg and Triggle (1977).

The isolated portal mesenteric vein preparation was set up as described by Sutter (1965). Following isolation and ligation the vein was punctured and then gently squeezed to remove luminal blood.

The paired anococcygeus muscles were removed from the rat according to the method described by Gillespie (1972). The tail artery was removed, and helical strips were prepared using the proximal portion by modifying the technique described by Palaty and Todd (1978). Tail artery segments were placed in oxygenated physiological buffer and helical strips prepared under a dissecting microscope. The length of the strips were about 8 to 10 mm, and they were about 1 mm wide.

These isolated tissue preparations were suspended individually in 10 ml double-jacketed organ baths containing physiological buffer maintained at 37°C and aerated with a 95% O_2/5% CO_2 mixture. The pH of the buffer was 7.4. All tissues were set at a preload of 0.5 g tension, except for the aortic ring preparation which was maintained at a preload tension of 2.0 g. Isometric tension was recorded on either a Beckman R-411 or Grass 7D polygraph using Grass FT 03C force transducers.

The mesenteric bed was cannulated and isolated according to McGregor (1965). The superior mesenteric

artery was isolated and traced to the origin from the aorta. This was then cannulated with PE50 tubing, and perfused with buffer to clear the mesenteric arcade of blood. The mesenteric bed was then removed from the animal by cutting the blood vessels close to the intestine. The mesenteric preparation was perfused with oxygenated physiological buffer at 37°C at a constant flow of 4 ml/min, since this rate is not far from the expected superior mesenteric blood flow in an adult rat (Kondo et al, 1979). A site was chosen for an injection portal and all injections of vasoactive agents were made in volumes of 0.1 ml. A side-arm cannula was connected to a pressure transducer (Statham P 23AA) at a point between the injection site and the mesenteric bed for the detection of perfusion pressure. A LKB microperpex pump (model 2132) was used for controlling the flow rate, and the perfusion pressures recorded on a Gould Model 220 pen recorder (courtesy of Dr. T. Hoekman, Faculty of Medicine, Memorial University of Newfoundland).

G. EXPERIMENTAL PROTOCOL

Study 1: Postsynaptic noradrenaline sensitivity and uptake of noradrenaline.

This study was performed in the following animals - SHR, F_1, WKY, BC_1(S) and BC_1(W) at three age groups: 6-8 weeks, 12-16 weeks and >52 weeks old. In addition, 12-16 weeks old SHR, F_1, WKY rats treated with α-methyldopa were also used.

In studies with isolated strips of aorta, tail artery and whole tissue mounts of anococcygeus and portal vein, the protocol used was to initially equilibrate the tissues for 90 minutes at a resting pre-load of 0.5 mg. During this time, the buffer solution was replaced every 15 minutes. Two complete cumulative dose-response curves to noradrenaline were determined. The range of noradrenaline doses used was 10^{-10}M to 10^{-5}M for the aortic strips, and 10^{-9}M to 10^{-5}M for the remaining tissues. After allowing a 45-60 minute recovery period, the tissues were exposed to 4 x 10^{-5}M cocaine for twenty minutes. A final noradrenaline dose-response curve was then constructed. From the individual dose-response curves, the noradrenaline ED_{50}(M) values were obtained before and after cocaine. The ratio of the noradrenaline ED_{50} before/ED_{50} after was calculated.

In a few cases, the anococcygeus muscle responded directly to 4×10^{-5}M cocaine by contracting; when this occurred the preparation was not used as part of the experiment.

Pilot studies were also conducted using portal vein and tail artery preparations where dose-response curves to noradrenaline were determined before and after a 20 minute exposure to a given dose of cocaine. In all studies, tissues were exposed to only one dose of cocaine. In other studies with the tail artery, following two complete dose-response curves to noradrenaline, the curves were repeated (after a 30 minute recovery time between curves) following

the additions of (i) 4×10^{-5}M cocaine (20 min.) (ii) 4×10^{-5}M cocaine and 1×10^{-7}M propranolol (45 min.) and (iii) 4×10^{-5}M cocaine, 1×10^{-7}M propranolol and 5×10^{-6}M β-estradiol (30 min).

As noradrenaline is a mixed α and β-adrenoceptor agonist, experiments summarized in tables 4 and 5, were designed to establish if the dose-response curves for noradrenaline in tail artery strips from 12 - 16 weeks old SHR and WKY were influenced by β-adrenoceptor mediated events and extraneuronal uptake (a possible route of agonist removal from the biophase) that could differ in the SHR and WKY. The dose of propranolol used was 1×10^{-7}M since this is approximately ten times its pA2 (8.2) value for β-adrenoceptor mediated events elsewhere in rat tissues (Bowman and Rand, 1982). The estradiol dose (5μM) was chosen to inhibit uptake 2 (without simultaneous activity on uptake 1) at a concentration sufficent to inhibit extraneuronal uptake of noradrenaline by over 90% (Iversen and Salt, 1970; Salt, 1972). Estradiol was dissolved in absolute ethanol and thus control experiments were performed to determine the effect of its solvent. Ethanol (100 μl in a 10 ml tissue bath) had no effect on the sensitivity of tail artery strips to noradrenaline.

Study 2: Dahl rat study

A similar study, as outlined in the methods for study 1, was also performed in Dahl DS and DR rats that were 15-16 weeks old. Again, the tissues used were helical strips of

aorta and tail artery and whole tissue mounts of anococcygeus and portal vein.

Where studies were performed in the McGregor preparation (McGregor, 1965), the tissue was perfused at a constant flow (4 ml/min) for 20 minutes. Thereafter a noradrenaline dose-response curve was determined; when the response to a single dose of agonist had terminated and the baseline perfusion pressure had returned to control levels, the next dose of agonist was introduced.

Following a 20 minute recovery period, a second dose-response curve to noradrenaline was determined, followed by curves to serotonin (5HT) and phenylephrine. In addition to perfused mesenteric beds isolated from DS and DR rats, noradrenaline dose-response curves were also determined in mesenteric preparations from 4-6 week and 12-14 week SHR and WKY rats.

In some studies, aortic strips were obtained from DS and DR rats and following an equilibration period of 90 minutes, the tissues were exposed to 1×10^{-5}M noradrenaline. This agonist was washed out and following an equilibration period, the same dose of noradrenaline was added. This procedure was repeated until a reproducible maximal response was obtained. In the presence of the 1×10^{-5}M noradrenaline, a cumulative dose-response curve to papaverine was determined.

In other studies, when a reproducible maximal response to 1×10^{-5}M noradrenaline had been obtained, the buffer was

replaced once and then again (2-4 seconds later) with either normal buffer or buffer containing 5.0×10^{-5}M papaverine. This wash out response was followed by presetting the chart speed at a known value.

Chronotropic responses of isolated (right) atria were determined as previously described (Laher and McNeill, 1980). The whole heart was removed and placed in warm oxygenated physiological buffer to expel blood from the chambers. Thereafter, the heart was placed in a petri dish containing cold buffer, and the right atrium dissected. The atrium was carefully threaded so that it could be connected to the tension transducer when placed in an isolated-tissue organ bath containing physiological buffer at 37°C, under a resting tension of 1.0g.

Study 3: Lanthanum study

Here, ring preparations of aorta were used exclusively. In some studies, cumulative dose-response curves to La^{3+} (as $LaCl_3$) and H^+ (as HCl) were determined - a given tissue being used for only one of these dose-response curves. The tissues were then gently blotted, (twice) and weighed on a Cahn electrobalance (Model 4100).

In other studies, after a reproducible response to noradrenaline (1×10^{-5}M) had been obtained, the response to a maximally effective dose of La^{3+} was recorded. The tissue was then weighed as before.

The tissues were obtained from the following rats at three age groups:-

4 week: SHR, WKY

6-8 week: SHR, WKY, F_1, F_2, DS, DR

12-16 week: SHR, WKY, F_1, F_2, $BC_1(S)$, $BC_1(W)$, Sprague-Dawley, Wistar, Wistar x SHR, Wistar x WKY, DS and DR.

In addition, tissues were also obtained from 12-16 week old SHR, WKY and F_1 mantained from birth on α-methyldopa therapy, and from 16 week old DS and DR rats maintained on MK421 or hydrochlorothiazide therapy.

H. COMPOSITION OF BUFFER (Krebs bicarbonate buffer, adapted from Janis and Triggle, 1973).

	mM
NaCl	118
KCl	4.7
$NaHCO_3$	12.5
$CaCl_2.2H_2O$	2.5
KH_2PO_4	1.2
$MgSO_4$	1.2
Dextrose	11.1

I. STATISTICS

The ED_{50} values were obtained by graphically calculating the concentration of agonist producing 50% of its maximum response using the method described by Fleming et al, 1972.

Where indicated, results are expressed as the mean $\pm$ 1 standard error of the mean (S.E.M.), calculated with a Texas Instrument TI55 calculator. Statistical significances were determined by the use of the Student's t-test (one-tailed) or analysis of variance (ANOVA) as outlined in the (SPSS) manual by Nie et al (1970). The Scheffe test of significance was used in the ANOVA procedures. Differences by the t-test or ANOVA were considered to be significant if $P < 0.05$. The sample size (n value) is indicated in all tables.

In some data tables, both an ANOVA (for multiple comparison of groups of data) as well as a Student's t-test (for a comparison of two particular groups of data on which an ANOVA would be performed) were calculated. This is a statistically questionable analysing method (eg. see review by Wallenstein et al 1980). However, it was deemed desirable to simply compare two groups by the t-test (eg. SHR vs WKY), since other studies, which parts of this thesis were designed to re-evaluate, (see Objectives, page 55) used only two strains of rats. For comparison with such studies, a t-test was performed on the two groups in

question. And for a complete analysis of the data obtained with a greater strain selection, ANOVA tests were also performed.

DRUGS AND REAGENTS

Calcium chloride dihydrate ($CaCl_2.2H_2O$). J.T. Baker, Phillipsburg, N.J.

Dextrose (anhydrose) Matheson, Coleman and Bell, Norwood, Ohio.

Cocaine (HCl) BHD Chemicals, Montreal.

Ascorbic acid, Fisher Scientific Co., Fair Lawn, New Jersey.

β-estradiol, Sigma Chemicals, St. Louis, Mo.
Ethyleneglycol-bis-(-aminoethyl ether) N_1N^1-tetra-acetic acid (EGTA) Sigma Chemicals, St. Louis, Mo.

Hydrochloric Acid (HCl), J.T. Baker, Phillipsburg, N.J.

6-hydroxydopamine (HCl), Sigma Chemicals, St. Louis, Mo.

5-hydroxytryptamine (oxalate) [serotonin; 5-HT], Sigma Chemicals, St. Louis, Mo.

Isoproterenol HCl Sigma Chemicals, St. Louis, Mo.

Lanthanum chloride ($LaCl_3.7H_2O$), B.D.H. Chemicals Ltd. Poole, England.

Magnesium sulphate ($MgSO_4.7H_2O$). J.T. Baker, Phillipsburg, N.J.

Noradrenaline HCl (L-form) Sigma Chemicals, St. Louis, Mo.

Papaverine HCl. Sigma Chemicals, St. Louis, Mo.

Phenylephrine HCl (L-form) Sigma Chemicals, St. Louis, Mo.

Potassium chloride (KCl) J.T. Baker, Phillipsburg, N.J.

Propranolol HCl (DL form) Sigma Chemicals, St. Louis, Mo.

Sodium bicarbonate ($NaHCO_3$), J.T. Baker, Phillipsburg, N.J.

Sodium chloride (NaCl) J.T. Baker, Phillipsburg, N.J.

Sodium pentobarbital, M.T.C. Pharmaceuticals, Hamilton, Ontario.

Tyramine HCl, Sigma chemicals, St. Louis, Mo.

RESULTS

Study 1

Blood Pressures of rats used in Study 1

The blood pressures of the rats (male) used are shown in table 1. For this part of the study, rats of three age groups were used. At the age of 6 - 8 weeks, the blood pressure trend for the rats was WKY = F_1 < SHR. While these are not significantly different by the analysis of variance (ANOVA) test, there is a significant difference ($P < 0.05$) between the SHR and WKY. In the rats with established hypertension the trend for the blood pressure to increase with age (6 - 8 weeks to 12 - 16 weeks to > 52 weeks) is significant for the F_1 and SHR rats. At 12 - 16 weeks and >52 weeks the F_1, SHR, BC_1(S) and (BC_1(W) in > 52 weeks only) rats all have a higher blood pressure than the corresponding age-matched WKY rats. The individual blood pressures of the rats were converted to mean arterial pressures and these values are sumarized in table 2.

Factors affecting noradrenaline dose-response curves: studies with cocaine, propranolol and estradiol.

In order to determine the optimal dose of cocaine required to cause a maximal leftward shift in the dose-response curve, the effect of various doses on the effect of noradrenaline were studied in the portal-vein and tail artery preparations from > 52 weeks old SHR and WKY. The results of these experiments are shown in table 3.

In this (and all subsequent studies), the following methodology was employed. Following a control dose-response curve to the agonist, the tissue was exposed to cocaine for 20 minutes. In the presence of cocaine, the dose-response curve was repeated. From these curves, the agonist ED_{50} (M) was calculated for the tissue response both in the absence and presence of cocaine, where the maximal tissue response in the absence and presence of cocaine was used in the respective calculations. These ED_{50} values were used to calculate a ratio (ED_{50}(M) in the absence of cocaine divided by ED_{50}(M) in the presence of cocaine) such that the greater the ratio, the larger the shift in the dose-response curve due to cocaine. Therefore, a leftward shift in the dose-response curve is represented by a ratio exceeding unity.

The results in table 3 indicated 4×10^{-5}M cocaine to produce a maximal shift in the dose-response curve for noradrenaline for tissues from both SHR and WKY. This dose of cocaine was then used in all further studies.

In tail artery strips from both control WKY (table 4) and control SHR (table 5), cocaine caused a leftward shift in the dose-response curve for noradrenaline. The ED_{50} for noradrenaline in the absence and presence of cocaine were not statistically different in tissue from WKY (table 4) while in the SHR, the ED_{50} for noradrenaline was significantly reduced when the dose-response curve was performed in the presence of cocaine (table 5). The alterations in the ED_{50} for noradrenaline when dose-response

curves were performed in the presence of cocaine were not further significantly influenced by the addition of either propranolol or estradiol (tables 4 and 5) in tissues from WKY and SHR. In the SHR, there was a non-significant effect of estradiol that added to the leftward shift in the dose-response curve to noradrenaline produced by cocaine.

A group of WKY and SHR were also pretreated with the neurotoxin 6-hydroxydopamine at a dose of 250 mg/kg (i.p.). Compared to the ED_{50} for noradrenaline in tail artery strips from untreated WKY (1.5×10^{-7}M $\pm$ 1.1×10^{-7}M), pretreatment with 6-hydroxydopamine caused a non-significant reduction in the ED_{50} for noradrenaline (6.0×10^{-8}M $\pm$ 2.1×10^{-8}). Furthermore, the ED_{50} for noradrenaline in cocaine-treated tail artery strips from untreated WKY ($7.4 \times 10^{-8} \pm 5.9 \times 10^{-8}$M) was not significantly different from the ED_{50} for noradrenaline in tail artery strips from treated WKY ($6.0 \times 10^{-8} \pm 2.1 \times 10^{-8}$M). In tail artery strips from control and treated WKY, the noradrenaline ED_{50} was not further influenced by the addition of cocaine (with or without estradiol and/or propranolol) (table 4).

In tail-artery strips from treated SHR, the noradrenaline ED_{50} ($8.0 \times 10^{-8} \pm 4.4 \times 10^{-8}$ M) was significantly different from the value obtained in untreated SHR ($3.1 \times 10^{-7} \pm 1.4 \times 10^{-7}$ M), but not different from the ED_{50} or noradrenaline in the presence of cocaine in tail artery strips from untreated SHR (5.8×10^{-8} M $\pm$ 2.4×10^{-8} M) (table 5). As in the case with tissues from WKY, the

addition of estradiol and/or propranolol did not further alter the ED_{50} of noradrenaline, in the presence of cocaine, in tissues from control and treated SHR (table 5). The results of these experiments with propranolol and estradiol in tail artery strips from 12 - 16 weeks old untreated and 6-hydroxydopamine treated WKY and SHR are graphically illustrated in figures 1 to 4. During the course of these experiments, the maximal response to noradrenaline was always within 90% of the control noradrenaline maximum (in the absence of cocaine, estradiol or propranolol) (figures 1 to 4).

A summary of the ratios for the noradrenaline ED_{50} in tail artery strips from untreated and treated WKY and SHR is presented in table 6. The noradrenaline ED_{50} ratios in tail-artery strips from untreated SHR is significantly different from the corresponding WKY values (table 6). In tissues from untreated WKY and SHR cocaine caused a leftward shift in the dose-response curve that was not altered by the further additions of propranolol or estradiol (table 6). In tissues from 6-hydroxydopamine treated WKY the ratio for the ED_{50} for noradrenaline in the absence of cocaine and in the presence of cocaine (with or without estradiol and/or propranolol) was not significantly different from unity. A similar result is shown for tail-artery strips from treated SHR (table 6). Thus subsequent experiments did not employ pretreatment with either propranolol or estradiol.

Factors influencing phenylephrine dose-response curves in tissues from WKY, SHR

The next series of experiments examined the effect of various doses of cocaine on the dose-response curves to phenylephrine in the aorta, portal vein, tail artery and anococcygeus from >52 weeks old WKY and SHR. In the aorta, cocaine did not alter the maximum response to phenylephrine in WKY (table 7) or SHR (table 8). Also, the three doses of cocaine used (1×10^{-7}M, 1×10^{-6}M and 4×10^{-5}M) did not significantly alter the phenylephrine ED_{50} with the resulting ED_{50} ratios being similar for WKY and SHR aortic strips at the three doses of cocaine (tables 7 and 8). The ED_{50} for phenylephrine, either in the absence or presence of cocaine, did not differ between WKY and SHR aortic strips (table 7 and 8).

In the portal vein of WKY and SHR the three doses of cocaine did not significantly alter the ED_{50} or the maximal response to phenylephrine (table 9 and 10). Similar results were obtained in tail artery strips from WKY and SHR (table 11 and 12). However, while the three doses of cocaine (1×10^{-7}M, 1×10^{-6}M, and 4×10^{-5}M) did not significantly alter the maximal response to phenylephrine in the anococcygeus of WKY and SHR (table 13 and 14), 1×10^{-6}M cocaine caused a significant shift in the phenylephrine dose-response curve in both WKY and SHR. For example, the ED_{50} value for phenelephrine in separate experiments had values of 1×10^{-6}M $\pm$ 4.0×10^{-7}M (in the absence of cocaine) and

2.4×10^{-7}M 8.3×10^{-7}M (also in the absence of cocaine). These values are statistically different ($P < 0.1$; table 13).

Noradrenaline uptake and sensitivity of tissues from 6 - 8 weeks and 12 - 16 weeks

The sensitivity (ED_{50}) of tail arteries from 6 - 8 week old WKY, F_1 and SHR in the absence and presence of 4×10^{-5}M cocaine is summarized in table 15. In these tissues, the ED_{50} for noradrenaline was not different in WKY, F_1 or SHR, either in the absence or presence of cocaine. While the trend for the ED_{50} ratios is SHR > F_1 > WKY, it was not statistically significant. A significant trend for a greater ED_{50} ratio with increasing blood pressure was evident in tail artery strips from 12 - 16 week old rats, with the order of the uptake 1 activity index (ED_{50} ratio) being SHR > BC_1(S) > F_1 > BC_1(W) > WKY. The ED_{50} value for noradrenaline (in the absence of cocaine) is similar to the values reported by Webb et al (1981) for SHR (1.0×10^{-7}M) and WKY (8.1×10^{-8}M) using 14 to 24 week old rats. A graphical representation of the complete dose-response curves for noradrenaline in tail-artery strips from F_1 and WKY and SHR and WKY is shown in figures 5 and 6 respectively.

In the aorta of 12 - 16 week old rats, the ED_{50} ratio was not significantly different from unity for tissues from WKY, F_1, SHR, BC_1(S) or BC_1(W), since cocaine did not

Noradrenaline uptake and sensitivity of tissues from >52 week old rats

Similar experiments were performed in isolated tissues from >52 week old rats, initially using only WKY, F_1 and SHR (table 18). When >52 week old BC_1(S) and BC_1(W) became available about a year later, the noradrenaline sensitivity in tissues from these rats was also examined (table 19). Cocaine had no effect on the noradrenaline sensitivity or ED_{50} ratio in aortae from these rats, (table 19); an age related decrease in sensitivity (increase in ED_{50}) was apparent when the noradrenaline ED_{50} value in >52 weeks old WKY, F_1, SHR, BC_1(S) and BC_1(W) was compared to results from 12 - 16 week old rats (table 17). No clear trends in age-related sensitivity changes existed in the other tissues studied (tables 16, 17 and 18). In tail artery strips from the >52 week old animals, the ED_{50} ratio trend was SHR > BC_1(S) F_1 > BC_1(W) > WKY (table 18 and 19). The effect of cocaine was significant on the ED_{50} value for noradrenaline when the results from F_1, SHR, BC_1(S) and BC_1(W) were compared to WKY, since the ED_{50} for noradrenaline was lowered to a greater extent in the F_1, SHR, BC_1(S) and BC_1(W) tail artery strips (table 18 and 19). Essentially similar results to these were obtained when portal veins and anococcygeus muscles from >52 week old rats were measured for noradrenaline ED_{50} and sensitivity to cocaine. Again, the order of the ED_{50} ratio in these two tissues was SHR > BC_1(S) > F_1 > BC_1(W) (tables 17 and 18).

The correlation coefficients relating mean arterial pressure to the noradrenaline ED_{50} ratio in tail artery, portal vein and anococcygeus for 12 - 16 week old rats (SHR, F_1, WKY, BC_1(W), BC_1(S) and >52 week old rats (SHR, F_1 and WKY with or without BC_1(W) and BC_1(S)) are given in table 21 (and illustrated in figures 7 to 12). There was a significant correlation between mean arterial pressure and ED_{50} ratio in tail artery strips from 12 - 16 weeks and >52 week old animals. In the case of the later group, the correlation was improved when the data from the BC_1(S) and BC_1(W) rats were included. For the portal vein and anococcygeus ($P < 0.1$) the correlation was also significant in the older group of animals, and in this case, the correlation coeffjcient reduced when the data from BC_1(S) and BC_1(W) animals were included.

ANTIHYPERTENSIVE TREATMENT

Groups of SHR, WKY and F_1 were treated with a combinaton of 100 mg/kg α-methyldopa and 50 mg/kg carbidopa per day. The blood pressures of these rats, and aged-matched controls are shown in table 22. At the time of sacrifice, this particular group of untreated SHR had a significantly greater blood pressure than a similarly aged group of SHR (12 - 16 weeks) used in the earlier phase of this study (table 1). Possible explanations for this observation were that these animals were part of a newly purchased stock, and additionally, these and all the animals

used thereafter, were kept under minimal disease conditions. When under minimal disease conditions the rats developed less respiratory disease, had a better overall external appearance, and showed less vulnerability to the toxic effects of the pentobarbital injection.

The antihypertensive therapy was without significant effect in WKY and F_1 rats, but the blood pressure lowering effects of the drug combination was significant in SHR rats, such that the treated SHR rats had only a moderate but significantly elevated blood pressure compared to treated and control WKY (table 22). In aortae from these treated and control 12 - 16 week old SHR, F_1 and WKY, cocaine had no effect on the ED_{50} for noradrenaline, and there was no difference for the ED_{50} between the various groups of animals. Unlike the markedly elevated noradrenaline sensitivity of aorta from F_1 rats recorded earlier (table 16), the noradrenaline sensitivity in this group of 12 - 16 week old F_1 rats was not different from WKY and SHR values (table 23).

Cocaine did reduce the noradrenaline ED_{50} values for noradrenaline in the portal vein and anococcygeus from WKY, F_1 and SHR (tables 24 and 26). However, the noradrenaline sensitivities, in the absence or presence of cocaine, were not affected by antihypertensive treatment of the rats (tables 24 and 26). The leftward shifts in the dose-response curves for noradrenaline in the portal vein was similar for tissues from WKY, F_1 and SHR; and were not

altered by α-methyldopa therapy (table 27). Similar results were found in the anococcygeus (table 27); however, unlike the results in table 16, the magnitude of the ED_{50} ratio's in the anococcygeus from these groups of rats were markedly reduced.

In tail artery strips from this group of 12 - 16 weeks old WKY, F_1 and SHR, cocaine also caused a reduction in the noradrenaline ED_{50} value that was unaffected by α-methyldopa treatment (table 25).

The largest leftward shift caused by cocaine in the dose-response curve for noradrenaline in tail artery strips was for tissues from SHR (ED_{50} ratio of 3.5 in control and α methyldopa treated rats). Similar to the trend in table 16, this ratio was significantly greater than the value obtained in tissues from WKY, with the value in F_1 tail artery strips being intermediate (table 27).

Study 2.

Blood pressure of rats used in study 2

Dahl (DS and DR) rats were subdivided so that groups of DS and DR received one of three diets - containing 0.4%, 4.0% or 8.0% NaCl by weight. These rats were sacrificed at 15 weeks of age (after they had received the diet for a 10 week period) and their blood pressures at the time of sacrifice are shown in table 28. The blood pressures of the DR rats were not changed by feeding the rats diets rich in

NaCl, while there was a significant blood pressure elevating effect of the 0.4%, 4.0% and 8.0% NaCl diet in DS rats (table 28). The blood pressure rose with increasing amounts of NaCl in the diet (table 28), and always exceeded the blood pressures of DR rats fed a matched diet.

Noradrenaline uptake and sensitivity in tissues from Dahl DS and DR rats

Experiments similar to those discussed in study 1 were also performed in aorta, portal vein, tail artery and anococcygeus from DR and DS rats fed 8.0% NaCl. The dose of cocaine used was also 4×10^{-5}M, and the same protocol used as in earlier studies. The results of these studies are summarized in table 29.

The noradrenaline ED_{50} in aorta from 8% DS and DR was not different, and cocaine had no significant effect on the dose-response curve to noradrenaline in these tissues (table 29). In the other tissues used (portal vein, anococcygeus and tail artery) there were also no differences in the ED_{50} for noradrenaline when tissues from 8% DS and DR were compared. Cocaine did cause a leftward shift in the dose-response curves in these three tissues, but the ED_{50} ratio was similar for tissues from DS and DR rats (table 29).

Studies with the isolated mesenteric bed

In the Krebs perfused isolated mesenteric bed from 0.4% and 8.0% NaCl fed DS and DR rats, noradrenaline,

phenylephrine and serotonin (5HT) all caused increases in perfusion pressure (figures 13 to 18). The pressor effects of noradrenaline were similar for preparations from DS and DR, and did not differ when 0.4% NaCl Dahl rats (DS, DR) were compared to 8.0% NaCl Dahl rats (figures 13 and 18). Similar observations were made when phenylephrine and serotonin were used as the agonist. The properties of the perfused mesenteric beds from 4 week old and 12-16 week old WKY and SHR were also compared with noradrenaline as the agonist (figures 19 and 20). Identical dose-response curves were obtained for perfused beds from 4 week old WKY and SHR, with the threshold dose and the maximal pressor response being similar for both beds (figure 19). In perfused beds from 12 - 16 week old WKY and SHR, the threshold doses were again not significantly different, but the pressor responses were significantly greater in the SHR (at all doses about 0.1 g noradrenaline) (figure 20).

Relaxation of aorta from Dahl rats

The relaxation of aortic strips from 4% NaCl fed DS and DR rats was studied by initially performing dose-response curves for papaverine in aortic strips precontracted with 1 x 10^{-5}M noradrenaline (figure 22). The tissues from DS and DR rats were equally sensitive to the relaxing effects of papaverine, with the ED_{50} for the relaxant being about 5 x 10^{-5}M. Experiments were also performed to determine if the rates of relaxations were different in aortic strips from DS

and DR, either in the absence (figure 23) or presence (figure 24) of 5×10^{-5}M papaverine. This was also done by initially precontracting the tissues with 1×10^{-5}M noradrenaline. While papaverine did reduce the time required to relax these tissues in a Krebs washout solution, the rates of relaxation for aortae from DS and DR did not differ (figures 23 and 24).

Study 3

Blood pressures of rats used in Study 3

Thirteen strains of rats were used in study 3. Table 30 shows the blood pressures of the SHR and WKY rats, and the rats derived from the back-cross breeding of these two parent strains. The rats were sacrificed at 4 weeks of age (SHR and WKY), 6 - 8 weeks (SHR, WKY, F_1 and F_2) and at 12 - 16 weeks of age (SHR, WKY, F_1, F_2 and $BC_1(S)$ and $BC_1(W)$.

There were significant age and sex related differences in blood pressures. In general, the blood pressures of the rats increased with age from 4 weeks to 12 - 16 weeks, while the female rats always had a lower blood pressure than the male counterpart (except in the 12 - 16 week old WKY where the differences were significant at the 0.1 level) (table 30). Female $BC_1(S)$ and $BC_1(W)$ were not used in these studies. The Wistar rat was also used to produce the following offspring:- WISTAR x SHR and WISTAR x WKY. The blood pressure of the WISTAR x WKY rats were not

statistically different from the parent strains (table 31). The blood pressure of another normotensive strain, the Sprague-Dawley rat (Table 31), did not differ from the Wistar, WKY or WISTAR x WKY rats either. On the other hand, the WISTAR x SHR had a significantly higher pressure than the Wistar rat (table 31) but was significantly lower than the SHR rat (table 30).

Dahl DS and DR rats were also used in this study, and the blood pressures of these rats are given in table 32. A group of six-week old DS and DR were placed on a 0.4% NaCl for one week, and their blood pressure at the time of sacrifice is shown in table 32.

ANTIHYPERTENSIVE THERAPY

The α-methyldopa treated rats used in study 1 (table 22) also provided aortic tissues for this part of the study, and their blood pressures are included in table 33, which also include the blood pressure of 0.4% and 8.0% DS and DR rats treated with MK421 or hydrochlorothiazide. Both the treatments were effective in reducing the blood pressure of 8.0% DS rats, while little effect was seen in the other groups of rats except in the 0.4% DR where MK421 reduced the blood pressure (table 33).

Cumulative dose-response curves to La^{3+} and H^{+} were performed in aortic rings from 12 - 16 weeks old SHR, Wistar and WKY and these results are illusrated in figures 25 and 26 respectively where the La^{3+} response is expressed as a

percentage of the response to 1 x 10^{-5}M noradrenaline. La^{3+} and H^+ caused a dose-dependent increase in tension in tissues from SHR and WKY only (figure 25 and 26). The La^{3+} response was also observed in 4 week old, 6 - 8 week and 12 - 16 week SHR, WKY, F_1, F_2 and BC_1 rats. The La^{3+} response (when expressed as a percentage of the tissue response to 1 x 10^{-5}M noradrenaline) was always greatest in tissues from SHR, and increased with the age of the animal (table 34). The La^{3+} response was not significantly different in aortic rings from male or female rats when these were compared within a strain (table 34). The order of the La^{3+} response (when expressed as a percentage of the tissue response to 1 x 10^{-5}M noradrenaline) was SHR > F_2 > F_1 > WKY > BC_1(S) > BC_1(W) for the 12 - 16 week old male rats. In the Dahl rats, the La^{3+} response was always absent in DR rats, and in the DS rats the response increased with increasing levels of NaCl intake (8% > 4 % > 0.4%).

The effect of drug therapy of SHR, WKY and F_1 rats (with α-methyldopa) and DS and DR rats (with MK421 and hydrochlorothiazide) on the La^{3+} response was also studied, and the results are summarized in table 35. Antihypertensive therapy of DS rats abolished the La^{3+} response in 0.4% DS and 8.0% DS, while α-methyldopa therapy did not significantly affect the La^{3+} response in SHR, F_1 and WKY (table 35).

When the La^{3+} response was expressed as mg tension per mg wet weight aortic tissue response there were no

significant age-related or strain related differences within the SHR, WKY and related rats (table 36, figure 29).

The La^{3+} response was absent in Wistar and Sprague-Dawley rats (table 37), but present in SHR x Wistar and WKY x Wistar rats. These responses in the SHR x Wistar and WKY x Wistar were significantly different from the responses obtained in SHR or WKY either when expressed as a percentage of the maximal response to noradrenaline (table 34) or on a mg tension/mg wet weight basis (table 36). Table 38 summarizes the noradrenaline (1×10^{-5}M) response (in a mg tension/mg tissue wet weight basis) for some of the rat strains used in study 3. The noradrenaline response so expressed was always lowest in the SHR (at all ages) and in the 12 - 16 week old group of rats, the order of the noradrenaline response was WKY > F_1 > BC_1(S) > F_2 > SHR > BC_1(W). Aortic rings from SHR x Wistar developed a significantly greater response to noradrenaline than tissues from SHR (table 36), while response in tissues from WKY and Wistar x WKY were not different (table 38).

The results for the regression analysis for the mean arterial pressure versus the La^{3+}-response (expressed as a percent of the tissue response to 1×10^{-5}M noradrenaline) is summarized in table 39 (and figure 27) for tissues from WKY, SHR, F_1, F_2, BC_1(S) and BC_1(W). In the 6 - 8 week group and in the 12 - 16 week group, the correlation coefficient is significant when the results from WKY, SHR and F_1 rats are combined. While this correlation is not

affected by including data from F_2 or $BC_1(W)$ and $BC_1(S)$ rats in the 12 - 16 week group of rats, inclusion of the F_2 rat data does reduce the correlation coefficient in the 6 - 8 week group of rats (table 39). A negative correlation of mean arterial pressure and the noradrenaline response (mg tension per mg tissue wet weight) was calculated (table 38, figure 30). The correlation coefficient for both the La^{3+} response (table 29) and the noradrenaline response (table 39) was greater in the 12 - 16 week group of rats (figures 27 and 28).

Table 1: Blood pressure (systolic ± S.D./diastolic ± S.D.) of rats used in study 1.

Results expressed as mean ± S.D. of 5-13 animals, and were obtained from femoral artertery cannulations of pentobarbital anesthetised rats.

Table 1

	6-8 weeks	12-16 weeks	>52 weeks
WKY	105 ± 8	107 ± 6	113 ± 18
	75 ± 4	72 ± 5	81 ± 11
F_1	109 ± 6	129 ± 4 [a,d]	151 ± 8 [a,d]
	80 ± 5	111 ± 5	110 ± 6
SHR	130 ± 22 [c]	154 ± 6 [a,d]	184 ± 7 [a,d]
	95 ± 17	107 ± 3	124 ± 9
BC_1(W)		117 ± 7	130 ± 6 [c]
		84 ± 4	84 ± 6
BC_1(S)		152 ± 6 [a]	149 ± 7 [a]
		115 ± 4	94 ± 7

a) Sign. different from age-matched WKY by ANOVA (Scheffe's test) ($P < 0.05$)

c) Sign. different from age-matched WKY by Student t-test ($P < 0.05$)

d) Sign. different from corresponding blood-pressure at 6 - 8 weeks of age by Student t-test ($P < 0.05$)

Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

Table 2: Mean arterial pressure $= \frac{(\text{systolic pressure} + 2\text{diastolic pressure})}{3}$

of rats used in study 1.

Results expressed as mean ± S.E.M. (n = 5-13)

Table 2

	6-8 weeks	12-16 weeks	>52 weeks
WKY	84 ± 2	84 ± 5	87 ± 3
F_1	94 ± 4	119 ± 5[a,d]	124 ± 4[a,b,d]
SHR	111 ± 7[c]	123 ± 6[a,b]	158 ± 5[a,d]
BC_1(W)		96 ± 6	99 ± 6
BC_1(S)		110 ± 4[a,b]	112 ± 7[a]

a) Sign. different from age-matched WKY by ANOVA (Scheffe's Test) ($P < 0.05$)

b) Sign. different from age-matched BC(W) by ANOVA (Scheffe's Test) ($P < 0.05$)

c) Sign. different from age-matched WKY by Student t-test $P < 0.05$)

d) Sign. different from corresponding 6 - 8 week mean arterial pressure by Student t-test ($P < 0.05$)

Blood pressure values are given in mmHg (1mm Hg = 0.133 kPa).

Table 3: Effect of cocaine pretreatment of noradrenaline DRC expressed as a ratio (ED_{50} to NA before/after cocaine), and are obtained on tissues from animals > 52 weeks old.

Results expressed as mean ± S.E.M.

Table 3

	SHR		WKY		
	P. Vein	Tail Art.	P. Vein	Tail Art.	n
10^{-7} M	1.1 ± 0.1	2.7 ± 1.7	1.1 ± 0.2	1.8 ± 0.6	4
10^{-6} M	2.0 ± 0.5	2.7 ± 1.8	2.0 ± 0.6	1.9 ± 0.6	4
4×10^{-5} M	7.6 ± 2.4[c,d]	6.0 ± 0.8[c,d]	1.8 ± 0.2	2.2 ± 0.3	6

c) Sign. different from corresponding WKY value by Student t-test ($P < 0.05$).

d) Sign. different from WKY ratio in the presence of 1×10^{-7}M cocaine ($P < 0.1$).

Table 4: Effect of cocaine (4×10^{-5}M), propranolol (1×10^{-7}M), and β-estradiol (5×10^{-6}M) on noradrenaline dose-response curves in tail artery strips from 12-16 weeks old untreated and 6-hydroxydopamine treated WKY.

ED_{50} of noradrenaline expressed as mean ± S.E.M.

Table 4

	ED_{50} (M) before cocaine	ED_{50} (M) after cocaine	ED_{50} (M) after cocaine + propranolol	ED_{50} (M) after cocaine + propranolol + estradiol
Control WKY	1.5×10^{-7}	7.4×10^{-8}	7.1×10^{-8}	7.8×10^{-8}
n = 6	±	±	±	±
	1.1×10^{-7}	5.9×10^{-8}	3.3×10^{-8}	1.0×10^{-8}
6-hydroxydopamine	6.0×10^{-8}	7.7×10^{-8}	9.2×10^{-8}	4.9×10^{-8}
treated WKY	±	±	±	±
n = 8	2.1×10^{-8}	3.5×10^{-8}	5.5×10^{-8}	1.8×10^{-8}

Table 5: Effect of cocaine (4×10^{-5}M), propranolol (1×10^{-7}M) and β-estradiol (5×10^{-6}M) on noradrenaline dose-response curves in tail artery strips from 12 - 16 weeks old untreated and 6-hydroxydopamine treated SHR.

ED_{50} of noradrenaline (M) expressed as mean ± S.E.M.

Table 5

	ED_{50} (M) before cocaine	ED_{50} (M) after cocaine	ED_{50} (M) after cocaine + propranolol	ED_{50} (M) after cocaine + propranolol + estradiol
Control SHR	3.1×10^{-7}	5.8×10^{-8} [a]	6.1×10^{-8} [a]	2.2×10^{-8} [a]
	±	±	±	±
n = 6	1.4×10^{-7}	2.4×10^{-8}	2.0×10^{-8}	1.3×10^{-8}
6-hydroxydopamine	8.0×10^{-8}	6.2×10^{-8} [a]	4.1×10^{-8}	2.8×10^{-8} [a]
treated SHR	±	±	±	±
n = 10	4.4×10^{-8} [a]	3.3×10^{-8}	1.5×10^{-8} [a]	1.0×10^{-8}

a) Sign. different from control SHR (ED_{50} before cocaine) by ANOVA (Scheffe's Test. ($P < 0.05$).

Table 6: Effect of propanolol (1×10^{-7}) and β-estradiol (5×10^{-6}M) on ED_{50} ratio for noradrenaline before and after 4×10^{-5}M cocaine in tail artery strips from 12 - 16 weeks old untreated and 6-hydroxydopamine treated WKY and SHR.

Results expressed as mean ± S.E.M.

Table 6

ED_{50} ratio after	WKY control (n=6)	WKY treated (n=8)	SHR control (n=6)	SHR treated (n=10)
cocaine	1.8 ± 0.1	0.8 ± 0.1[c]	4.8 ± 0.5	1.3 ± 0.2[c*]
cocaine + propranolol	1.3 ± 0.4	0.9 ± 0.4[c]	4.4 ± 1.0	1.2 ± 0.2[c*]
cocaine + propranolol + estradiol	1.6 ± 0.1	1.4 ± 0.4	4.4 ± 1.0	1.7 ± 0.6[c*]

c) Sign. different from WKY control ED_{50} ratio after cocaine by Student t-test ($P < 0.05$) [or $P < 0.1$ for d]

c*) Sign. different from SHR control ED_{50} ratio after cocaine by Student t-test ($P < 0.05$)

Table 7: Effect of various doses of cocaine on the phenylephrine dose-response curve in helical strips of aorta from > 52 week old WKY.

Results expressed as mean ± S.E.M.

Table 7

Dose of cocaine	ED_{50} (M) value Before cocaine	After cocaine	Ratio	% Potentiation by cocaine	n
1×10^{-7} M	3.2×10^{-7} ± 8.7×10^{-8}	3.4×10^{-7} ± 8.7×10^{-8}	1.1 ± 0.4	7 ± 12	4
1×10^{-6} M	2.9×10^{-7} ± 2.2×10^{-7}	4.6×10^{-7} ± 6.4×10^{-7}	0.7 ± 0.1	-3 ± 9	4
4×10^{-5} M	2.7×10^{-7} ± 1.1×10^{-7}	2.4×10^{-7} ± 8.9×10^{-8}	1.2 ± 0.2	3 ± 18	5

Table 8: Effect of various doses of cocaine on the phenylephrine dose-response curve in helical strips of aorta from > 52 week old SHR. Results are expressed mean ED_{50} ± S.E.M.

Table 8

Dose of cocaine	ED_{50} (M) value before cocaine	ED_{50} (M) value After cocaine	Ratio	% Potentiation by cocaine	n
1×10^{-7} M	3.7×10^{-7} ± 2.7×10^{-8}	2.8×10^{-7} ± 2.3×10^{-8}	1.6 ± 0.4	2 ± 3	5
1×10^{-6} M	3.0×10^{-7} ± 1.7×10^{-8}	3.9×10^{-7} ± 8.3×10^{-9}	0.8 ± 0.2	1 ± 7	4
4×10^{-5} M	1.4×10^{-7} ± 8.3×10^{-8}	2.4×10^{-7} ± 1.5×10^{-7}	0.8 ± 0.4	1 ± 13	4

Table 9: Effect of various doses of cocaine on the phenylephrine dose-response curve in portal vein preparations from > 52 week old WKY.
Results expressed as mean ED_{50} ± S.E.M.

Table 9

Dose of cocaine	ED_{50} (M) value Before cocaine	After cocaine	Ratio	% Potentiation by cocaine	n
1×10^{-7} M	5.6×10^{-7} ± 1.6×10^{-7}	4.2×10^{-7} ± 1.7×10^{-7}	1.3 ± 0.8	-7 ± 7	4
1×10^{-6} M	4.1×10^{-7} ± 1.3×10^{-7}	2.6×10^{-7} ± 1.2×10^{-7}	1.6 ± 0.2	-3 ± 13	3
4×10^{-5} M	5.9×10^{-7} ± 1.1×10^{-7}	5.0 10^{-7} ± 2.4 10^{-7}	1.3 ± 0.4	-13 ± 26	4

Table 10: Effect of various doses of cocaine on the phenylephrine dose-response curve in portal vein preparations from > 52 weeks old SHR.

Results are expressed a mean ED_{50} ± S.E.M.

Table 10

Dose of cocaine	ED_{50} (M) value Before cocaine	After cocaine	Ratio	% Potentiation by cocaine	n
1×10^{-7}M	3.6×10^{-7} ± 2.6×10^{-7}	2.9×10^{-7} ± 2.1×10^{-7}	1.2 ± 0.1	3 ± 2	4
1×10^{-6}M	1.1×10^{-6} ± 1.0×10^{-7}	7.8×10^{-7} ± 9.0×10^{-8}	1.3 ± 0.2	9 ± 10	4
4×10^{-5}M	1.7×10^{-6} ± 7.1×10^{-7}	1.3×10^{-6} ± 8.3×10^{-7}	1.3 ± 0.4	6 ± 14	4

Table 11: Effect of various doses of cocaine on the phenylephrine dose-response curve in helical strips of tail artery from > 52 week old WKY

Results expressed as mean ED_{50} ± S.E.M.

Table 11

Dose of cocaine	ED_{50} (M) value Before cocaine	After cocaine	Ratio	% Potentiation by cocaine	n
	9.8×10^{-7}	2.0×10^{-6}			
1×10^{-7}M	±	±	0.6 ± 0.5	3 ± 1	5
	4.3×10^{-7}	8.4×10^{-6}			
	1.0×10^{-7}	1.1×10^{-7}			
1×10^{-6}M	±	±	1.1 ± 0.1	-7 ± 14	3
	5.6×10^{-7}	8.0×10^{-7}			
	3.3×10^{-7}	2.7×10^{-7}			
4×10^{-5}M	±	±	1.3 ± 0.7	-2 ± 8	6
	2.5×10^{-7}	2.5×10^{-7}			

Table 12: Effect of various doses of cocaine on the phenylephrine dose-response curve in helical strips of tail artery from > 52 week old SHR. Results are expressed as mean ED_{50} ± S.E.M.

Table 12

Dose of cocaine	ED_{50} (M) value: Before cocaine	After cocaine	Ratio	% Potentiation by cocaine	n
	1.9×10^{-7}	1.2×10^{-7}			
1×10^{-7} M	±	±	1.6 ± 1.0	3 ± 1	4
	1.5×10^{-7}	4.2×10^{-7}			
	6.0×10^{-7}	4.8×10^{-7}			
1×10^{-6} M	±	±	1.1 ± 0.1	-7 ± 14	4
	1.1×10^{-7}	2.6×10^{-7}			
	2.1×10^{-7}	1.1×10^{-7}			
4×10^{-5} M	±	±	1.9 ± 0.7	-2 ± 8	4
	9.5×10^{-7}	6.4×10^{-7}			

Table 13: Effect of various doses of cocaine on the phenylephrine dose-response curve in anococcygeus muscle from 50 week old WKY.

Results expressed as mean ED_{50} ± S.E.M.

Table 13

Dose of cocaine	ED_{50} (M) value Before cocaine	After cocaine	Ratio	% Potentiation by cocaine	n
1×10^{-7}M	2.4×10^{-7} ± 8.3×10^{-8}	1.3×10^{-7} ± 5.6×10^{-8}	1.5 ± 0.2	2 ± 5	5
1×10^{-6}M	1.0×10^{-6} [c] ± 4.0×10^{-7}	1.4×10^{-7} [d] ± 4.0×10^{-8}	8.0 ± 1.1[c]	3 ± 4	6
4×10^{-5}M	1.0×10^{-6} [c] ± 4.1×10^{-7}	1.8×10^{-7} [d] ± 2.7×10^{-8}	6.9 ± 6.0	-2 ± 10	5

c) Sign. different from corresponding ED_{50} value obtained with 1×10^{-7}M cocaine (Student t-test, $p < 0.05$) ((e) $P < 0.1$).

d) Sign. different from corresponding ED_{50} value obtained in the absence of cocaine (Student t-test, $P < 0.1$).

Table 14: Effect of various doses of cocaine on the phenylephrine dose-response curve in anococcygeus muscle preparations from > 52 week old SHR. Results expressed as mean ED_{50} ± S.E.M.

Table 14

Dose of cocaine	ED_{50}(M) value Before cocaine	After cocaine	Ratio	% Potentiation by cocaine	n
1×10^{-7}M	$4.5 \times 10^{-7} \pm 1.5 \times 10^{-7}$	$3.0 \times 10^{-7} \pm 1.1 \times 10^{-7}$	1.6 ± 0.1	5 ± 2	9
1×10^{-6}M	$6.9 \times 10^{-7} \pm 3.0 \times 10^{-7}$	$6.6 \times 10^{-8} \pm 1.3 \times 10^{-8}$	10.3 ± 1.7[c]	1 ± 7	5
4×10^{-5}M	$1.2 \times 10^{-6} \pm 9.1 \times 10^{-7}$	$1.9 \times 10^{-7} \pm 6.3 \times 10^{-8}$	6.2 ± 6.1	2 ± 19	9

c) Sign different from corresponding value obtained with 1×10^{-7}M cocaine (Student t-test) $p < 0.05$.

Table 15: Noradrenaline ED_{50} values for tail arteries from 6 - 8 week old Rats

Results expressed as the noradrenaline ED_{50}(M) ± S.E.M.

The individual ED_{50} values of tissues before and after cocaine was used to obtain a ratio (±S.E.M.).

Table 15

Cocaine (4×10^{-5}M)

	ED_{50} Before		ED_{50} After		Ratio	n
WKY	9.7×10^{-8} ±	8.1×10^{-8}	7.3×10^{-8} ±	5.6×10^{-8}	1.3 ± 0.1	4
F	2.3×10^{-7} ±	1.3×10^{-7}	1.1×10^{-7} ±	6.7×10^{-8}	2.3 ± 0.9	6
SHR	1.2×10^{-7} ±	9.9×10^{-8}	7.3×10^{-8} ±	8.6×10^{-8}	2.8 ± 2.2	9

Table 16: Noradrenaline ED_{50} values (± S.E.M.) in the absence and presence of cocaine (4.0×10^{-5}M) for tissues from 12 - 16 week old SHR and genetically related rats.)

Table 16

Cocaine (4.0×10^{-5}M)

	ED_{50} Before	ED_{50} After	Ratio	n
Aorta				
WKY	$3.1 \times 10^{-9} \pm 1.0 \times 10^{-9}$	$4.5 \times 10^{-9} \pm 1.7 \times 10^{-9}$	0.8 ± 0.2	9
F_1	$1.5 \times 10^{-10} \pm 3.1 \times 10^{-11}$[a]	$1.5 \times 10^{-10} \pm 3.8 \times 10^{-11}$[a]	0.9 ± 0.1	6
SHR	$2.3 \times 10^{-9} \pm 9.9 \times 10^{-10}$	$3.4 \times 10^{-9} \pm 1.8 \times 10^{-9}$	0.9 ± 0.1	7
BC_1 (S)	$4.7 \times 10^{-9} \pm 2.3 \times 10^{-9}$	$3.3 \times 10^{-9} \pm 1.1 \times 10^{-9}$	1.4 ± 0.6	5
BC_1 (S)	$1.8 \times 10^{-9} \pm 9.5 \times 10^{-10}$	$6.0 \times 10^{-9} \pm 3.4 \times 10^{-9}$	0.9 ± 0.2	6
Tail Artery				
WKY	$7.0 \times 10^{-8} \pm 2.2 \times 10^{-8}$	$5.0 \times 10^{-8} \pm 1.7 \times 10^{-8}$	1.2 ± 0.1	8
F_1	$1.4 \times 10^{-7} \pm 2.0 \times 10^{-8}$	$6.0 \times 10^{-8} \pm 1.7 \times 10^{-8}$[b]	2.8 ± 0.7[a]	6
SHR	$2.1 \times 10^{-7} \pm 1.1 \times 10^{-7}$	$4.3 \times 10^{-8} \pm 1.7 \times 10^{-8}$[b]	4.0 ± 0.9[a]	9
BC_1 (S)	$6.1 \times 10^{-8} \pm 2.7 \times 10^{-8}$	$1.5 \times 10^{-8} \pm 4.6 \times 10^{-8}$[b]	3.7 ± 0.6[a]	5
BC_1 (W)	$2.0 \times 10^{-7} \pm 5.1 \times 10^{-8}$	$1.0 \times 10^{-7} \pm 2.2 \times 10^{-8}$[b]	2.1 ± 0.4[a]	6

TABLE 16 (continued)

Portal Vein				
WKY	$1.3 \times 10^{-7} \pm 2.2 \times 10^{-8}$	$5.6 \times 10^{-8} \pm 1.6 \times 10^{-8}$	3.8 ± 1.4	6
F_1	$5.6 \times 10^{-7} \pm 1.6 \times 10^{-7}$	$2.2 \times 10^{-7} \pm 8.7 \times 10^{-8}$	3.2 ± 0.8	6
SHR	$2.2 \times 10^{-7} \pm 1.2 \times 10^{-7}$	$4.2 \times 10^{-8} \pm 1.0 \times 10^{-8}$	4.3 ± 1.0	7
BC_1 (S)	$3.5 \times 10^{-7} \pm 1.4 \times 10^{-7}$	$1.3 \times 10^{-7} \pm 7.5 \times 10^{-8}$	4.8 ± 1.2	6
BC_1 (W)	$1.3 \times 10^{-7} \pm 2.3 \times 10^{-8}$	$2.3 \times 10^{-8} \pm 5.7 \times 10^{-9}$	4.6 ± 0.9	6
Anococcygeus				
WKY	$1.9 \times 10^{-6} \pm 5.9 \times 10^{-7}$	$1.0 \times 10^{-7} \pm 3.1 \times 10^{-8}$	19.3 ± 1.4	9
F_1	$3.0 \times 10^{-6} \pm 3.8 \times 10^{-7}$	$1.3 \times 10^{-7} \pm 2.9 \times 10^{-8}$	26.7 ± 4.0	6
SHR	$8.5 \times 10^{-6} \pm 2.9 \times 10^{-7}$	$3.7 \times 10^{-8} \pm 1.5 \times 10^{-8}$	26.9 ± 3.5	6
BC_1 (S)	$1.7 \times 10^{-6} \pm 3.7 \times 10^{-7}$	$1.0 \times 10^{-7} \pm 2.4 \times 10^{-8}$	18.7 ± 3.6	6
BC_1 (W)	$1.2 \times 10^{-6} \pm 2.5 \times 10^{-7}$	$6.4 \times 10^{-8} \pm 1.6 \times 10^{-8}$	19.9 3.7	6

a) Sign. different from corresponding WKY value ($P < 0.05$) ANOVA (Scheffe's Test).

b) Sign. different from ED_{50} value in the absence of cocaine (Student t-test $P < 0.1$)

Table 17: Effect of 4×10^{-5}M cocaine pretreatment on maximum response of tissues to noradrenaline.

Data from 12 - 16 week old animals.

Results expressed as mean % potentiation* ± S.E.M.

Table 17

	Aorta	Tail Artery	Portal Vein	Anoccoccygeus
WKY	0.2 ± 8	-14 ± 3	7 ± 3	19 ± 5
F_1	-15 ± 9	0.2 ± 14	9 ± 16	19 ± 4
SHR	10 ± 12	9 ± 13	1 ± 9	30 ± 5
BC_1(S)	-17 ± 9	6 ± 2	22 ± 15	24 ± 4
BC_1(W)	-2 ± 7	1 ± 5	10 ± 9	27 ± 8

* $\%POTENTIATION = \frac{NA_{MAX(COCAINE)} - NA_{MAX(CONTROL)} \times 100}{NA_{MAX(CONTROL)}} \pm S.E.M.$

Results obtained from 6 - 9 tissues.

Table 18: Noradrenaline ED_{50} values in the absence and presence of cocaine (4.0×10^{-5}M) for tissues from > 52 week old SHR and genetically related rats (± S.E.M.).

Table 18

	ED_{50} Before	ED_{50} After	Ratio	n
Aorta				
WKY	$1.6 \times 10^{-8} \pm 3.9 \times 10^{-9}$[e]	$3.0 \times 10^{-8} \pm 6.3 \times 10^{-9}$[e]	0.9 ± 0.5	6
F_1	$2.4 \times 10^{-8} \pm 6.3 \times 10^{-9}$[e]	$3.4 \times 10^{-8} \pm 9.3 \times 10^{-9}$[e]	0.9 ± 0.2	6
SHR	$5.6 \times 10^{-8} \pm 2.2 \times 10^{-8}$[e]	$5.9 \times 10^{-8} \pm 1.4 \times 10^{-8}$[e]	0.9 ± 0.2	7
Tail Artery				
WKY	$4.7 \times 10^{-7} \pm 1.5 \times 10^{-7}$	$2.7 \times 10^{-7} \pm 1.1 \times 10^{-7}$	2.2 ± 0.3	5
F_1	$3.0 \times 10^{-7} \pm 1.7 \times 10^{-7}$	$5.3 \times 10^{-8} \pm 2.6 \times 10^{-8}$[a]	4.9 ± 0.6[a]	6
SHR	$1.6 \times 10^{-7} \pm 4.5 \times 10^{-8}$	$2.5 \times 10^{-8} \pm 6.2 \times 10^{-9}$[a]	6.0 ± 0.8[a]	8

TABLE 18 (continued)

Portal Vein				
WKY	$5.1 \times 10^{-7} \pm 2.4 \times 10^{-7}$	$2.5 \times 10^{-7} \pm 8.8 \times 10^{-8}$	1.8 ± 1.2	5
F_1	$1.5 \times 10^{-6} \pm 8.3 \times 10^{-7}$	$2.0 \times 10^{-7} \pm 6.1 \times 10^{-8}$	4.1 ± 0.7^{a}	7
SHR	$7.2 \times 10^{-7} \pm 1.8 \times 10^{-7}$	$1.1 \times 10^{-7} \pm 3.1 \times 10^{-8}$	7.6 ± 1.1^{a}	10
Anococcygeus				
WKY	$9.6 \times 10^{-7} \pm 2.4 \times 10^{-7}$	$2.2 \times 10^{-7} \pm 7.8 \times 10^{-8}$	5.2 ± 0.7	6
F_1	$8.6 \times 10^{-7} \pm 1.9 \times 10^{-7}$	$1.4 \times 10^{-7} \pm 2.8 \times 10^{-8}$	7.6 ± 1.7	6
SHR	$1.4 \times 10^{-6} \pm 1.8 \times 10^{-7}$	$2.7 \times 10^{-7} \pm 1.6 \times 10^{-7}$	12.3 ± 1.2^{a}	9

a) Sign. different from corresponding WKY value ($P < 0.05$) by ANOVA.

b) Sign. different from corresponding SHR value ($P < 0.05$) by AVOVA.

(ANOVA using Scheffe's Test)

e) Sign. different from corresponding ED_{50} value in 12 - 16 week old rats (table 16) by Student t-test ($P < 0.05$).

Table 19: NA ED_{50} values in the absence and presence of cocaine (4×10^{-5}M) for tissues from > 52 week old BC_1(W) and BC_1(S) rats (± S.E.M.)

Table 19

	Before	After	Ratio	n
Aorta				
BC_1 (W)	$5.3 \times 10^{-8} \pm 2.0 \times 10^{-8}$ [e]	$6.9 \times 10^{-8} \pm 2.3 \times 10^{-8}$ [e]	1.0 ± 0.2	7
BC_1 (S)	$6.1 \times 10^{-8} \pm 3.0 \times 10^{-8}$ [e]	$8.7 \times 10^{-8} \pm 2.9 \times 10^{-8}$ [e]	0.9 ± 0.3	5
Tail Artery				
BC_1 (W)	$1.6 \times 10^{-8} \pm 4.2 \times 10^{-9}$	$5.8 \times 10^{-9} \pm 1.7 \times 10^{-9}$ [a]	3.0 ± 0.7	6
BC_1 (S)	$1.8 \times 10^{-8} \pm 1.1 \times 10^{-8}$ [a]	$4.6 \times 10^{-9} \pm 1.7 \times 10^{-9}$ [a]	4.0 ± 0.7	13
Portal Vein				
BC_1 (W)	$2.2 \times 10^{-8} \pm 7.4 \times 10^{-9}$	$1.2 \times 10^{-8} \pm 6.0 \times 10^{-9}$	3.1 ± 0.7	6
BC_1 (S)	$3.9 \times 10^{-8} \pm 2.5 \times 10^{-8}$ [a]	$5.7 \times 10^{-9} \pm 1.6 \times 10^{-8}$	7.6 ± 2.4 [a]	6
Anococcygeus				
BC_1 (W)	$4.9 \times 10^{-8} \pm 2.1 \times 10^{-8}$ [ab]	$9.1 \times 10^{-9} \pm 4.8 \times 10^{-9}$ [ab]	7.9 ± 1.6	5
BC_1 (S)	$1.7 \times 10^{-7} \pm 3.5 \times 10^{-8}$	$2.0 \times 10^{-8} \pm 7.4 \times 10^{-9}$ [ab]	11.4 ± 1.5 [a]	7

a) Sign. different from corresponding WKY value ($P < 0.05$) by ANOVA.

b) Sign. different from corresponding SHR value ($P < 0.05$) by ANOVA.

e) Sign. different from corresponding ED_{50} value in 12 - 16 week old rats (table 16) by Student t-test ($P < 0.05$).

Table 20: Effect of 4×10^{-5}M cocaine pretreatment on maximum response of tissues to noradrenaline.

Data from > 52 week old animals

Results expressed as mean % *Potentiation* ± S.E.M.

Table 20

	Aorta	Tail Artery	Portal Vein	Anoccoccygeus
WKY	-7 ± 5	9 ± 8	23 ± 19	57 ± 21
F_1	1 ± 6	9 ± 4	23 ± 25	82 ± 32
SHR	-15 ± 13	13 ± 9	15 ± 5	46 ± 6
$BC_1(S)$	7 ± 1	-2 ± 8	-8 ± 2	5 ± 9[c]
$BC_1(W)$	10 ± 5	19 ± 15	5 ± 6	19 ± 6

* %POTENTIATION =

$$\frac{NA_{MAX(COCAINE)} - NA_{MAX(CONTROL)}}{NA_{MAX(CONTROL)}} \times 100 \pm S.E.M.$$

Results obtained from 5 - 8 tissues.

c) Sign. different from corresponding WKY value by Student t-test ($P < 0.05$)

Table 21: Correlation coefficients relating mean arterial pressure to $NA_{ED_{50}}$ ratio (before/after cocaine)

Table 21

Tissue	12 - 16 Weeks	> 52 Weeks excluding BC data	> 52 Weeks including BC data
Tail Artery	0.59 (23) * [a]	0.44 (21) * [a]	0.60 (41) * [a]
Portal Vein	0.09 (32) *	0.68 (25) * [a]	0.46 (35) * [a]
Anococcygeus	0.32 (33) * [b]	0.55 (22) * [b]	0.33 (34) * [b]

*Total number of tissues used in this study.

a) Significant at 0.05 probability level.

b) Significant at 0.1 probability level.

Table 22: Blood pressure (systolic ± S.D./diastolic ±S.D.) of control and treated (100 mg/kg/day α-methyl-dopa plus 50 mg/kg carbidopa) WKY, F_1 and SHR (12 - 16 weeks old). Results expressed as mean ± S.D. (n = 5 - 7).

Table 22

	Control	Treated
WKY	120 ± 12 / 76 ± 10	114 ± 11 / 72 ± 8
F_1	158 ± 10 / 103 ± 11	137 ± 19 / 113 ± 29
SHR	203 ± 16 [a] / 130 ± 14	151 ± 15 [a,c] / 99 ± 14

a) Sign. different from untreated WKY by ANOVA (Scheffe's test) $P < 0.05$.

c) Sign. different from untreated SHR control by Student t-test ($P < 0.05$).

Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

Table 23: Effect of α-methyldopa (100 mg/kg/day) treatment on postjunctional sensitivity of aorta to noradrenaline (ED_{50} ± S.E.M) before and after 4 x 10^{-5}M cocaine.

(animals 12 - 16 weeks old) n = 5-7

Table 23

	WKY		F_1		SHR	
cocaine	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine
control	3.7×10^{-9} ± 1.5×10^{-9}	4.8×10^{-9} ± 2.4×10^{-9}	3.7×10^{-9} ± 8.0×10^{-10}	4.1×10^{-9} ± 1.3×10^{-9}	3.9×10^{-9} ± 1.6×10^{-9}	8.3×10^{-9} ± 4.7×10^{-9}
treated	5.0×10^{-9} ± 1.8×10^{-9}	5.4×10^{-9} ± 2.0×10^{-9}	4.0×10^{-9} ± 1.1×10^{-9}	4.7×10^{-9} ± 1.2×10^{-9}	1.1×10^{-9} ± 6.0×10^{-10}	1.3×10^{-9} ± 8.0×10^{-10}

Table 24: Effect of α-methyldopa (100 mg/kg/day) treatment on postjunctional sensitivity of portal veins to noradrenaline (ED_{50} ± S.E.M.) before and after 4×10^{-5}M cocaine.

(animals 12 - 16 weeks old) n = 5-7

Table 24

	WKY		F_1		SHR	
cocaine	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine
control	1.4×10^{-7} ± 3.0×10^{-8}	3.7×10^{-8} ± 9.0×10^{-9}	1.2×10^{-7} ± 4.0×10^{-8}	3.0×10^{-8} ± 8.0×10^{-9}	8.8×10^{-8} ± 4.7×10^{-8}	1.9×10^{-8} ± 6×10^{-9}
treated	1.2×10^{-7} ± 6.0×10^{-8}	4.1×10^{-8} ± 2.0×10^{-8}	8.9×10^{-8} ± 2.1×10^{-8}	2.7×10^{8} ± 9.0×10^{9}	4.1×10^{-8} ± 1.7×10^{-8}	1.5×10^{-8} ± 8.0×10^{-9}

Table 25: Effect of α-methyldopa (100 mg/kg/day) treatment on postjunctional-sensitivity of tail artery to noradrenaline (ED_{50} ± S.E.M.) before and after 4 x 10^{-5}M cocaine.

(animals 12 - 16 weeks old) n = 5-8

Table 25

	WKY		F_1		SHR	
	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine
control	2.3×10^{-7} ± 1.0×10^{-7}	1.8×10^{-7} ± 7.0×10^{-8}	2.2×10^{-7} ± 1.0×10^{-7}	6.2×10^{-8} ± 2.8×10^{-8}	7.9×10^{-8} ± 2.8×10^{-8}	2.7×10^{-8}[a] ± 3.0×10^{-8}
treated	2.2×10^{-7} ± 1.2×10^{-7}	1.0×10^{-7} ± 4.0×10^{-8}	5.2×10^{-8} ± 1.4×10^{-8}	3.4×10^{-8} ± 9.0×10^{-9}	1.6×10^{-7} ± 6.0×10^{-8}	5.0×10^{-8}[a] ± 1.8×10^{-8}

a) Sign. different from corresponding WKY value by ANOVA (Scheffe's test) $P < 0.05$.

Table 26: Effect of α-methyldopa (100 mg/kg/day) treatment on postjunctional sensitivity of anococcygeus to noradrenaine (ED_{50} ± S.E.M.) before and after 4 x 10^{-5}M cocaine.

(animals 12 - 16 weeks old) n = 5-7

Table 26

	WKY		F_1		SHR	
cocaine	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine	ED_{50} before cocaine	ED_{50} after cocaine
control	7.1×10^{-7} ± 2.2×10^{-7}	2.3×10^{-7} ± 5.0×10^{-8}	1.7×10^{-7} ± 5.0×10^{-8}	9.2×10^{-8} ± 3.0×10^{-8}	4.2×10^{-7} ± 1.7×10^{-7}	1.3×10^{-7} ± 9.1×10^{-8}
treated	4.9×10^{-7} ± 1.0×10^{-7}	2.2×10^{-7} ± 9.0×10^{-8}	5.5×10^{-7} ± 1.5×10^{-7}	3.1×1^{-7} ± 1.1×10^{-7}	2.5×10^{-7} ± 6.0×10^{-8}	8.1×10^{-8} ± 1.2×10^{-8}

Table 27: Effect α-methyldopa (100 mg/kg/day) treatment on ratio of noradrenaline ED_{50} (± S.E.M.) before and after 4 x 10^{-5}M cocaine in tissues from 12 - 16 weeks old rats.

n = 5-7

Table 27

	WKY		F_1		SHR	
	Control	Treated	Control	Treated	Control	Treated
Aorta	0.9 ± 0.2	1.0 ± 0.1	0.9 ± 0.2	0.9 ± 0.2	1.2 ± 0.2	0.9 ± 0.1
Portal Vein	3.9 ± 0.5	3.0 ± 0.6	3.5 ± 0.4	3.6 ± 0.6	3.4 ± 0.6	3.3 ± 0.6
Tail Artery	1.3 ± 0.1	1.7 ± 0.3	1.9 ± 0.2[a]	1.6 ± 0.2	2.5 ± 0.3[a]	3.6 ± 0.4[a,b]
Anococcygeus	2.8 ± 0.3	2.9 ± 0.5	2.0 ± 0.3	2.1 ± 0.3	3.5 ± 1.1	3.5 ± 1.5

a) Sign. different from corresponding WKY control value by ANOVA (Scheffe's Test) ($P < 0.05$)

b) Sign. different from untreated control (Student t-test, $P < 0.05$).

Table 28: Blood pressure of Dahl salt-sensitive (DS) and Dahl salt-resistant (DR) rats at 15 weeks of age; fed diets containing 0.3%, 4%, 8% sodium chloride rat food. Results expressed as systolic pressure/diastolic pressure ± S.D. of 6 - 8 rats.

Table 28

Diet (% NaCl)	DR	DS
0.4%	110 ± 6	136 ± 6 [d]
	83 ± 5	108 ± 7
4%	120 ± 4	152 ± 9 [c,d]
	83 ± 5	109 ± 9
8%	129 ± 4	228 ±13 [c,d]
	84 ± 6	165 ±13

c) Sign. different from 0.4% NaCl DS by Student t-test ($P < 0.05$)

d) Sign. different from corresponding DR rat (Student t-test, $P < 0.05$)

Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

Table 29: Noradrenaline ED_{50} before and after 4×10^{-5}M cocaine treatment of tissues from DS and DR fed 8% NaCl in their diet. Rats were 12 - 16 weeks old at sacrifice.

Table 29

	DR Rats Cocaine (4×10^{-5} M)			DS Rats Cocaine (4×10^{-5} M)			
	ED_{50} (NA) before	ED_{50} (NA) after	Ratio	ED_{50} (NA) before	ED_{50} (NA) after	Ratio	n
Aorta	$2.5 \times 10^{-8} \pm 1.1 \times 10^{-8}$	$4.6 \times 10^{-8} \pm 2.8 \times 10^{-8}$	0.8 ± 0.2	$2.1 \times 10^{-8} \pm 1.0 \times 10^{-8}$	$2.9 \times 10^{-8} \pm 1.8 \times 10^{-8}$	1.1 ± 0.3	7
Portal Vein	$7.7 \times 10^{-7} \pm 2.4 \times 10^{-7}$	$1.7 \times 10^{-7} \pm 2.0 \times 10^{-8}$	4.7 ± 1.2	$6.3 \times 10^{-7} \pm 1.5 \times 10^{-7}$	$2.5 \times 10^{-7} \pm 6.1 \times 10^{-8}$	3.9 ± 1.8	6
Anococcygeus	$5.0 \times 10^{-6} \pm 2.8 \times 10^{-6}$	$2.5 \times 10^{-7} \pm 1.0 \times 10^{-7}$	18.6 ± 4.2	$1.8 \times 10^{-6} \pm 3.1 \times 10^{-7}$	$1.6 \times 10^{-7} \pm 6.3 \times 10^{-8}$	18.3 ± 4.0	8
Tail Artery	$1.6 \times 10^{-7} \pm 1.3 \times 10^{-8}$	$3.4 \times 10^{-8} \pm 2.1 \times 10^{-8}$	4.4 ± 1.5	$1.5 \times 10^{-7} \pm 2.1 \times 10^{-8}$	$4.5 \times 10^{-8} \pm 1.5 \times 10^{-8}$	3.1 ± 0.6	7

Table 30: Blood pressure (systolic/diastolic ± S.D.) profile of SHR, WKY, and Genetically related rats

Table 30:

Rat Strain	4 week ♂	6 - 8 week ♂	6 - 8 week ♀	6 - 8 week combined	12 - 16 week ♂	12 - 16 week ♀	12 - 16 week combined
SHR	110 ± 24 (9) 65 ± 23	134 ± 5 (6) 91 ± 5	138 ± 4[c] (6) 92 ± 4	136 ± 5[c] (12) 91 ± 4	204 ± 14[c] (16) 136 ± 10	183 ± 15[cd] (19) 132 ± 15	193 ± 18[c] (35) 133 ± 13
WKY	83 ± 9 (12) 41 ± 14	107 ± 7 (8) 62 ± 5	82 ± 9 (6) 41 ± 2	96 ± 12 (16) 53 ± 12	129 ± 12 (7) 81 ± 10	118 ± 12[e] (12) 75 ± 4	122 ± 12 (19) 77 ± 8
F_1	-	126 ± 5 (7) 70 ± 6	114 ± 7 (8) 73 ± 8	120 ± 9 (14) 75 ± 8	165 ± 28 (10) 112 ± 20	143 ± 16[d] (10) 94 ± 15	154 ± 25 (20) 103 ± 19
F_2	-	132 ± 8 (9) 80 ± 8	109 ± 10 (10) 64 ± 9	120 ± 15 (19) 71 ± 13	164 ± 26 (9) 111 ± 17	125 ± 18[d] (10) 84 ± 16	143 ± 29 (19) 97 ± 21
BC_1(S)	-	-	-	-	156 ± 19 (12) 115 ± 11	-	-
BC_1(W)	-	-	-	-	122 ± 19 (15) 86 ± 10	-	-

Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa). Number in parenthesis represents the number of rats in each group.

c) Sign. different from corresponding WKY by Student t-test ($P < 0.05$).

d) Sign. different from corresponding ♂ blood pressure Student t-test ($P < 0.05$) (or $P < 0.1$ or e).

Table 31: Blood pressure (systolic/diastolic ± S.D.) of Wistar Sprague Dawley and related animals (♂)
(12 - 16 week old)

Table 31

WKY	129 ± 12 (7) / 81 ± 10
WISTAR	129 ± 3 (12) / 94 ± 16
WISTAR x SHR	160 ± 16 (14)[a] / 122 ± 11
WISTAR x WKY	116 ± 7 (13) / 83 ± 9
SPRAGUE-DAWLEY	119 ± 10 (10) / 87 ± 11

Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa). Number in parenthesis represents the number of rats in each group.

a) Sign. different from WISTAR by ANOVA (Scheffe's test) $P < 0.05$.

Table 32: Blood pressures (systolic/diastolic ± S.D.) of Dahl (DS and DR) rats

Table 32

Diet (% NaCl)	DS	DR
0.4%	91 ± 7 (6)	90 ± 4 (6)
(6 week)	60 ± 9	60 ± 7
0.4%	136 ± 6 [d] (6)	110 ± 6 (6)
(16 week)	108 ± 7	83 ± 5
4.0%	151 ± 9 [d] (6)	120 ± 4 (6)
(16 week)	109 ± 9	83 ± 5
8.0%	207 ± 17 [d] (10)	139 ± 11
(16 week)	135 ± 21	93 ± 9

Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

Number in parenthesis represents the number of rats in each group.

d) Sign. different from corresponding DR rat (Student t-test; $P < 0.05$).

Table 33: Effect of drug therapy on blood pressures of SHR, WKY, F_1, F_2, DS and DR rats (systolic/diastolic ± S.D.)

Table 33

RAT STRAIN	BLOOD PRESSURE AT 16 WEEKS			
	Control	+ α Methyldopa	MK421	Hydrochlorothiazide
SHR	203 ± 16 (8) 130 ± 14	161 ± 15 (8) 99 ± 15	-	-
WKY	120 ± 12 [a] (9) 76 ± 10	114 ± 11 (9) 72 ± 8	-	-
F	158 ± 10 [a] (8) 103 ± 11	136 ± 19 (8) 113 ± 29	-	-
DS (0.5% NaCl)	136 ± 6 (6) 60 ± 9	-	112 ± 14 (10) 74 ± 5	148 ± 10 (10) 100 ± 8
DS (8.0% NaCl)	207 ± 17 (10) 135 ± 21	-	138 ± 18 [c] (19) 86 ± 15	147 ± 18 [c] (19) 97 ± 13
DR (0.4% NaCl)	110 ± 6 (6) 83 ± 5	-	92 ± 11 [c] (10) 63 ± 9	136 ± 10 (9) 104 ± 10
DR (8.0% NaCl)	139 ± 11 (10) 93 ± 9	-	114 ± 9 (110) 79 ± 6	138 ± 6 (10) 97 ± 4

Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

Number in parenthesis represents the number of rats in each group.

a) Sign. different from WKY by ANOVA (Scheffe's test) $P < 0.05$.

c) Sign. different from corresponding untreated control value by Student t-test ($P < 0.05$).

Table 34: 5mM Lanthanum response expressed as percentage of maximum response to noradrenaline (1×10^{-5}M)

Table 34

Rat Strain	4 week ♂	6 - 8 week ♂	6 - 8 week ♀	6 - 8 week combined	12 - 16 week ♂	12 - 16 week ♀	12 - 16 week combined
SHR	42.2 ± 18.1 (14)	45.5 ± 3.9 (5)	64.8 ± 10.8 (6)	56.2 ± 12.9 (11)	118.5 ± 21.1 (11)	109.1 ± 25.9 (23)	112.1 ± 24.6 (34)
WKY	35.6 ± 8.0 (12)	28.1 ± 5.2 (8)	36.6 ± 7.9 (6)	31.7 ± 7.6 (14)	48.7 ± 15.0 (11)	64.6 ± 12.2 (11)	56.5 ± 15.7 (22)
F_1	-	40.0 ± 11.5 (7)	41.0 ± 8.4 (8)	40.5 ± 9.6 (15)	66.5 ± 20.1 (13)	60.6 ± 9.5 (10)	63.9 ± 16.3 (23)
F_2	-	23.1 ± 9.5 (8)	27.2 ± 17.8 (8)	25.1 ± 13.9 (16)	75.9 ± 38.0 (13)	64.8 ± 30.6 (12)	70.6 ± 34.4 (25)
BC_1(S)	-	-	-	-	39.0 ± 3.0 (12)	-	-
BC_1(R)	-	-	-	-	31.0 ± 5.0 (15)	-	-
DS (0.4% NaCl)	-	-	-	-	31.0 ± 1.0	-	-
DS (4.0% NaCl)	-	-	-	-	51.0 ± 1.0	-	-
DS (8.0% NaCl)	-	-	-	-	74.0 ± 4.0	-	-
DR (0.4% NaCl)	-	-	-	-	0	-	-
DR (4.0% NaCl)	-	-	-	-	0	-	-
DR (8.0% NaCl)	-	-	-	-	0	-	-

Table 35: Effect of drug therapy on 5mM lanthanum response, expressed as a percentage of tissue response to 1×10^{-5}M noradrenaline (mean ± S.E.M.)

Table 35:

Rat strain	Lanthanum response (16 weeks)	
	Control	Methyldopa
SHR	129 ± 16 (7)	107 ± 9 (8)
WKY	46 ± 5 (9)	51 ± 5 (11)
F	94 ± 12 (7)	85 ± 5 (8)

	Control	Hydrochlorothiazide	MK421
DS (0.4% NaCl)	31 ± 1	0	0
DS (8.0% NaCl)	74 ± 4	0	0
DR (0.4% NaCl)	0	0	0
DR (8.0% NaCl)	0	0	0

Table 36: Lathanum (5mM) response (mg tension/mg tissue wet weight) of SHR and WKY genetically related rats. Results expressed as mean ± S.E.M.

Table 36:

Rat Strain	4 week ♂	6 - 8 week ♂	6 - 8 week ♀	6 - 8 week combined	12 - 16 week ♂	12 - 16 week ♀	12 - 16 week combined
SHR	293 ± 151 (14)	508 ± 59 (5)	289 ± 46 (6)	394 ± 120 (11)	368 ± 146 (11)	562 ± 144 (23)	499 ± 170 (34)
WKY	396 ± 156 (12)	280 ± 53 (8)	237 ± 39 (6)	265 ± 51 (14)	398 ± 99 (11)	557 ± 97 (11)	432 ± 109 (22)
F_1	-	236 ± 92 (7)	233 ± 63 (8)	235 ± 75 (15)	397 ± 76 (13)	467 ± 127 (10)	478 ± 126 (23)
F_2	-	147 ± 79 (8)	195 ± 97 (8)	171 ± 89 (16)	406 ± 159 (13)	431 ± 117 (12)	418 ± 138 (25)
BC_1(S)	-	-	-	-	303 ± 47 (12)	-	-
BC_1(W)	-	-	-	-	266 ± 38 (15)	-	-

( ) number of tissues

Table 37: 5mM Lanthanum response of Wistar and related rats (12 -16 week old)

Table 37

Type	% of Noradrenaline Maximum Response	Lanthanum Response (mg tension) mg wet weight tissue
Wistar	0 (12)	0 (12)
SHR x Wistar	38 ± 2 (14)	189 ± 14 (14)
WKY x Wistar	7 ± 1 (13)	53 ± 8 (13)
Sprague Dawley	0 (10)	0 (10)

( ) number of tissues

Table 38: Noradrenaline (10^{-5}M) response (mg tension/mg tissue wet weight) of SHR and WKY genetically related rats

Table 38

Rat Strain	4 week ♂	6 - 8 week combined ♂	6 - 8 week combined ♀	6 - 8 week combined	12 - 16 week combined ♂	12 - 16 week combined ♀	12 - 16 week combined
SHR	735 ± 82 (14)	508 ± 26 (5)	474 ± 48 (6)	489 ± 28 (11)	322 ± 47 (11)	542 ± 42 (23)	465 ± 38 (34)
WKY	1077 ± 85 (12)	999 ± 39 (8)	633 ± 27 (6)	842 ± 56 (14)	860 ± 62 (11)	860 ± 79 (11)	860 ± 49 (22)
F	-	595 ± 73 (7)	599 ± 76 (8)	597 ± 51 (15)	659 ± 77 (13)	795 ± 81 (10)	718 ± 56 (23)
F	-	660 ± 76 (8)	812 ± 76 (8)	736 ± 56 (16)	584 ± 89 (13)	729 ± 60 (12)	653 ± 56 (25)
BC (S)	-	-	-	-	633 ± 79 (12)	-	-
BC (W)	-	-	-	-	243 ± 37 (15)	-	-
Wistar	-	-	-	-	614 ± 50 (12)	-	-
SHR x Wistar	-	-	-	-	507 ± 24 (14)	-	-
WKY x Wistar	-	-	-	-	770 ± 13 (13)	-	-

Table 39: Regression analysis of mean arterial pressure versus the lanthanum response

Table 39

	WKY + SHR	WKY + SHR + F	WKY + SHR + F + F
6 - 8 week			
n	25	40	56
slope	0.35	0.31	0.23
correlation	0.58 [a]	0.50 [a]	0.30 [a]
12 - 16 week			
n	56	79	103
slope	0.70	0.70	0.67
correlation	0.73 [a]	0.69 [a]	0.64 [a]

	WKY + SHR + F + BC (S) + BC (W)
12 - 16 week	
n	130
slope	0.84
correlation	0.63 [a]

(Lanthanum (5 mM) response expressed as percent maximal noradrenaline (10^{-5}M) response.)

a) Sign. at P 0.05 level.

Table 40: Regression analysis of mean arterial pressure versus Noradrenaline (10^{-5}M) response. Expressed as maximal tension (mg) per mg wet weight tissue.)

Table 40

	WKY + SHR	WKY + SHR + F	WKY + SHR + F_1 + F_2	WKY + SR + F_1 + F_2 + BC_1(S) + BC_1(W)
6 - 8 weeks				
n	(25)	(40)	(56)	
slope	-5.0	-5.3	-5.4	
correlation	-0.44[a]	-0.41[a]	-0.41[a]	
12 - 16 weeks				
n	56	79	103	130
slope	-5.8	-5.6	-5.6	-4.8
correlation	-0.64[a]	-0.57[a]	-0.53[a]	-0.45[a]

(Expressed as maximal tension (mg) per mg wet weight tissue.)

a) Sign. at P 0.05 level.

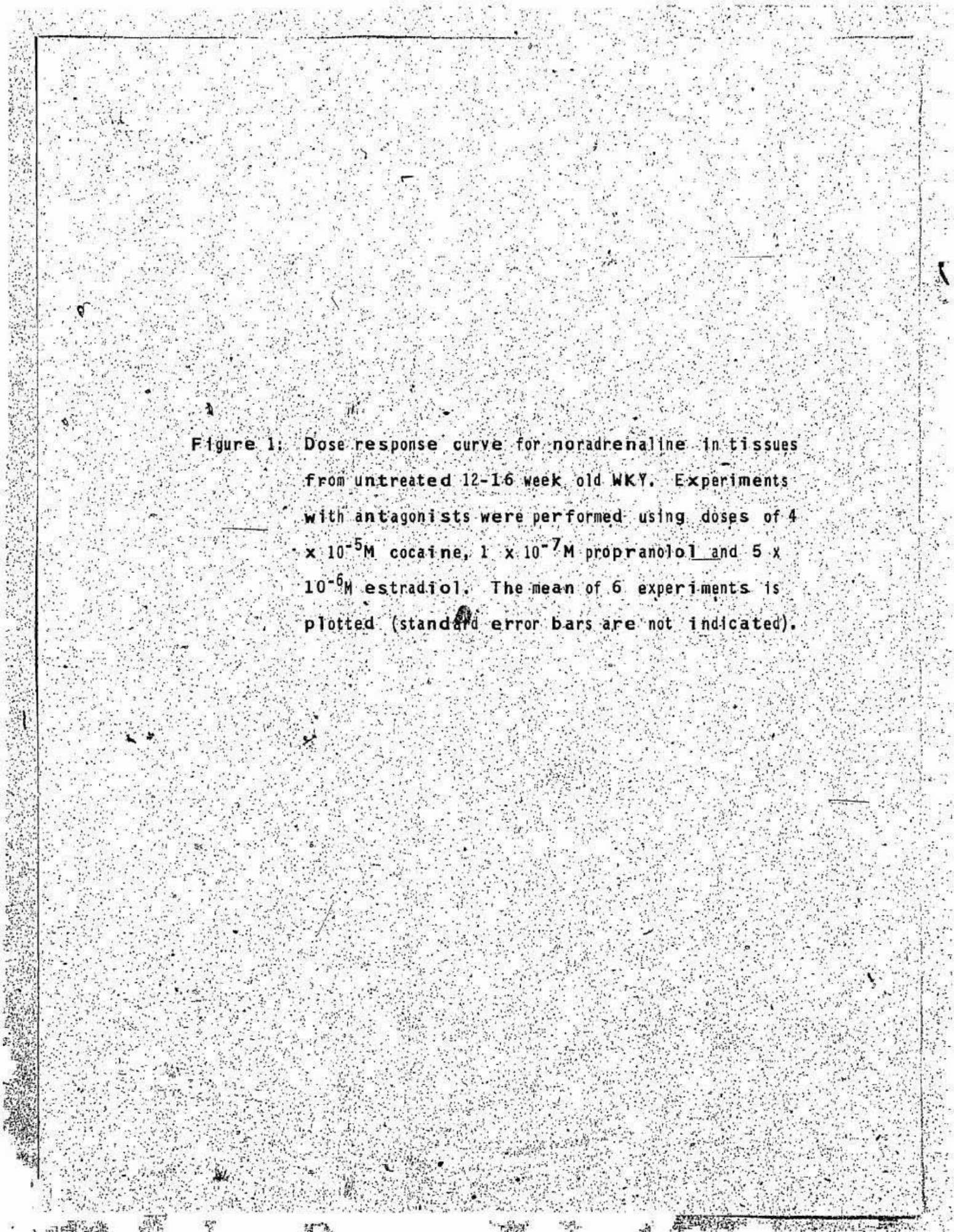


Figure 1: Dose response curve for noradrenaline in tissues from untreated 12-16 week old WKY. Experiments with antagonists were performed using doses of 4 x 10^{-5}M cocaine, 1 x 10^{-7}M propranolol and 5 x 10^{-6}M estradiol. The mean of 6 experiments is plotted (standard error bars are not indicated).

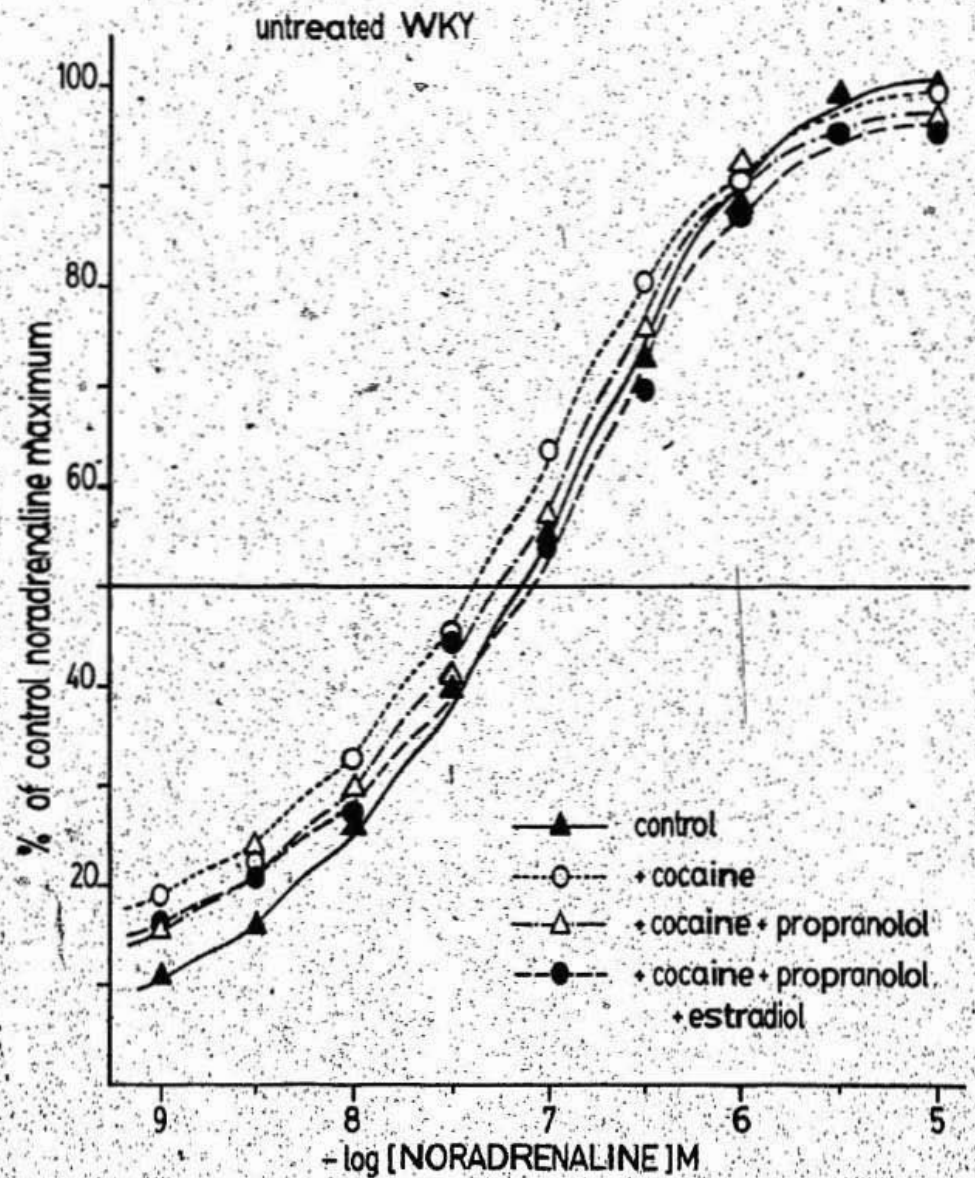

untreated WKY
100
80
60
40
20
% of control noradrenaline maximum
control
+ cocaine
+ cocaine + propranolol
+ cocaine + propranolol + estradiol
9
8
7
6
5
- log [NORADRENALINE] M

Figure 2: Dose response curve for noradrenaline in tissues from treated 12-16 week old WKY. Experiments with antagonists were performed using doses of 4 x 10^{-5}M cocaine, 1 x 10^{-7}M propranolol and 5 x 10^{-6}M estradiol. The mean of 8 experiments is plotted (standard error bars are not indicated). Rats were treated daily with 6-hydroxy dopamine at a dose of 250 mg/kg (i.p.) for 4 days.

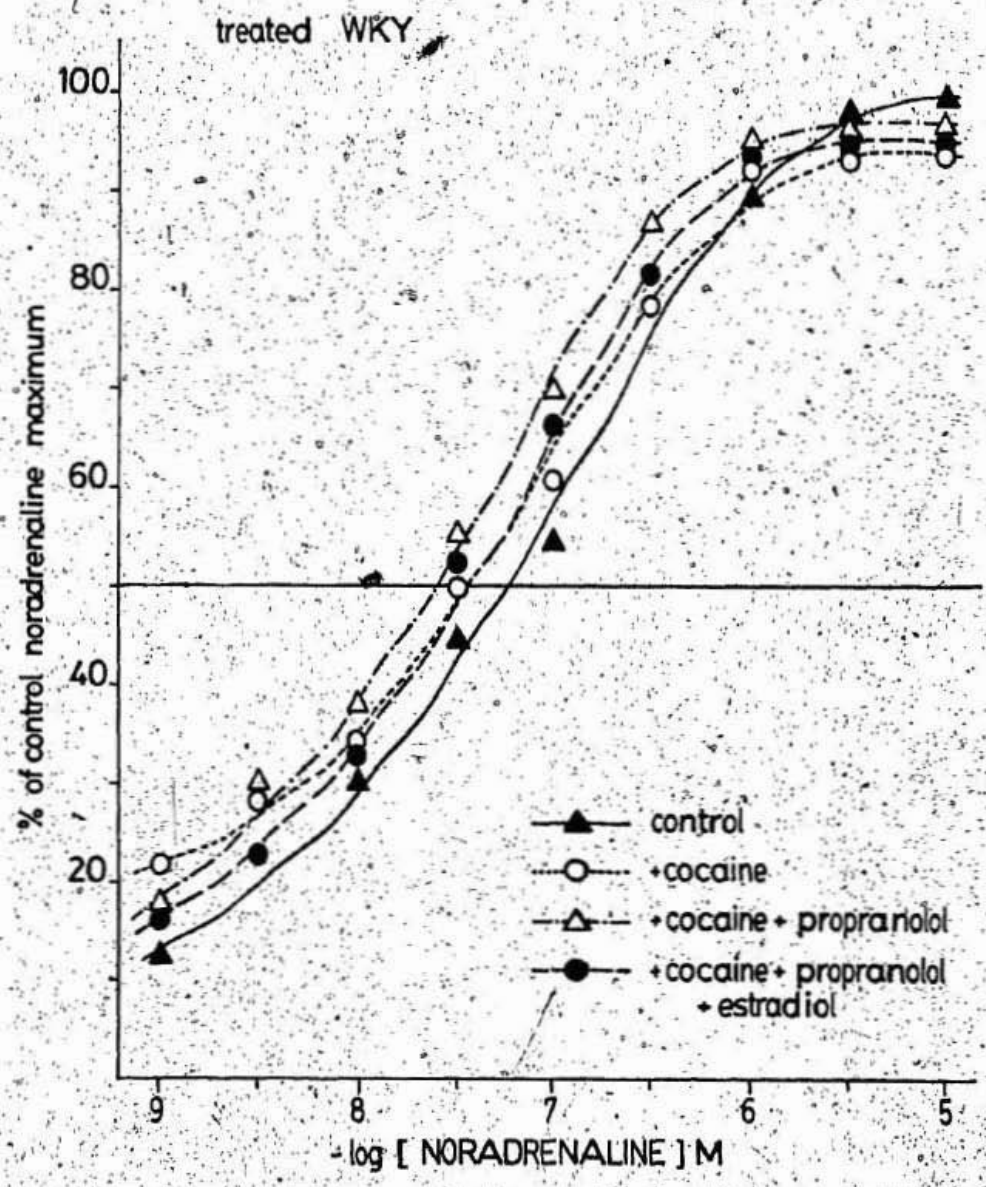

treated WKY
100
80
60
40
20
% of control noradrenaline maximum
control
+cocaine
+cocaine + propranolol
+cocaine + propranolol + estradiol
9
8
7
6
5
- log [NORADRENALINE] M

Figure 3: Dose response curve for noradrenaline in tissues from untreated 12-16 week old SHR. Experiments with antagonists were performed using doses of 4 x 10^{-5}M cocaine, 1 x 10^{-7}M propranolol and 5 x 10^{-6}M estradiol. The mean of 6 experiments is plotted (standard error bars are not indicated).

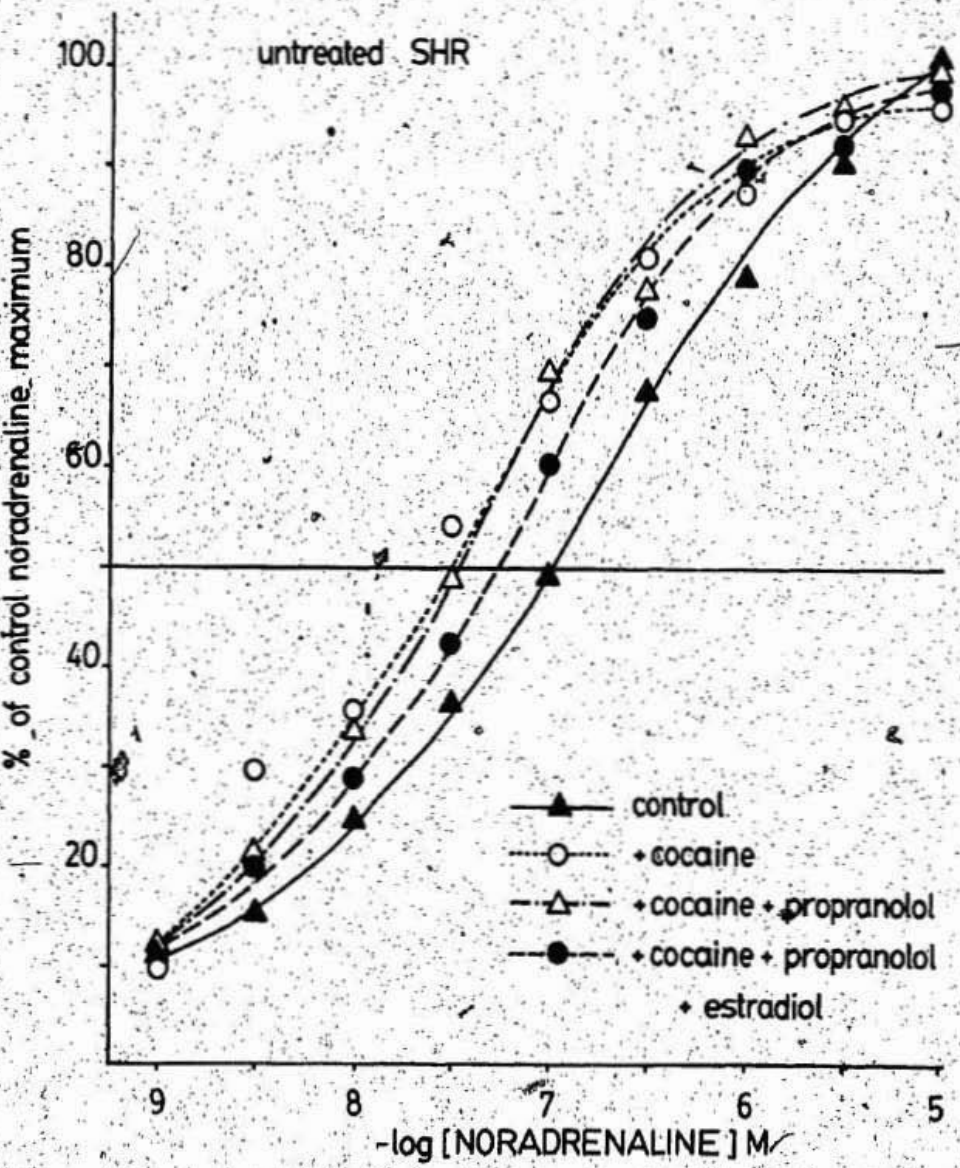

untreated SHR
100
80
60
40
20
% of control noradrenaline maximum
control
+ cocaine
+ cocaine + propranolol
+ cocaine + propranolol + estradiol
9
8
7
6
5
-log [NORADRENALINE] M

Figure 4: Dose response curve for noradrenaline in tissues from treated 12-16 week old SHR. Experiments with antagonists were performed using doses of 4 x 10^{-5}M cocaine, 1 x 10^{-7}M propranolol and 5 x 10^{-6}M estradiol. The mean of 10 experiments is plotted (standard error bars are not indicated). Rats were treated daily with 6-hydroxy dopamine at a dose of 250 mg/kg (i.p.) for 4 days.

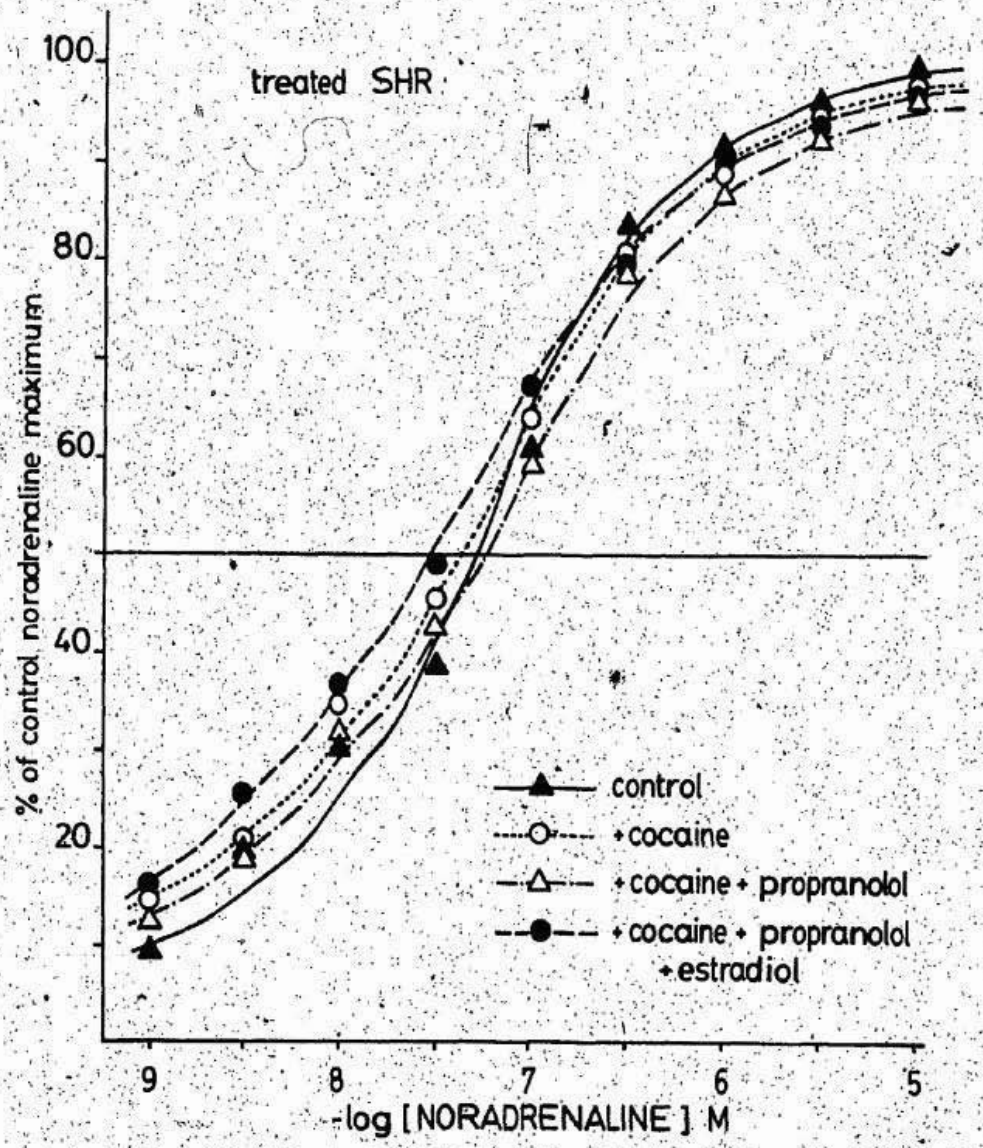

treated SHR
100
80
60
40
20
% of control noradrenaline maximum
9
8
7
6
5
-log [NORADRENALINE] M
control
+cocaine
+cocaine + propranolol
+cocaine + propranolol
+estradiol

Figure 5: Dose response curve for noradrenaline in tail artery strips performed either in the absence (A, closed symbols) or presence (B, open symbols) of 4 x 10^{-5}M cocaine. Graph compares the results obtained in 12-16 week old F_1 (n = 6) and WKY (n = 8) rats.

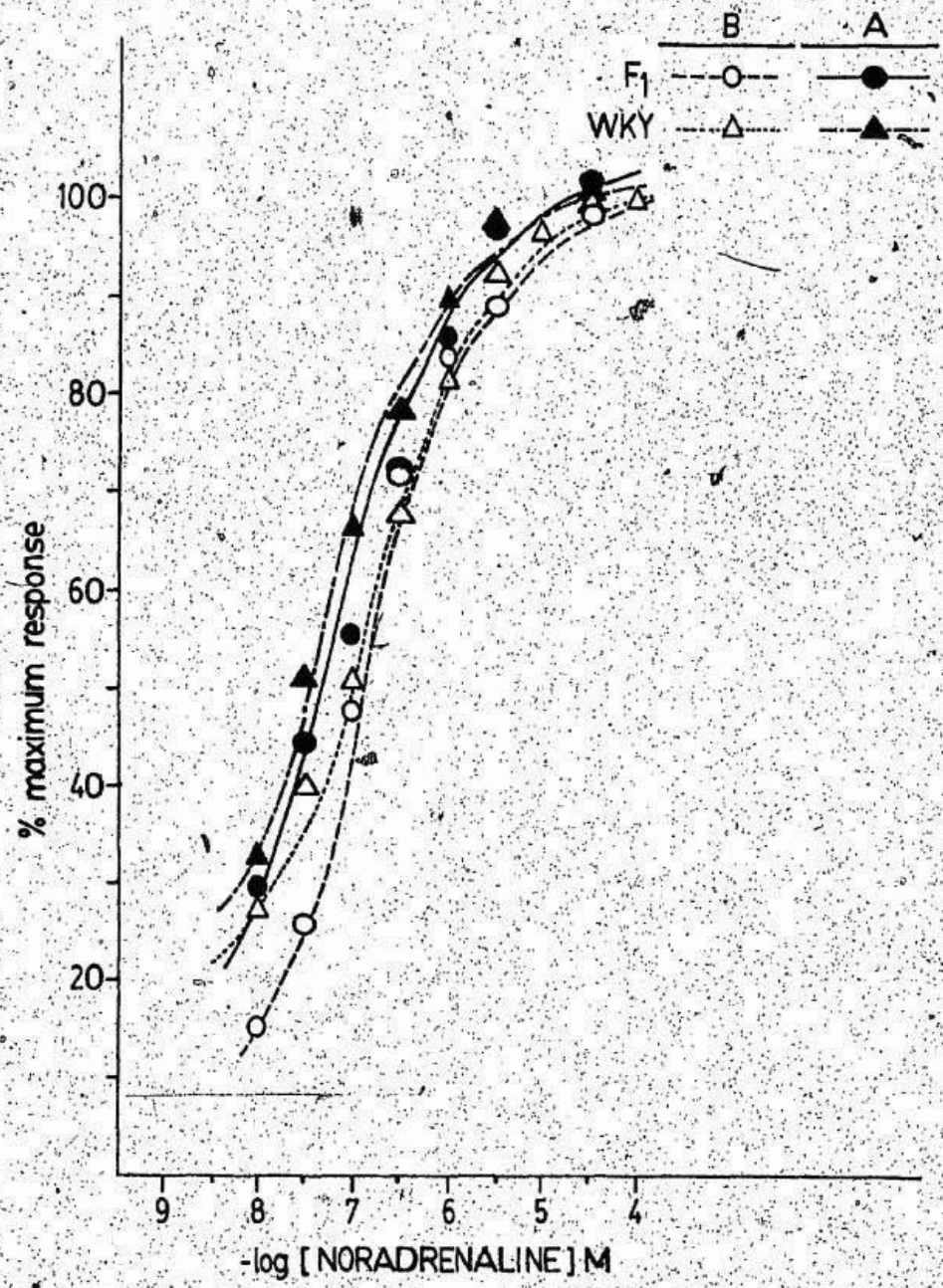

B
A
F1
WKY
100
80
60
40
20
% maximum response
9
8
7
6
5
4
-log [NORADRENALINE] M

Figure 6: Dose response curve for noradrenaline in tail artery strips performed either in the absence (A, closed symbols) or presence (B, open symbols) of 4 x 10^{-5} M cocaine. Graph compares the results obtained in 12-16 week old SHR (n = 9) and WKY (n = 8) rats.

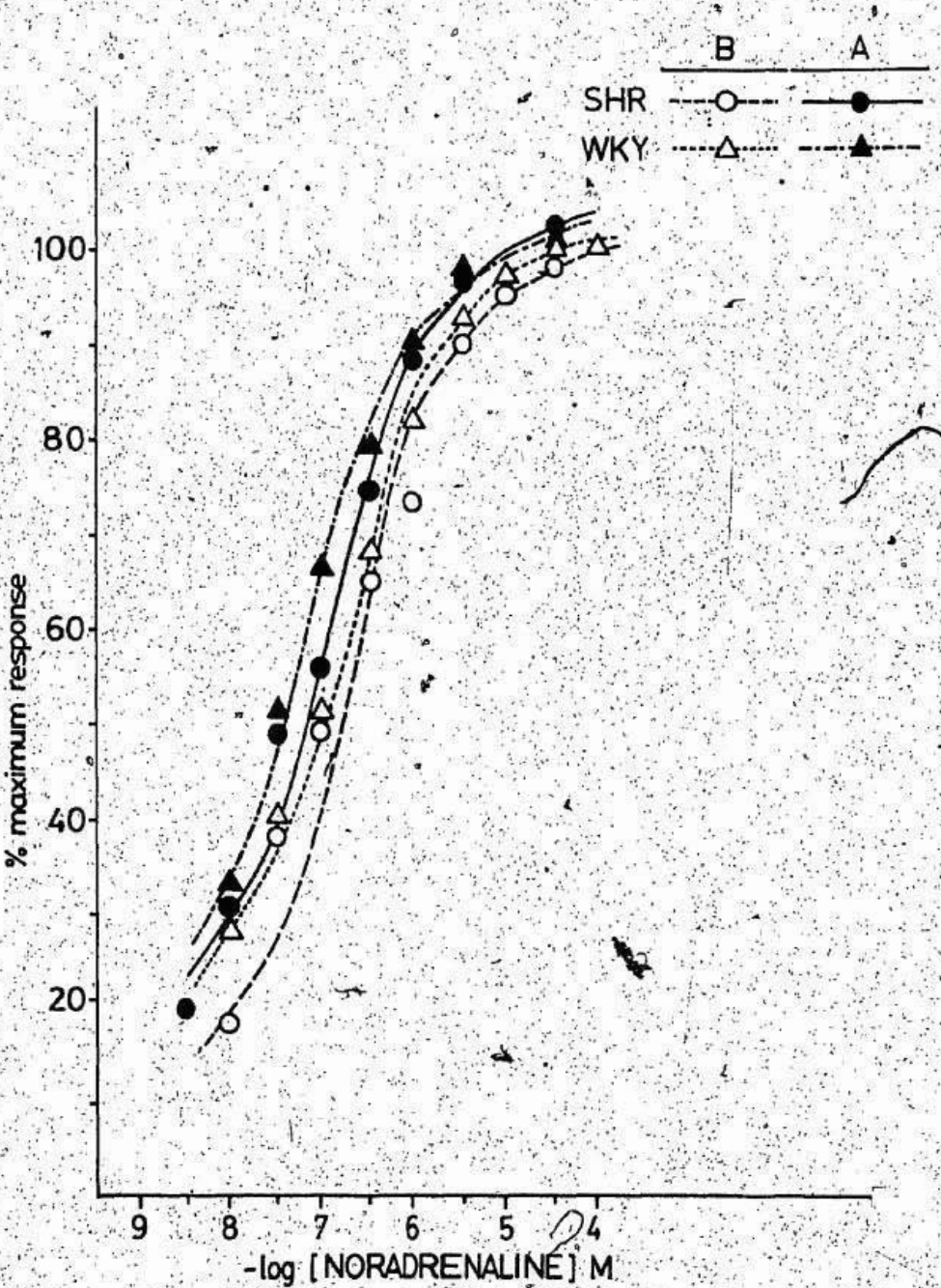

B
A
SHR
WKY
100
80
60
40
20
% maximum response
9
8
7
6
5
4
-log [NORADRENALINE] M

Figure 7: Regression analysis of mean arterial pressure and the ratio of noradrenaline ED_{50} ratios in the absence and presence of 4×10^{-5}M cocaine. The results are from portal veins from 12 - 16 week old rats. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

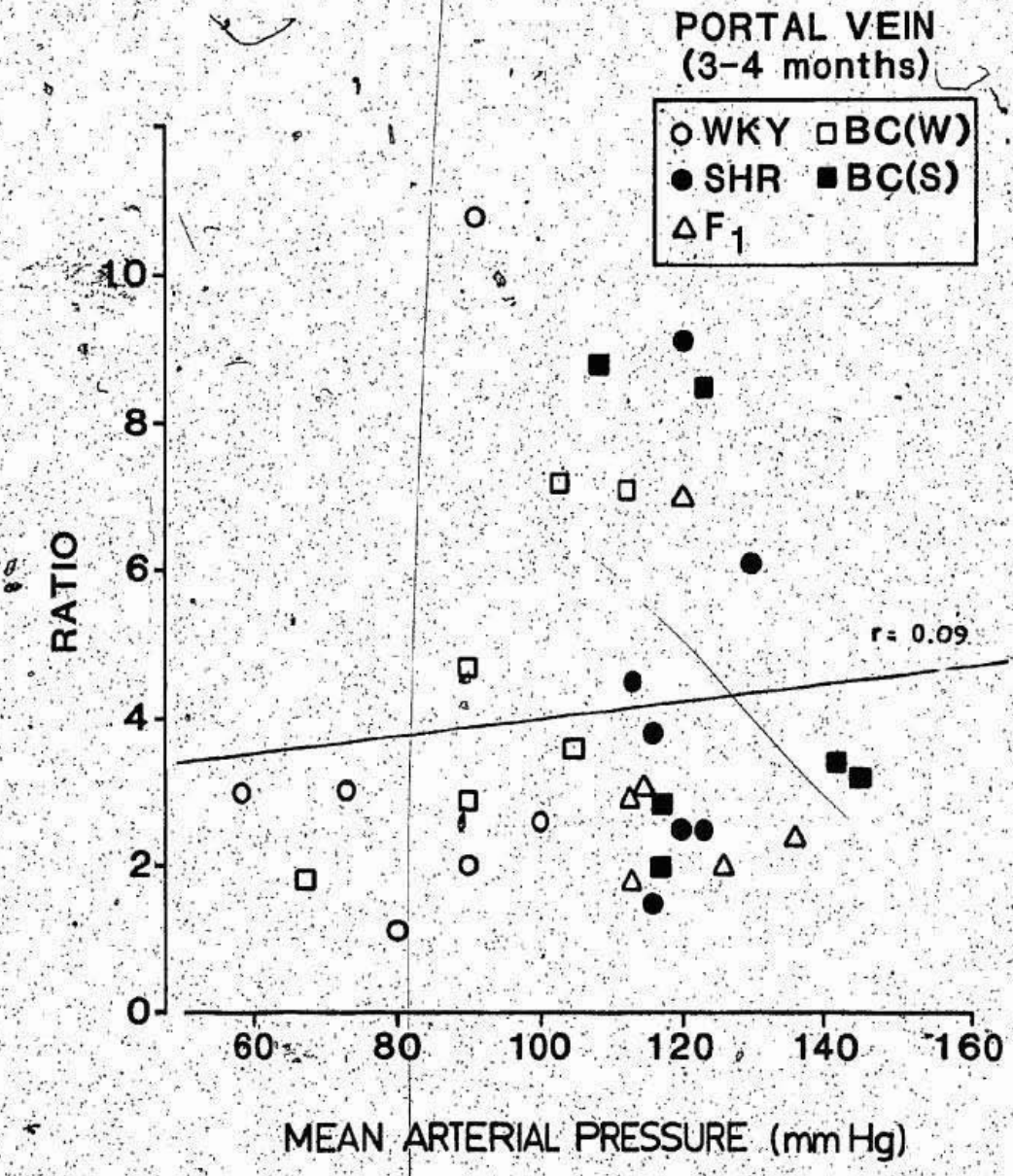

PORTAL VEIN
(3-4 months)
WKY
BC(W)
SHR
BC(S)
F1
RATIO
0
2
4
6
8
10
r= 0.09
60
80
100
120
140
160
MEAN ARTERIAL PRESSURE (mm Hg)

Figure 8: Regression analysis of mean arterial pressure and the ratio of noradrenaline ED_{50} ratios in the absence and presence of 4×10^{-5}M cocaine. The results are from tail artery strips from 12 - 16 week old rats. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

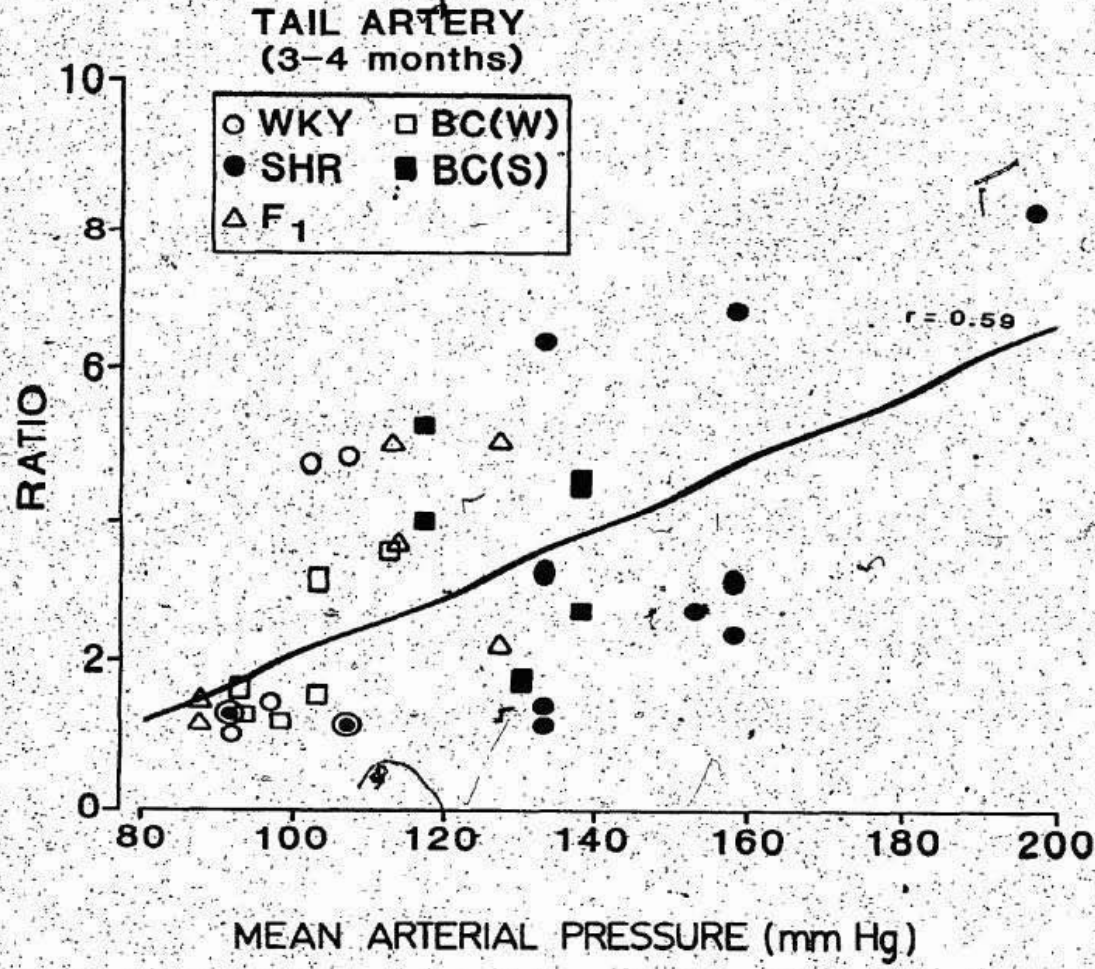

TAIL ARTERY
(3–4 months)
WKY
SHR
F1
BC(W)
BC(S)
r = 0.59
RATIO
0
2
6
8
10
80
100
120
140
160
180
200
MEAN ARTERIAL PRESSURE (mm Hg)

Figure 9: Regression analysis of mean arterial pressure and the ratio of noradrenaline ED_{50} ratios in the absence and presence of 4×10^{-5}M cocaine. The results are from anococcygeus muscles from 12 - 16 week old rats. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

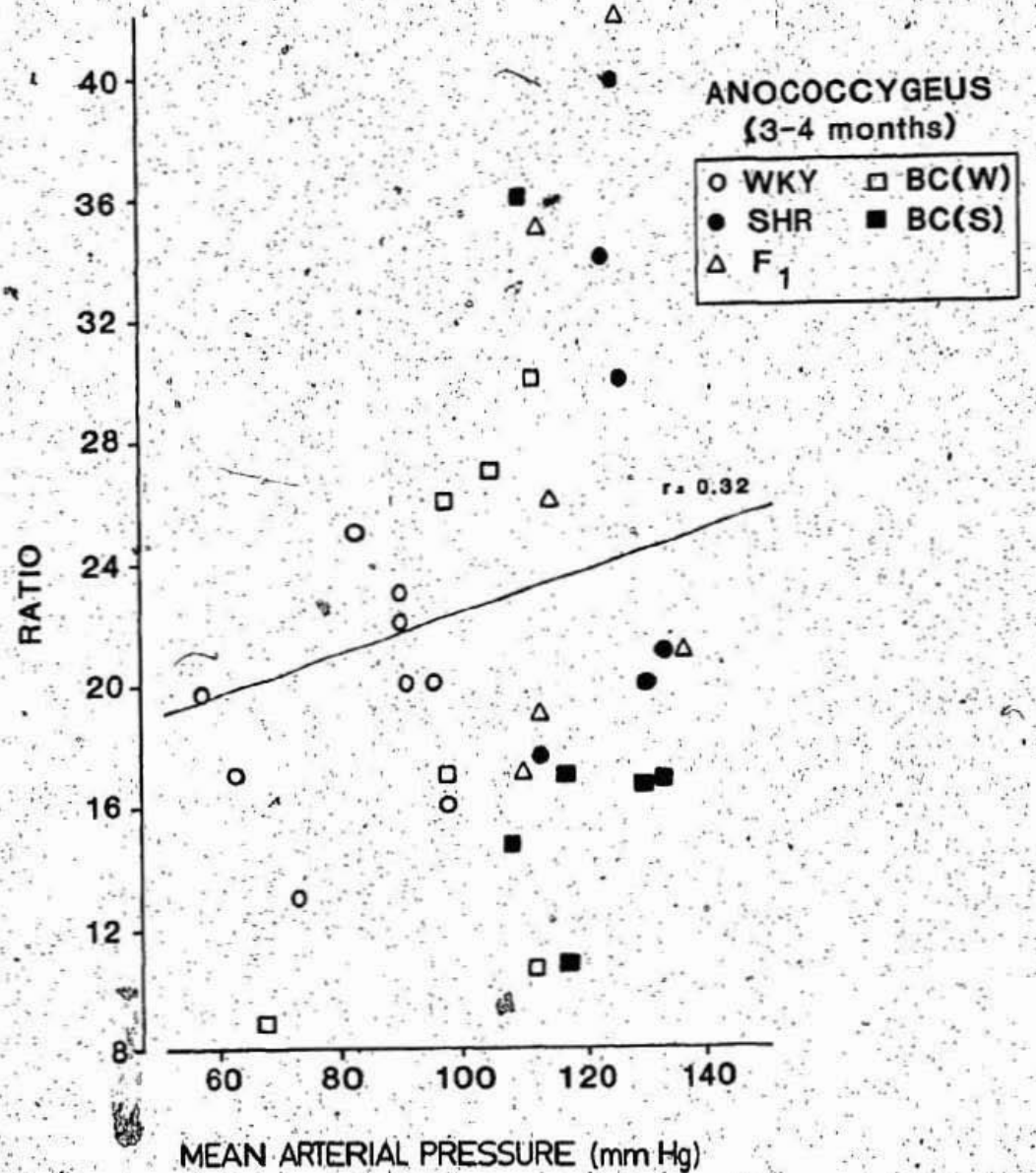

ANOCOCCYGEUS
(3-4 months)
WKY
SHR
F1
BC(W)
BC(S)
r = 0.32
RATIO
40
36
32
28
24
20
16
12
8
60
80
100
120
140
MEAN ARTERIAL PRESSURE (mm Hg)

Figure 10: Regression analysis of mean arterial pressure and the ratio of noradrenaline ED_{50} ratios in the absence and presence of 4×10^{-5}M cocaine. The results are from portal veins from > 52 week old rats. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

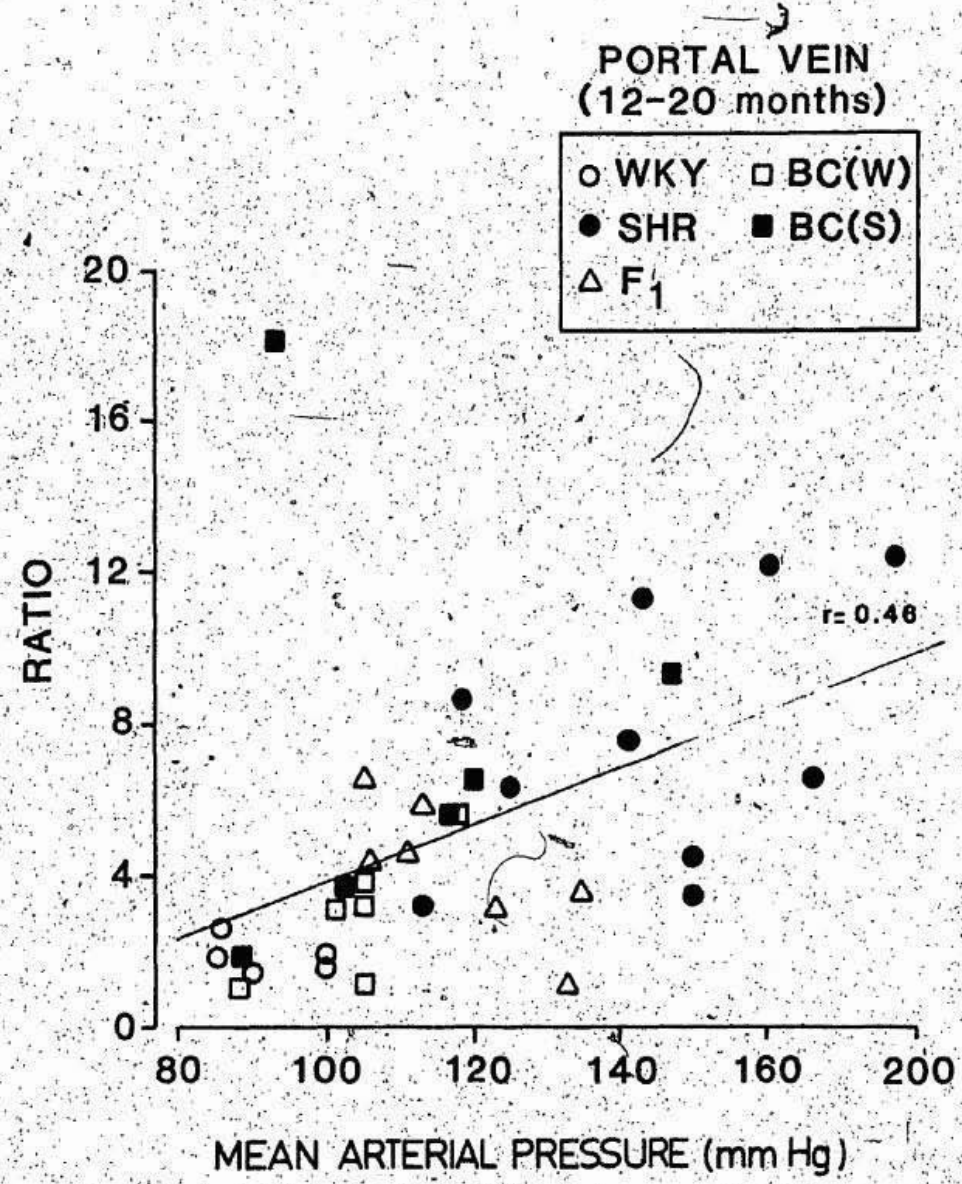

PORTAL VEIN
(12-20 months)
WKY
BC(W)
SHR
BC(S)
F1
RATIO
20
16
12
8
4
0
r= 0.46
80
100
120
140
160
200
MEAN ARTERIAL PRESSURE (mm Hg)

Figure 11: Regression analysis of mean arterial pressure and the ratio of noradrenaline ED_{50} ratios in the absence and presence of 4×10^{-5}M cocaine. The results are from tail artery strips from > 52 week old rats. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

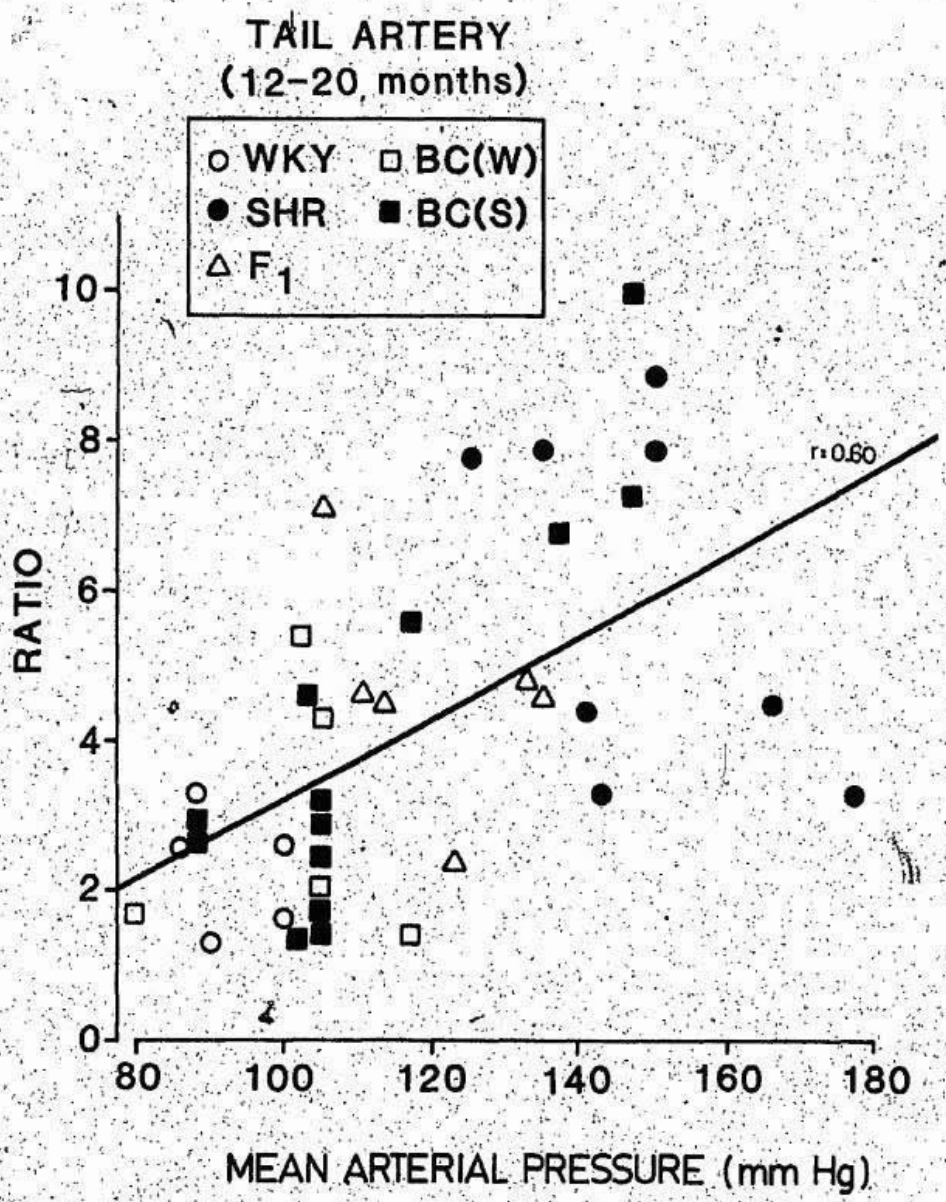

TAIL ARTERY
(12-20 months)
WKY
BC(W)
SHR
BC(S)
F1
r=0.60
RATIO
0
2
4
6
8
10
80
100
120
140
160
180
MEAN ARTERIAL PRESSURE (mm Hg)

Figure 12: Regression analysis of mean arterial pressure and the ratio of noradrenaline ED_{50} ratios in the absence and presence of 4×10^{-5}M cocaine. The results are from anococcygeus from > 52 week old rats. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

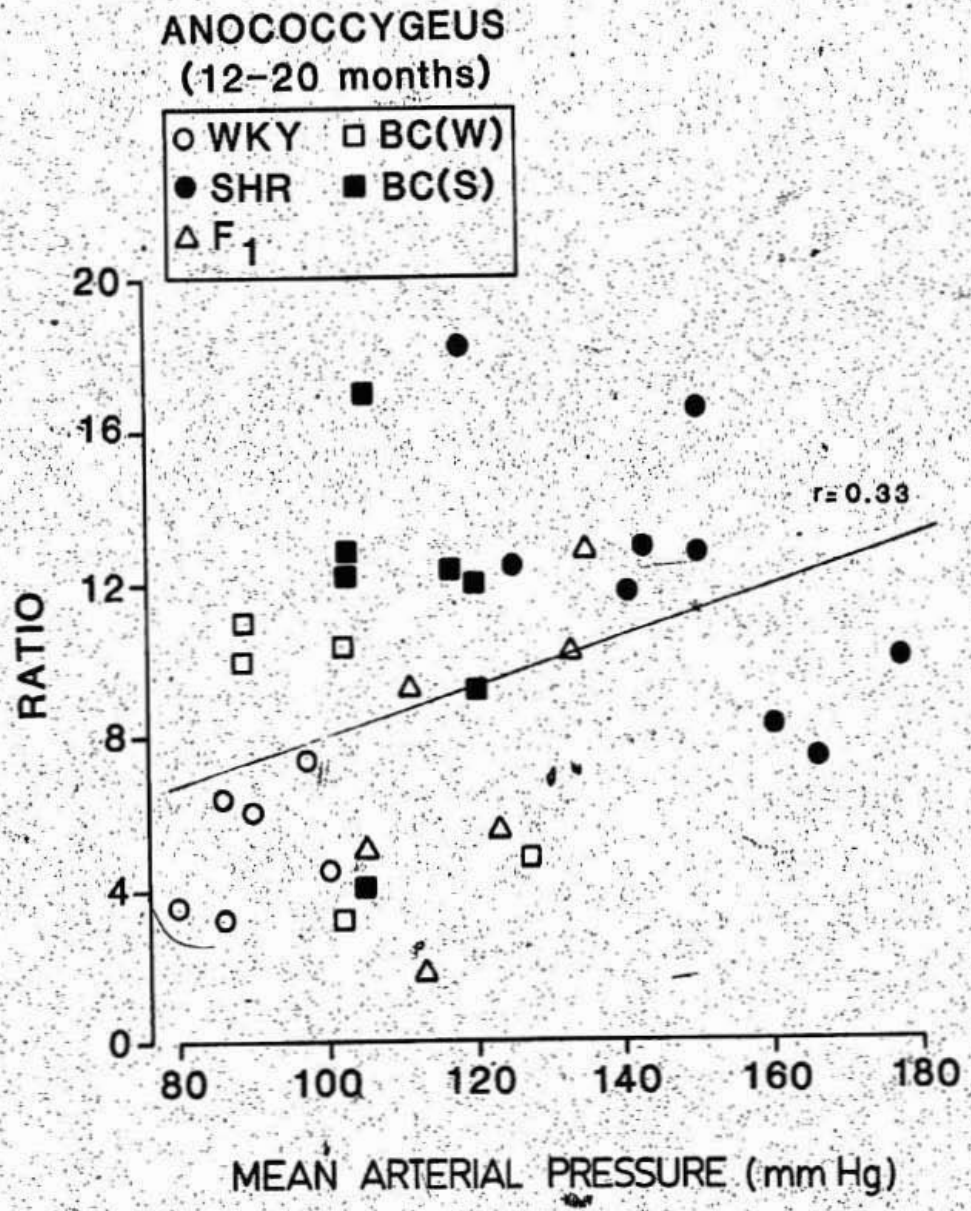

ANOCOCCYGEUS
(12–20 months)
WKY
BC(W)
SHR
BC(S)
F1
r= 0.33
RATIO
0
4
8
12
16
20
80
100
120
140
160
180
MEAN ARTERIAL PRESSURE (mm Hg)

Figure 13: Dose response curve for noradrenaline in perfused mesenteric beds isolated from 0.3% NaCl fed DS and DR rats. A flow rate of 4 mls/min was used (n = 6-8).

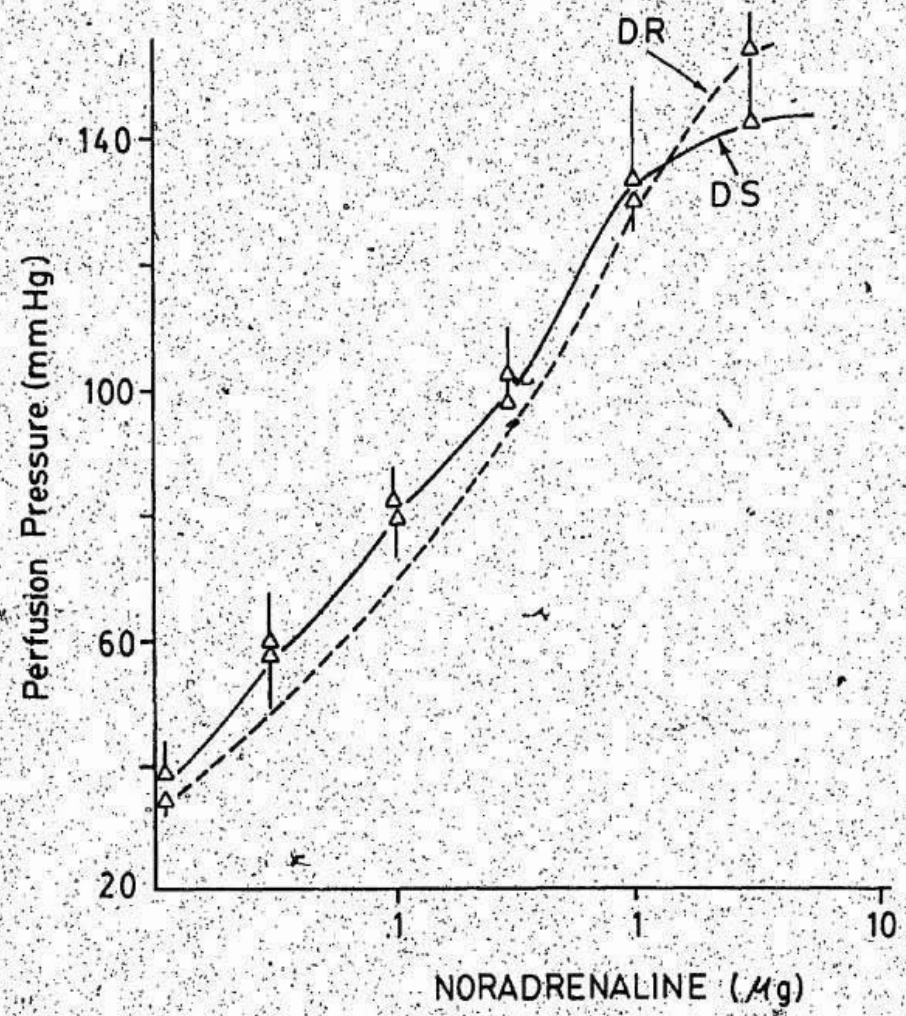

DR
DS
140
100
60
20
Perfusion Pressure (mm Hg)
1
1
10
NORADRENALINE (μg)

Figure 14: Dose response curve for phenylephrine in perfused mesenteric beds isolated from 0.3% NaCl fed DS and DR rats. A flow rate of 4 mls/min was used (n = 6-8).

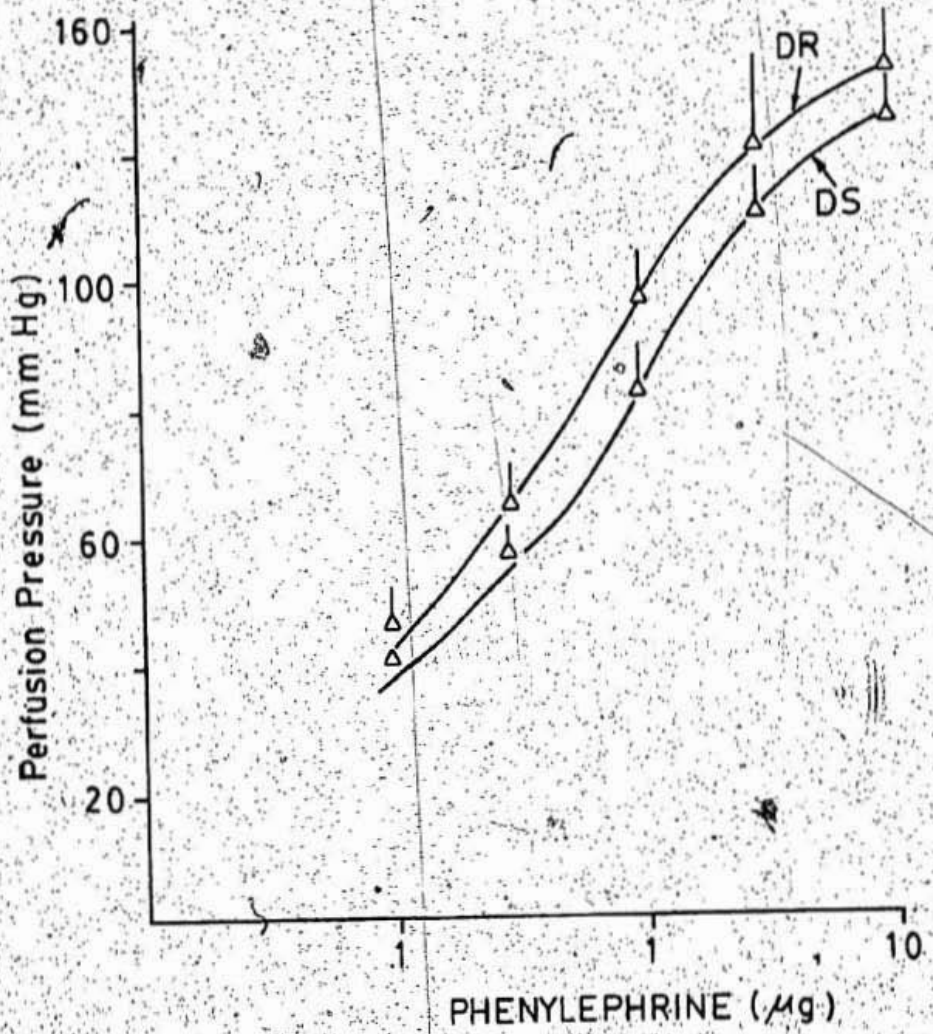

160
100
60
20
Perfusion Pressure (mm Hg)
DR
DS
1
1
10
PHENYLEPHRINE (μg)

Figure 15: Dose response curve for 5HT in perfused mesenteric beds isolated from 0.3% NaCl fed DS and DR rats. A flow rate of 4 mls/min was used (n = 6-8).

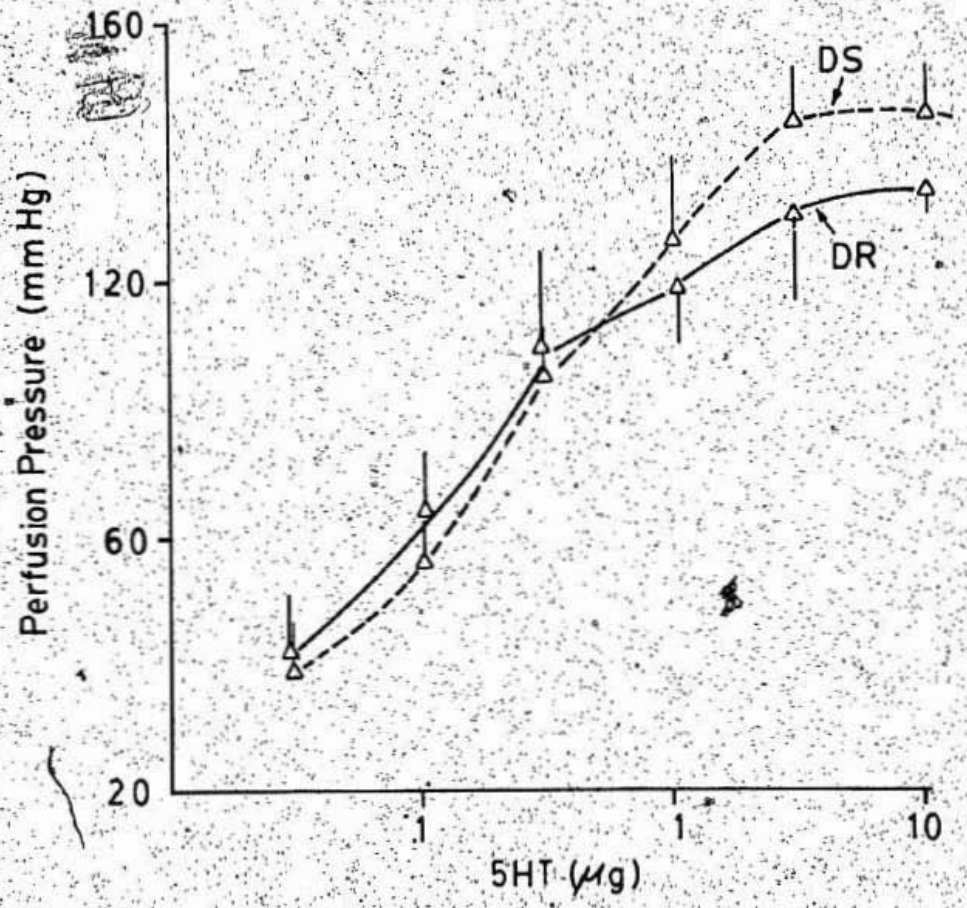

160
120
60
20
Perfusion Pressure (mm Hg)
DS
DR
.1
1
10
5HT (µg)

Figure 16: Dose response curve for noradrenaline in perfused mesenteric beds isolated from 8.0% NaCl fed DS and DR rats. A flow rate of 4 mls/min was used (n = 6-8).

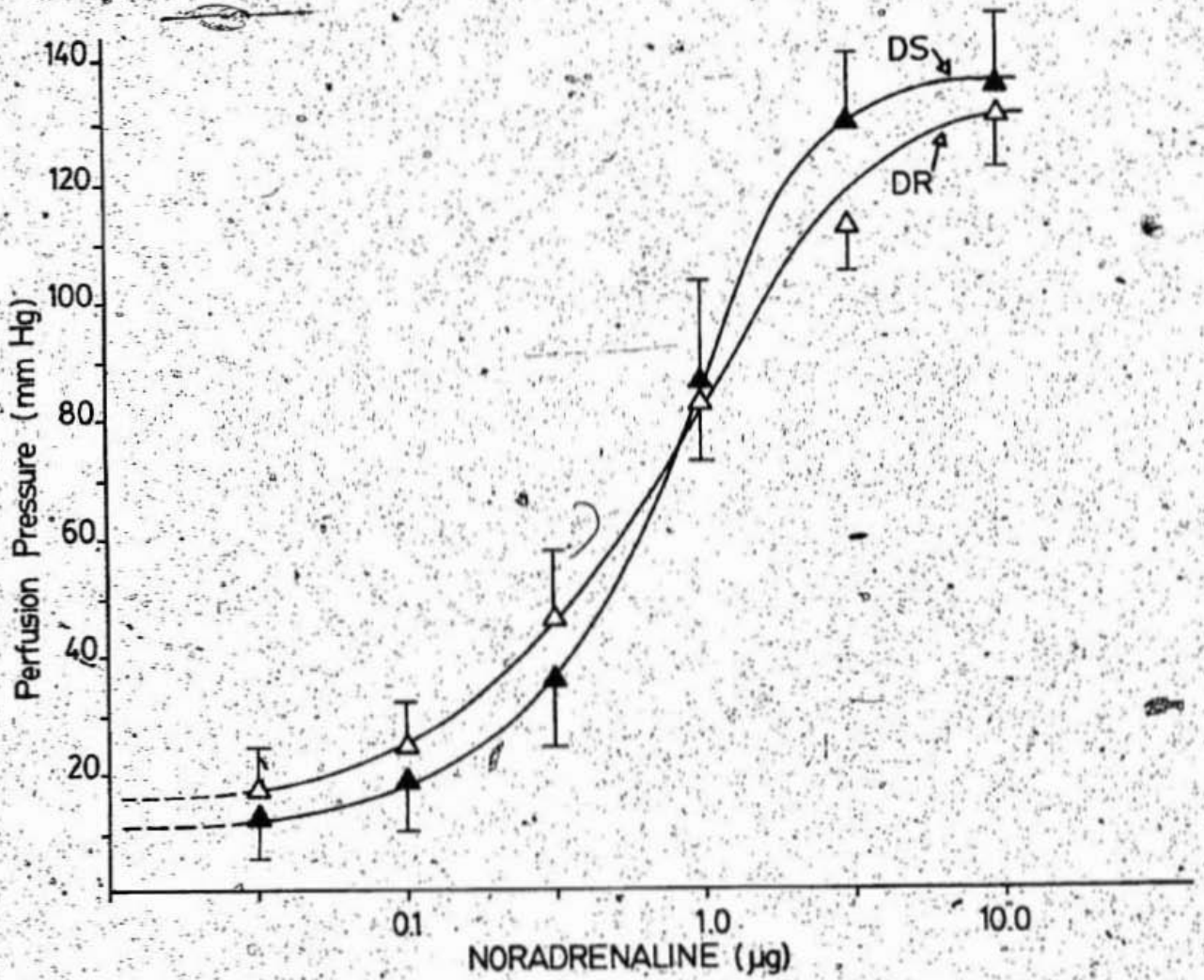

140
120
100
80
60
40
20
Perfusion Pressure (mm Hg)
DS
DR
0.1
1.0
10.0
NORADRENALINE (µg)

Figure 17: Dose response curve for phenylephrine in perfused mesenteric beds isolated from 8.0% NaCl fed DS and DR rats. A flow rate of 4 mls/min was used (n = 6-8).

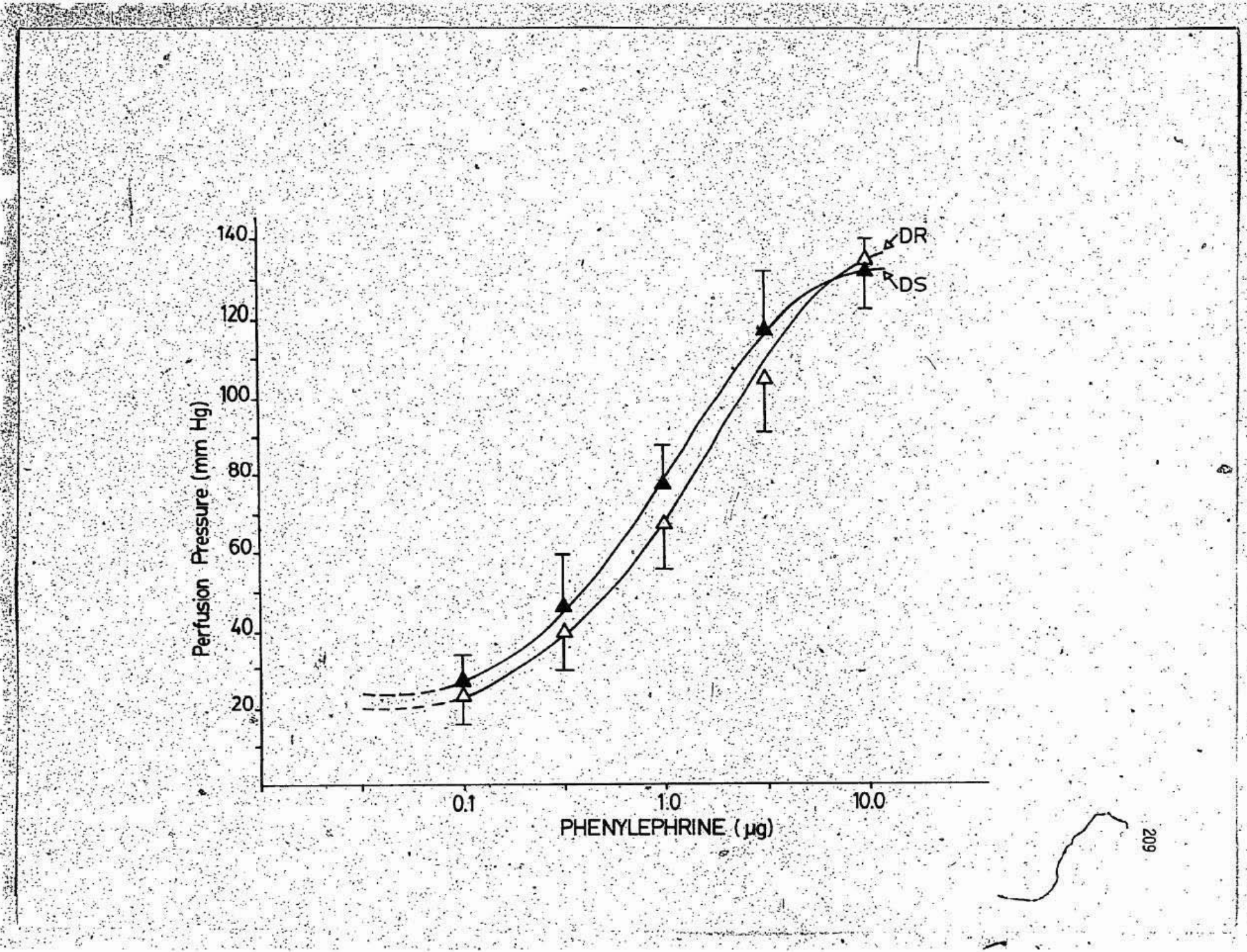

140
120
100
80
60
40
20
Perfusion Pressure (mm Hg)
DR
DS
0.1
1.0
10.0
PHENYLEPHRINE (µg)

Figure 18: Dose response curve for 5HT inperfused mesenteric beds isolated from 8.0% NaCl fed DS and DR rats. A flow rate of 4 mls/min was used (n = 6-8).

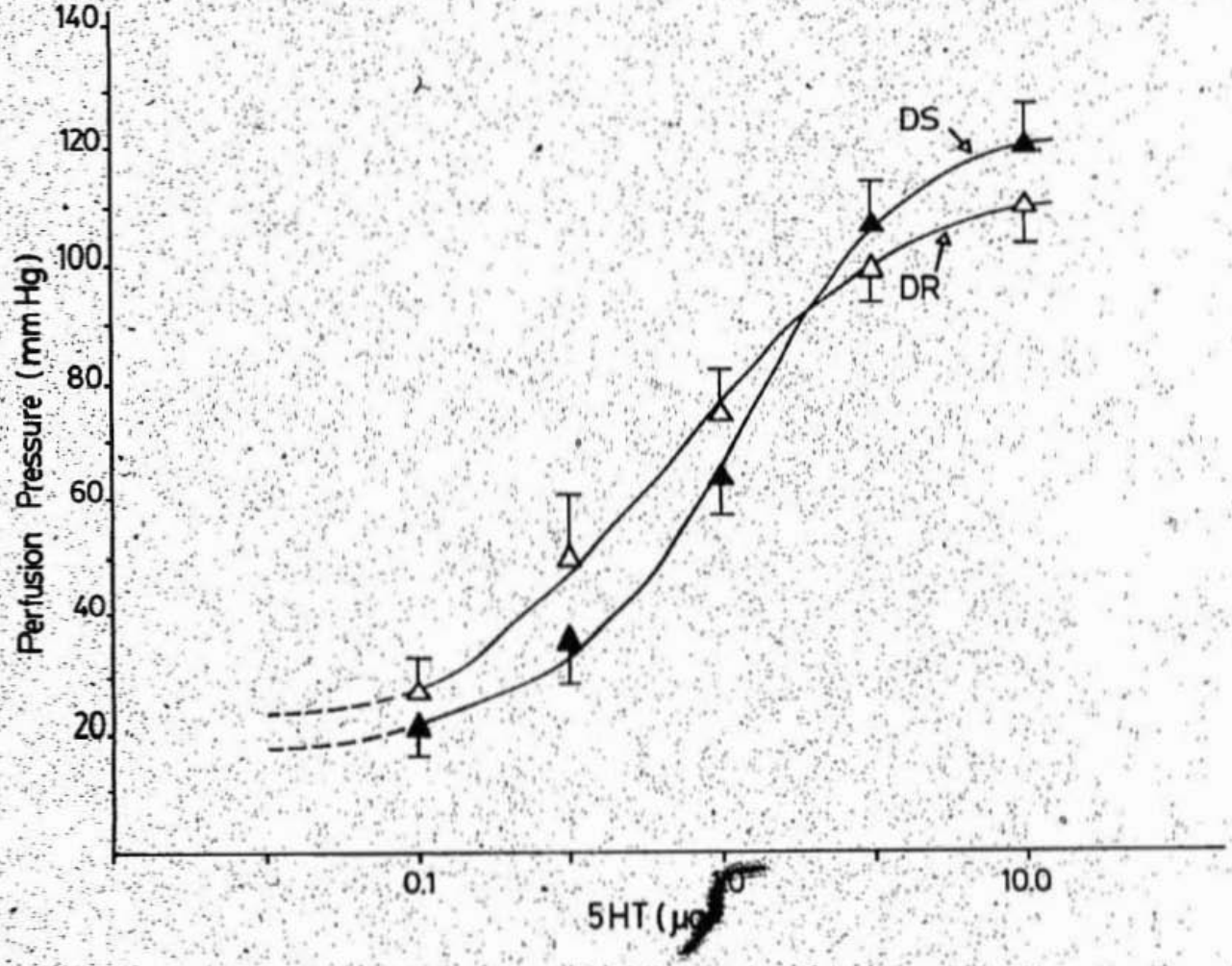

140
120
100
80
60
40
20
Perfusion Pressure (mm Hg)
DS
DR
0.1
10.0
5HT (μg

Figure 19: Dose response curve for noradrenaline in perfused mesenteric beds isolated from 4 week old WKY and SHR. A flow rate of 2 mls/min was used.

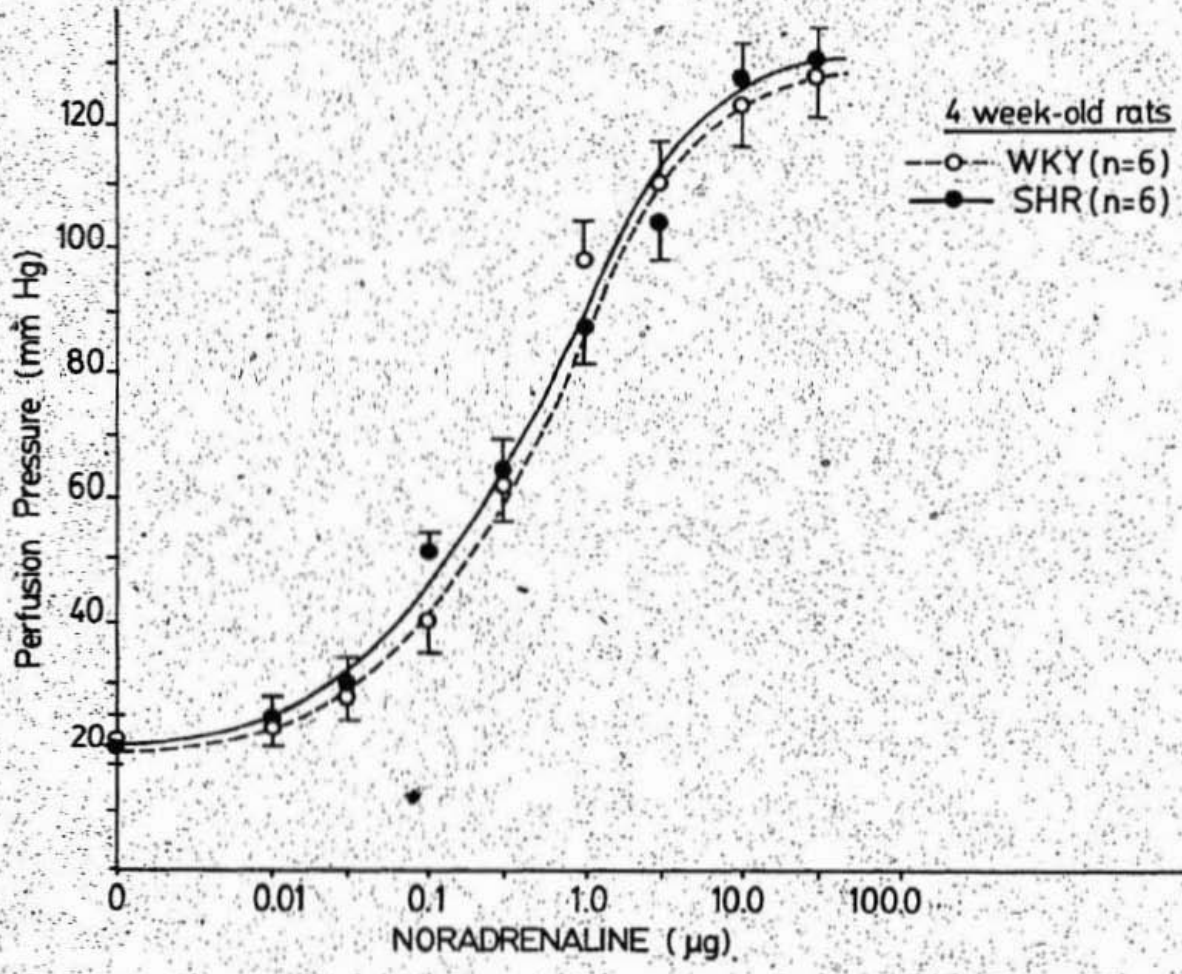

4 week-old rats
WKY (n=6)
SHR (n=6)
Perfusion Pressure (mm Hg)
120
100
80
60
40
20
0
0.01
0.1
1.0
10.0
100.0
NORADRENALINE (µg)

Figure 20: Dose response curve for noradrenaline in perfused mesenteric beds isolated from 12 - 16 week old WKY and SHR. A flow rate of 4 mls/min was used. Asterisks indicate significant differences from results from equieffective doses of noradrenaline (Student t-test, $P < 0.05$).

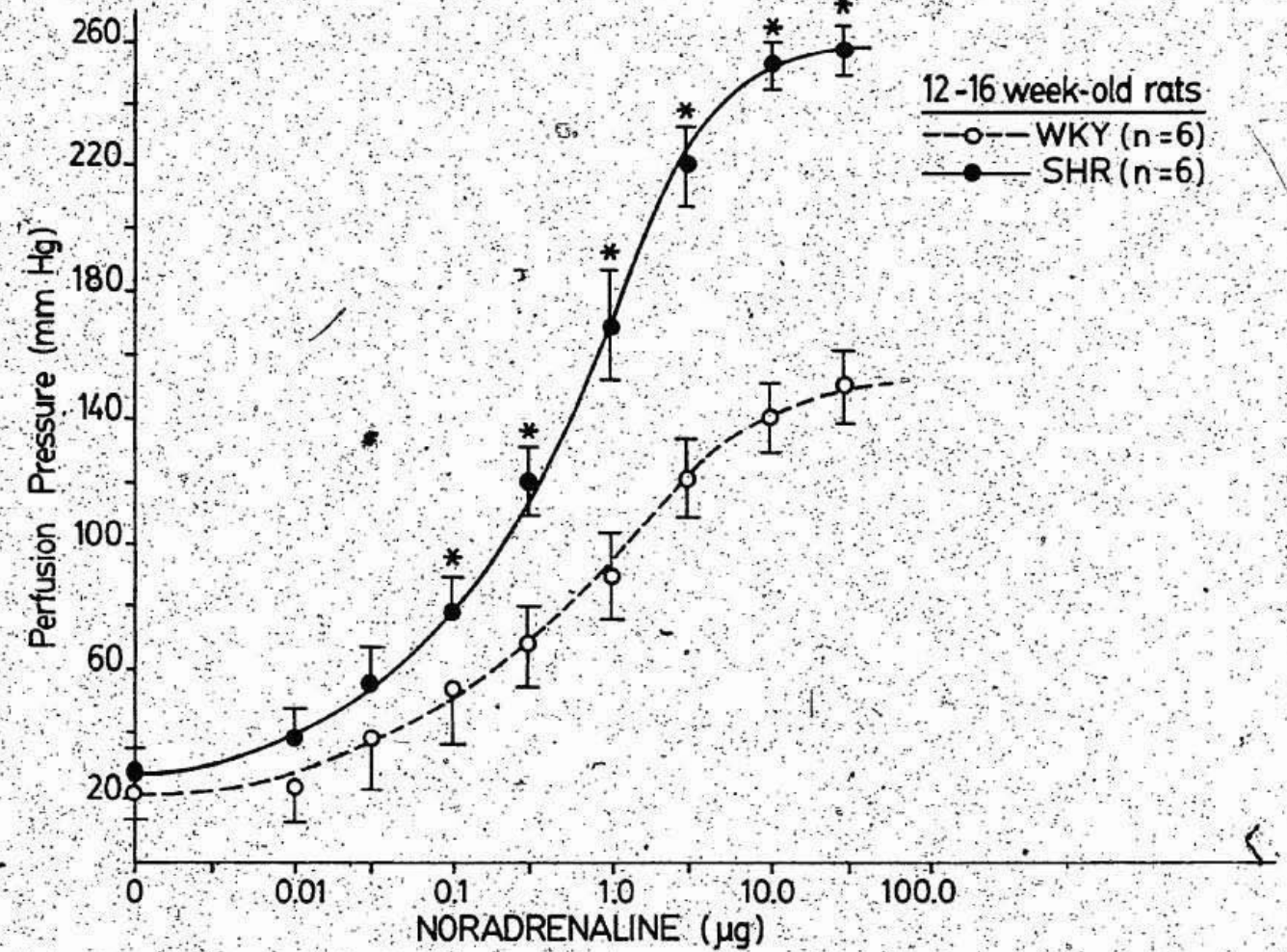

12-16 week-old rats
WKY (n=6)
SHR (n=6)
Perfusion Pressure (mm Hg)
260
220
180
140
100
60
20
0
0.01
0.1
1.0
10.0
100.0
NORADRENALINE (µg)
*

Figure 21: Dose response curve for the positive chronotropic response of isoprenaline in right atria isolated from DS and DR rats fed 4.0% NaCl (n = 6-8).

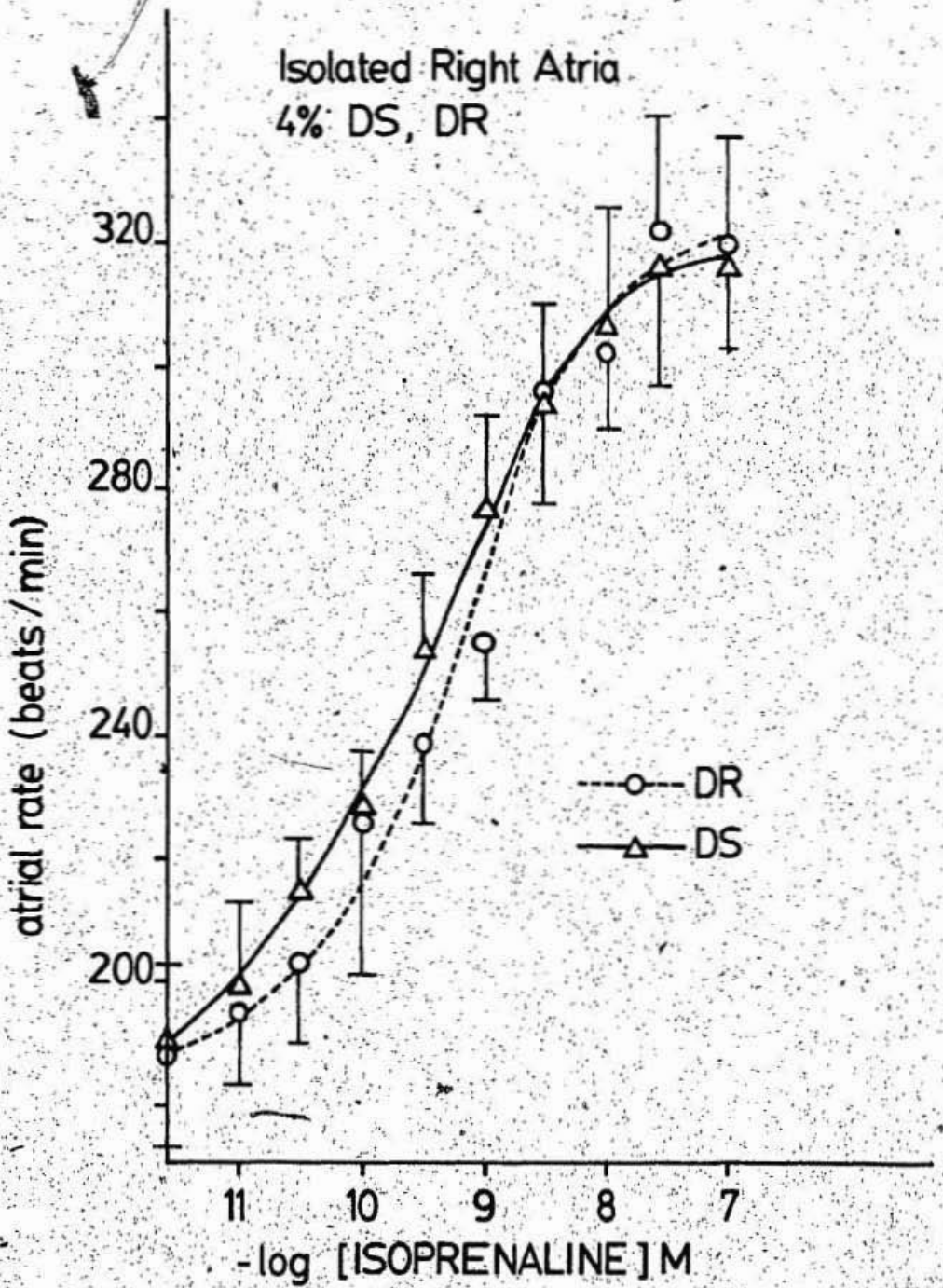

Isolated Right Atria
4% DS, DR
320
280
240
200
atrial rate (beats/min)
DR
DS
11
10
9
8
7
-log [ISOPRENALINE] M

Figure 22: Dose response curve for the papaverine in strips of aortae isolated from DS and DR rats fed 4.0% NaCl (n = 6-8). The tissues were precontracted with 1×10^{-5}M noradrenaline.

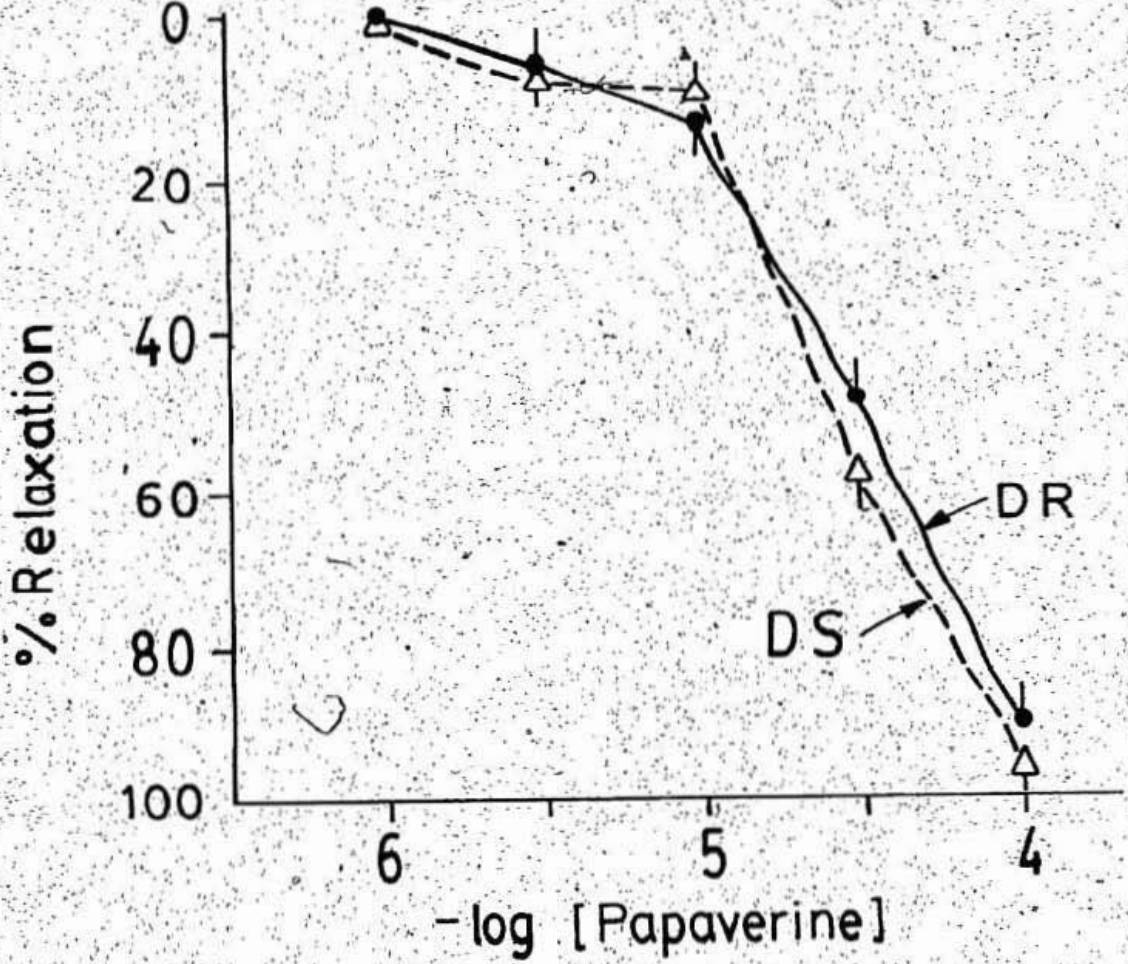

0
20
40
60
80
100
% Relaxation
6
5
4
-log [Papaverine]
DR
DS

Figure 23: Time course of the wash out of strips of aortae precontracted with 1 x 10^{-5} M noradrenaline. The wash out solution was normal Krebs buffer, and the tissues were obtained from 12 - 16 week old DS and DR rats fed 4.0% NaCl.

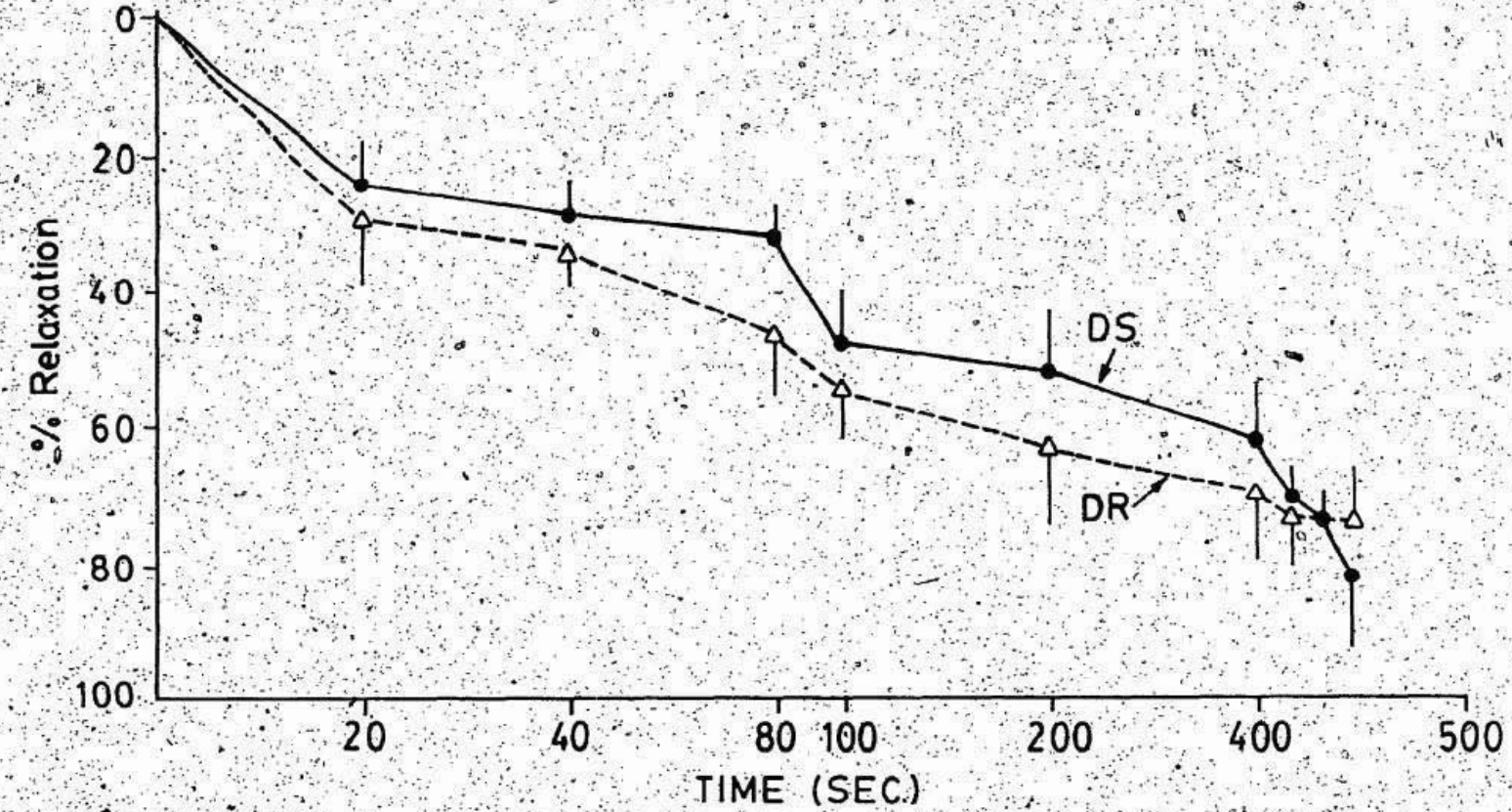

0
20
40
60
80
100
% Relaxation
DS
DR
20
40
80
100
200
400
500
TIME (SEC.)

Figure 24: Time course of the wash out of strips of aortae precontracted with 1×10^{-5} M noradrenaline. The wash out solution was Krebs buffer containing 5×10^{-5} M papaverine, and the tissues were obfrom 12 - 16 week old DS and DR rats fed 4.0% NaCl.

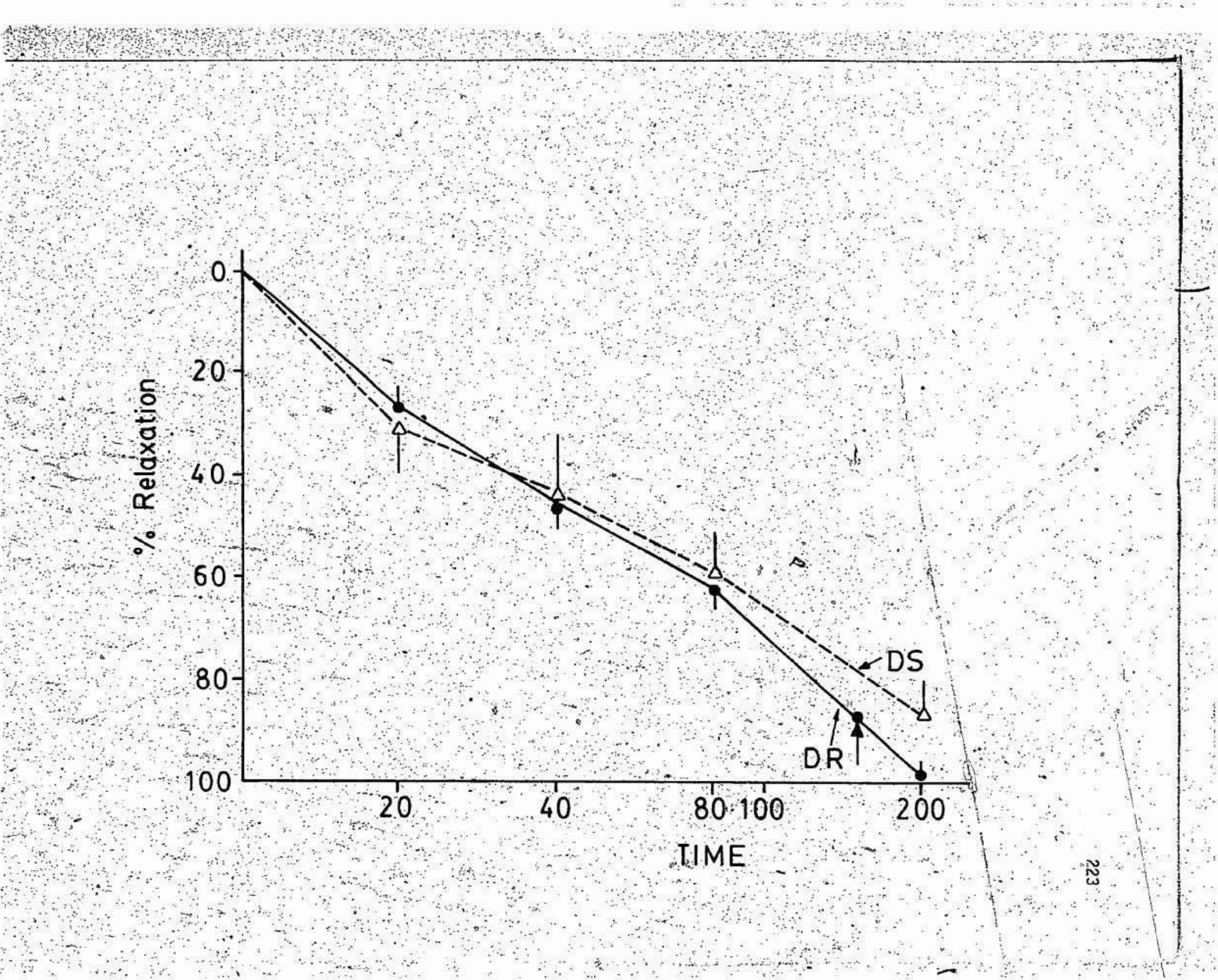

0
20
40
60
80
100
% Relaxation
20
40
80 100
200
TIME
DS
DR

Figure 25: Dose-response curve for lanthanum (La^{3+}) in rings of aortae isolated from 12 - 16 week old SHR, WKY and Wistar rats. The results are expressed as a percentage of the tissue response to a maximally effective dose of noradrenaline (1×10^{-5}M) and was performed in normal Krebs buffer.

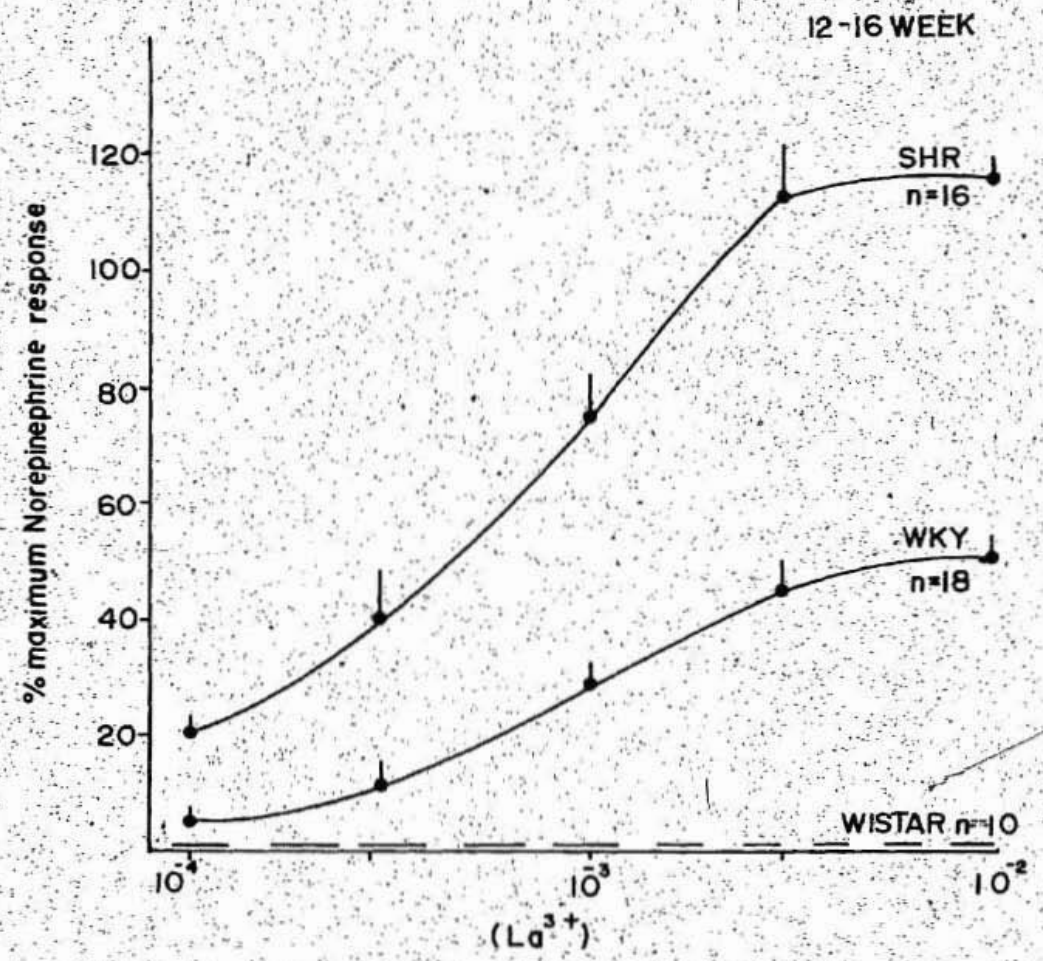

12-16 WEEK
% maximum Norepinephrine response
120
100
80
60
40
20
SHR
n=16
WKY
n=18
WISTAR n=10
10^{-4}
10^{-3}
10^{-2}
(La^{3+})



Figure 26: Dose-response curve for hydrochloric acid (H^+) in rings of aortae isolated from 12 - 16 week old SHR, WKY and Wistar rats. The results are expressed as a percentage of the tissue response to a maximally effective dose of noradrenaline (1×10^{-5}M) and was performed in normal Krebs buffer.

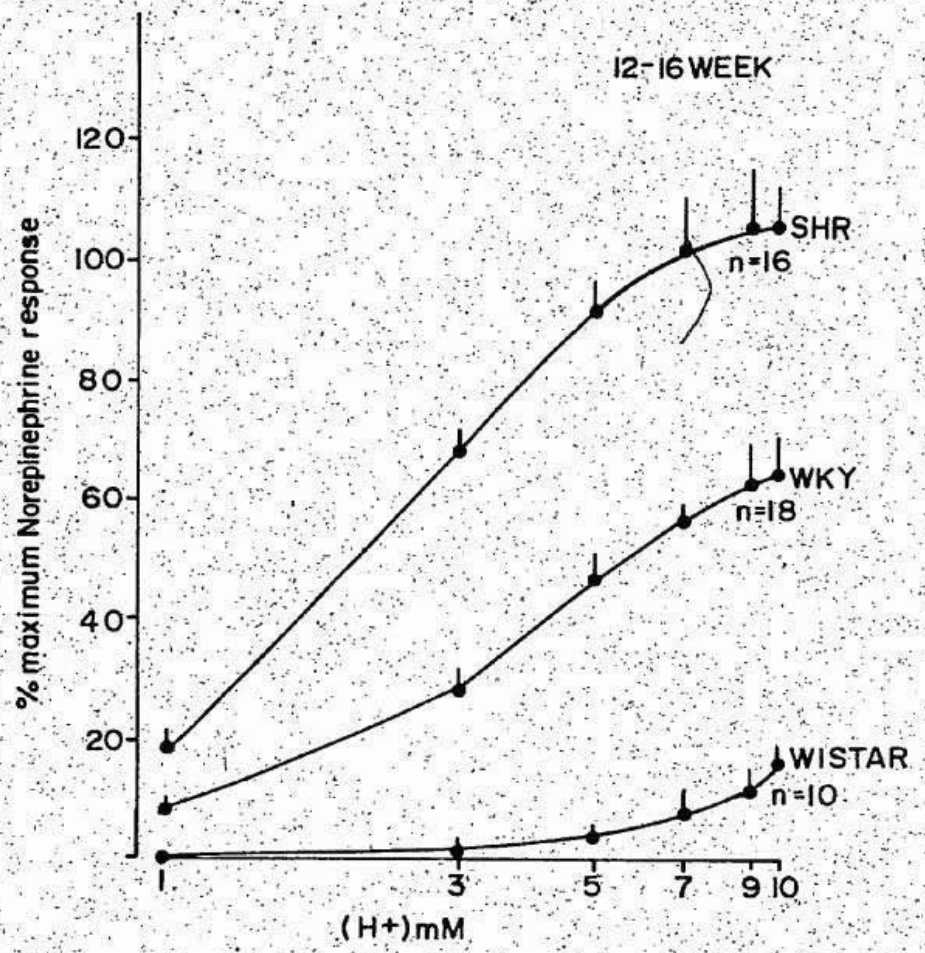

12-16 WEEK
% maximum Norepinephrine response
120
100
80
60
40
20
SHR
n=16
WKY
n=18
WISTAR
n=10
1
3
5
7
9
10
(H+)mM

Figure 27: Regression analysis of the lanthanum (5mM) response of aortic rings and mean arterial pressure of 6 - 8 week old animals. The response to lanthanum is calculated as a percentage of the tissues response to a maximally effective dose of noradrenaline (1×10^{-5}M) and were performed in normal Krebs buffer. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

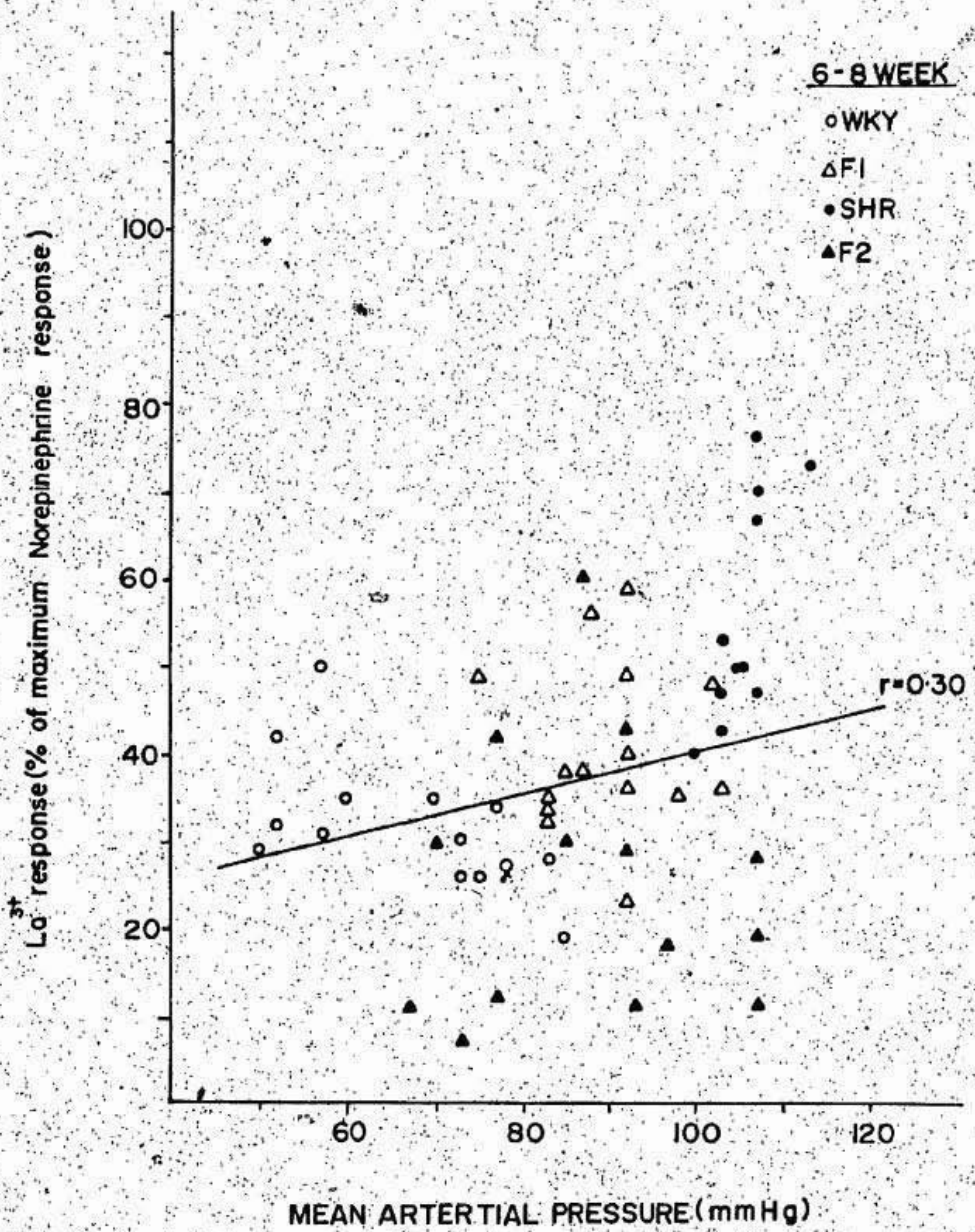
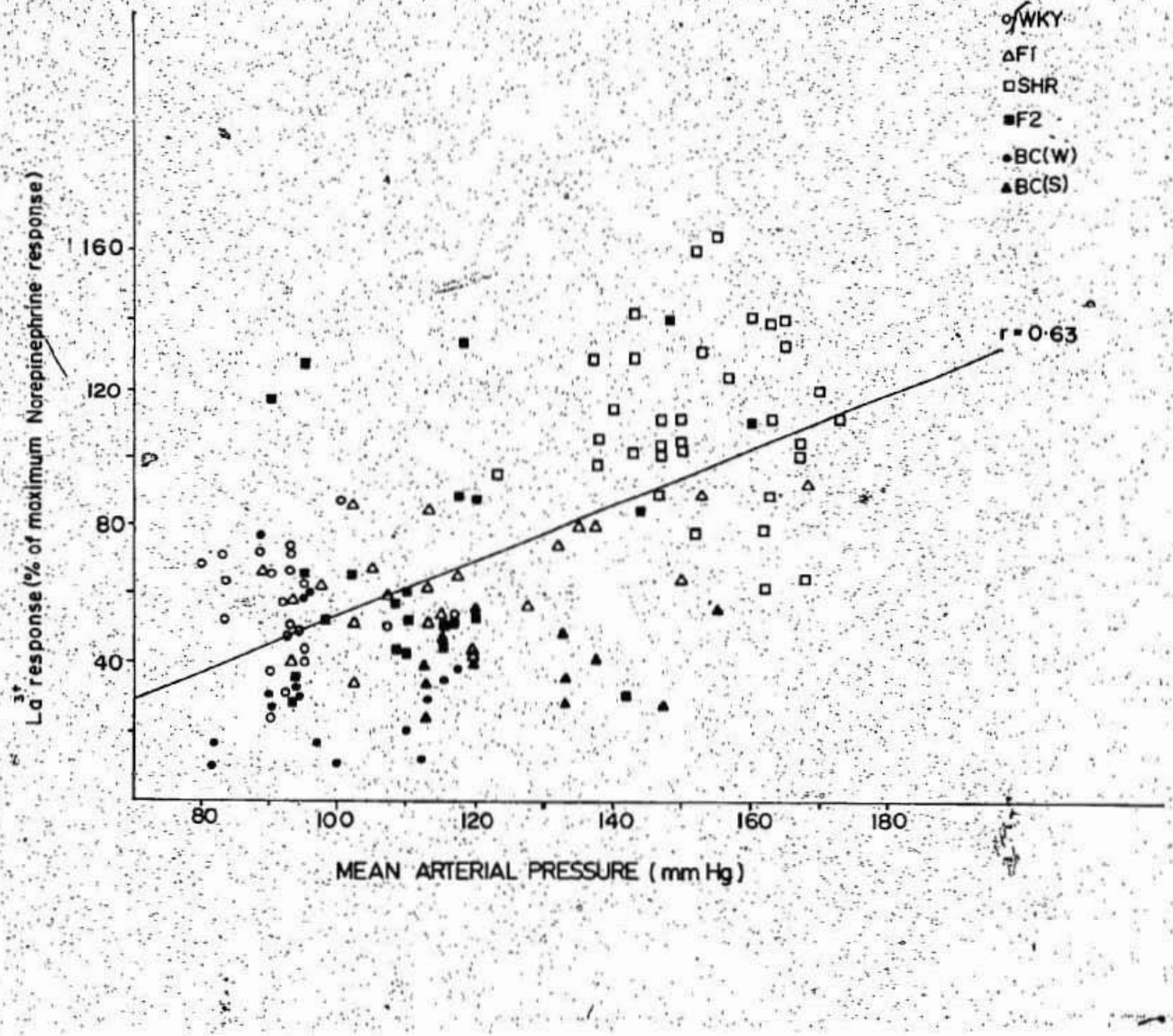

6-8 WEEK
o WKY
Δ F1
• SHR
▲ F2
r=0·30
100
80
60
40
20
60
80
100
120
La3+ response (% of maximum Norepinephrine response)
MEAN ARTERTIAL PRESSURE (mmHg)

Figure 28: Regression analysis of the lanthanum (5mM) response of aortic rings and mean arterial pressure of 12 - 16 week old animals. The response to lanthanum is calculated as a percentage of the tissues response to a maximally effective dose of noradrenaline (1×10^{-5}M) and were performed in normal Krebs buffer. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).


12-16 WEEK
WKY
F1
SHR
F2
BC(W)
BC(S)
r = 0·63
La3+ response (% of maximum Norepinephrine response)
160
120
80
40
80
100
120
140
160
180
MEAN ARTERIAL PRESSURE (mm Hg)

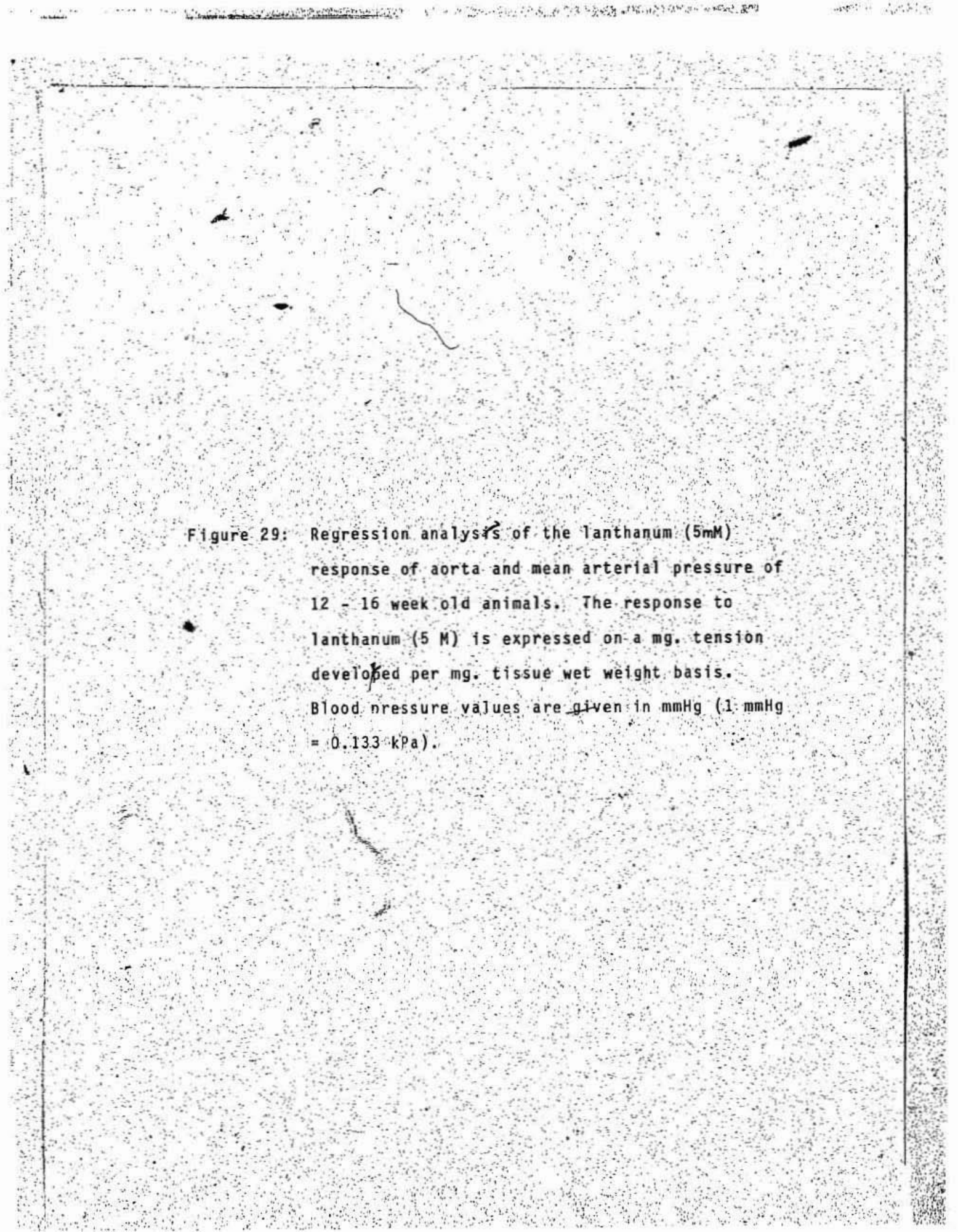


Figure 29: Regression analysis of the lanthanum (5mM) response of aorta and mean arterial pressure of 12 - 16 week old animals. The response to lanthanum (5 M) is expressed on a mg. tension developed per mg. tissue wet weight basis. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).

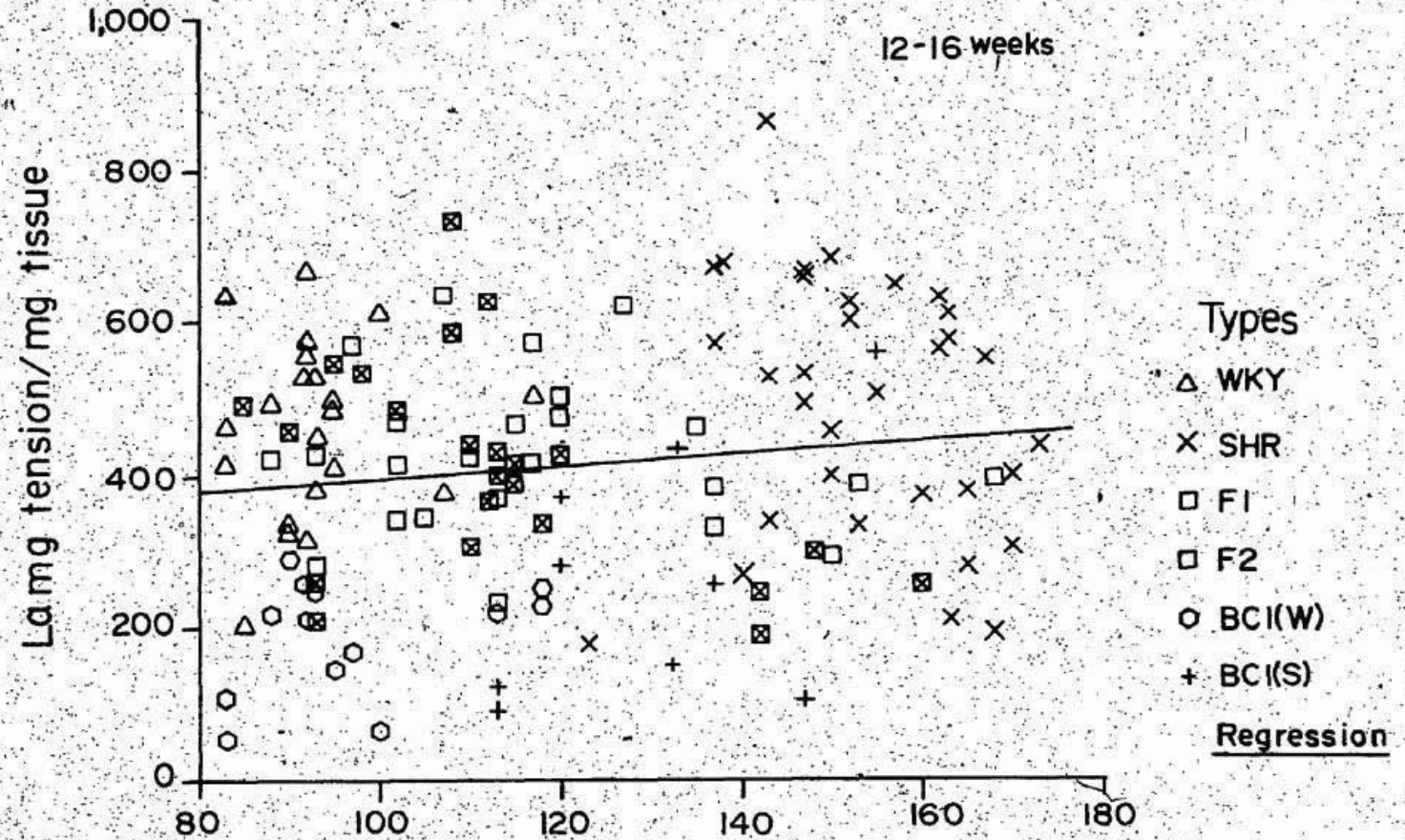
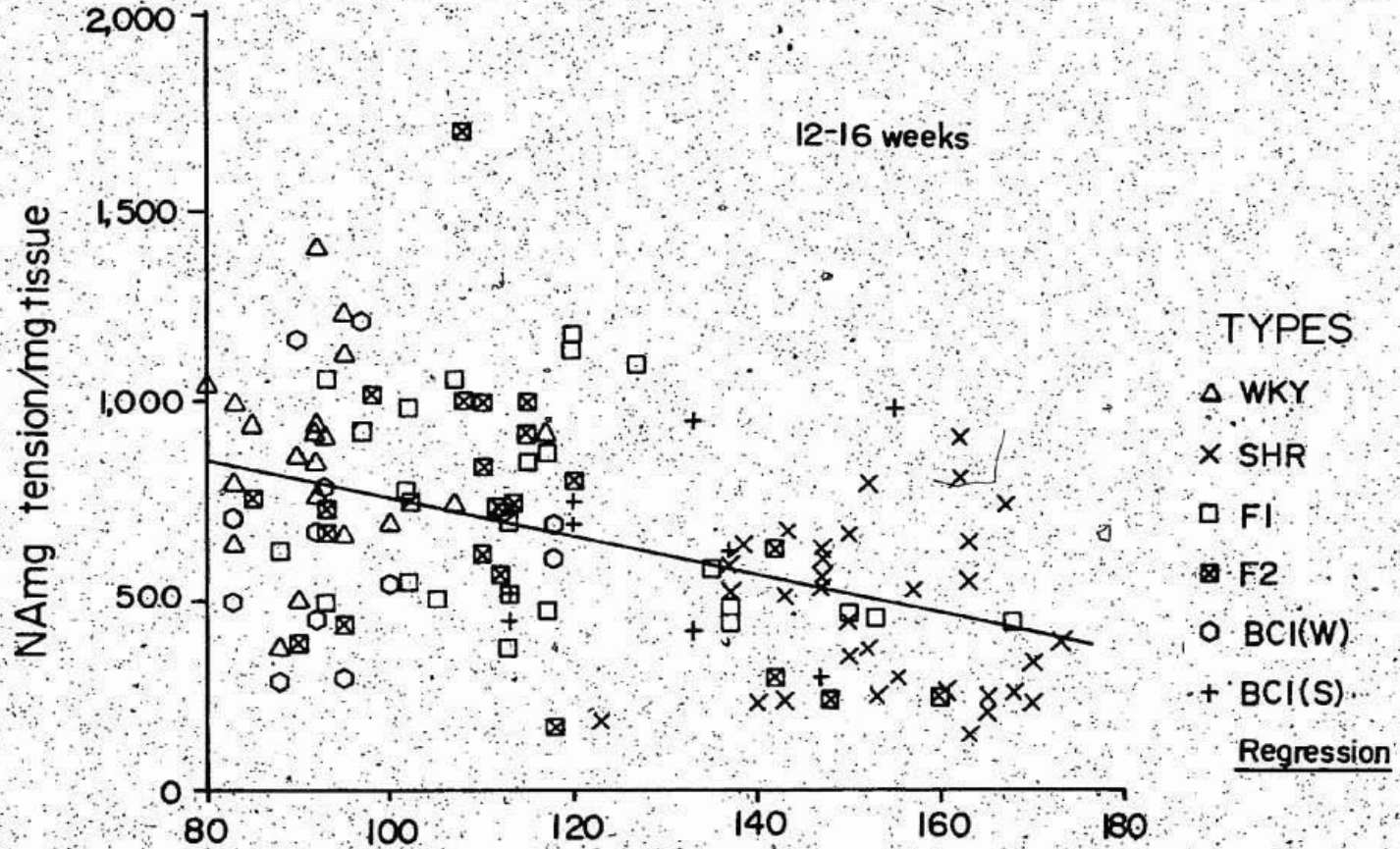

12-16 weeks
La mg tension/mg tissue
1,000
800
600
400
200
0
80
100
120
140
160
180
MEAN ARTERIAL PRESSURE (mm Hg)
Types
WKY
SHR
F1
F2
BC1(W)
BC1(S)
Regression

Figure 30: Regression analysis of the noradrenaline (1×10^{-5}M) response of aorta and mean arterial pressure of 12 - 16 week old animals. The response to noradrenaline (1×10^{-5}M) is expressed on a mg. tension developed per mg. tissue wet weight basis. Blood pressure values are given in mmHg (1 mmHg = 0.133 kPa).


12-16 weeks
NAmg tension/mg tissue
2,000
1,500
1,000
500
0
80
100
120
140
160
180
MEAN ARTERIAL PRESSURE (mmHg)
TYPES
WKY
SHR
F1
F2
BCI(W)
BCI(S)
Regression

DISCUSSION

A. General methodology

i) blood pressures of rats used

It is necessary to define a reference point in the description of hypertension, either in the clinical or experimental context. The World Health Organization, in 1959, defined hypertension as a blood pressure (sitting or recumbent) that exceeds 160/95 mmHg (normotensive as 110/70 mmHg). In experimental hypertension, animals with a systolic blood pressure of at least 150 mHg are considered by most investigators to be hypertensive (reviewed by Okamoto, 1969; Yamori, 1977 and by Schlager, 1981). By these criteria, and in agreement with most workers, the difference in blood pressure detected in young (up to 8 weeks) SHR and WKY would increase with age, such that the SHR would be considered hypertensive from a period between 8 to 12 weeks of age onwards. While there were differences in blood pressure between SHR and WKY at the three age groups used in this study, the mean systolic pressure of the SHR exceeded 150 mmHg only in the 12-16 weeks and > 52 week old animal groups (table 1, page 95).

In the Dahl strain of rats, there was a clear relationship between dietary sodium intake and blood pressure in the sensitive (DS) but not in the resistant (DR) group (table 28, 151). However, this strain of rats was

studied at only one age (15 weeks old), since maintaining the 8% DS beyond this was never successful. When compared to age matched SHR, both the systolic and diastolic pressures in the 8% DS were markedly elevated, even though the pulse-width was essentially unchanged (tables 1 and 28, pages 95 and 151). When a new group of breeding rats were introduced into our animal facilities, these SHR had a systolic and diastolic pressure not too different (table 30, page 155) from the 8% DS (table 28, 151).

While both the SHR and WKY group and the DS and DR group are highly inbred animals, the normotensive control in both groups (WKY and DR) had blood pressures not significantly different from the original parent strains (Wistar and Sprague Dawley) (Mulvany, 1983; Rapp, 1982b). These results are summarized in tables 28 and 31, pages 151 and 157.

The breeding programme used in this study (to produce SHR and WKY related offspring such a F_1F_2 and BC animals) is routinely used in studies to determine the genetic control of blood pressure regulation in rats (e.g. Tanase 1979; Yamori et al. 1972; Tanase et al. 1970; Yen et al. 1974). However, in the present studies, the method was employed to produce a spectrum of blood pressures ranging from SHR to WKY blood pressures, and then attempt to correlate pharmacological parameters to the blood pressure of the animal. A successful use of this approach has been reported by Judy et al. (1979) who were able to correlate the mean

arterial pressure of SHR and Wistar-Lewis related animals with sympathetic nerve activity. However, as discussed later, the fortuitous choice of the Wistar-Lewis control by Judy et al. (1979) may explain the excellent correlation they reported.

ii) Antihypertensive therapy

Some groups of SHR_1, F_1 and WKY and DS and DR (0.4% and 8.0%) were treated with antihypertensive therapy. In the SHR_1, F_1 and WKY, the treatment with α-methyldopa was started in utero, and terminated at sacrifice (12 - 16 weeks). There is currently a great deal of evidence supporting the hypothesis that alpha-methyldopa exerts its influence primarily via a central action where alpha-methyldopa undergoes biotransformation to α-methyl norepinephrine (Henning and van Zwieten, 1968 and De Jong, 1977) where it activates α_2-adrenoceptors and thereby reduces vasomotor tone. Alpha-methyldopa was used in this study in preference to other antihypertensive agents because of its ability to reduce tone in blood vessels by reducing sympathetic nerve-traffic activity. To prevent the peripheral conversion of α-methyldopa, carbidopa was concurrently administered to inhibit L-aromatic amino acid decarboxylase and thereby increase the availability of α-methyldopa for entry to the central nervous system (Henning and van Zwieten, 1968). Carbidopa is known not to cross the blood-brain barrier (Lotti and Porter, 1970), and since

peripheral decaboxylation of methyldopa in the rat is considerable (Porter and Titus, 1963), its inclusion was considered essential since an early attempt to control the blood pressures of SHR in this study was unsuccessful. This perhaps was related to the absence of carbidopa in the treatment, as well as to the adjustment of the pH of the drug solution to physiological ranges (at neutral and basic pH values, the drug solution was found to polymerize). Several other investigators have reported that the spontaneously hypertensive rat is either non-responsive or poorly responsive to α-methyldopa (Tomanek et al. 1979; Spech et al. 1980; Sen et al. 1974; Nagaoka et al. 1967), using drug concentrations of between 5 and 8 grams per litre. The treatment schedule outlined in the methods produced significant reductions in blood pressure of the SHR (when compared to untreated SHR), though the treated SHR did have higher blood pressures when compared to normotensive control WKY rats (table 22, page 139). Mulvany et al. (1981b) were also able to significantly reduce the blood pressure of SHR (by treatment with 6-hydroxydopamine on alternate days for twelve weeks). The treated SHR were still hypertensive when compared to age-matched WKY; but the treatment with 6-hydroxydopamine was sufficient to produce SHR that had significantly lower pressures than untreated age-matched SHR. Recent reviews of the literature by Armstrong and Massingham (1981) and by Giudicelli et al. (1981) also concluded that the SHR is resistant to most antihypertensive agents.

The situation regarding antihypertensive therapy in the Dahl rats was less of a problem (table 33, page 161), since thiazides as a group have proven efficacy in these animals (Tobian et al. 1979a; Iwai et al. 1977; Tobian 1979). In the present study, the blood pressure of 8% DS rats was well-controlled by hydrochlorothiazide and by the converting enzyme inhibitor MK-421. Although the antihypertensive effect of MK 421 was greater in DS rats, the calculated percentage fall in pressure was similar for the two groups (DS and DR). Thus, the antihypertensive effect of MK 421 was not specific for the DS rats. Sweet (1983) recently reported that MK 421 was more potent than captopril in lowering blood pressure in the SHR, yet equally active in inhibiting plasma angiotensin converting enzyme, suggesting that other mechanisms operated to decrease blood pressure. Such mechanisms could conceivably be involved in the antihypertensive effect of MK 421 in the DS and DR rats. Clearly, while renal mechanisms are very important in the genesis of hypertension in the DS rat, other mechanisms must exist to act either in partnership or independently of these primary renal defects, since interference of the renin-angiotensin system with MK-421 produces a larger antihypertensive effect than treatment with a thiazide diuretic (table 33, page 161). Other antihypertensive agents shown to have effect in the salt-loaded DS rat are the calcium-entry blockers (Kazda et al. 1982a, b), lending

further support to the concept that mechanisms unrelated to renal defects could either initiate or maintain high blood pressure in the DS strain.

iii) Assessing uptake 1

The method of indirectly assessing uptake 1 used in this study is one routinely used by other groups (e.g. Mulvany et al. 1979; 1980a, 1980b, 1981a; Webb and Vanhoutte 1979; Webb et al. 1980; Whall et al. 1980). The shift of the noradrenaline dose-response curve resulting from uptake 1 blockade with cocaine was evaluated by dividing the dose of noradrenaline which produced 50% of the maximal response (ED_{50}) before cocaine by the ED_{50} for noradrenaline in the presence of cocaine. This method has the advantage in that both the uptake and postsynaptic sensitivity to noradrenaline can be measured in the same tissue.

An alternate method is to directly measure the total rate (or amount) of accumulation of ^{3}H-noradrenaline in synaptosomal preparations, and to compare these in SHR and WKY (e.g. Rho et al. 1981a, 1981b). When this method is used, several drawbacks should be realized; for instance, the contractility of the tissue is not known, and the preparation not only contains nerve endings but also arterial, venous and connective tissue so that neuronal and extraneuronal uptake (total uptake) as well as tissue binding is measured. Furthermore the problem of the origin of the nerve-endings, arterial or venous, is unknown. As

far as can be determined from the literature, the indirect method does provide qualitatively similar results as the direct method with ^{3}H-noradrenaline when the two were compared (Vanhoutte, 1980; Whall et al. 1980; Collis et al. 1980).

iv) Effect of cocaine, propranolol and estradiol on dose-response curve

Preliminary studies indicated a dose of cocaine of 4 x 10^{-5}M caused a maximal shift in the dose-response curve to noradrenaline (table 3, page 99) in tissues from both SHR and WKY. Using this dose of cocaine, Webb et al (1981) observed a direct effect of the uptake 1 blocker, most of which was due to release of endogenous noradrenaline in their helical strip tail artery preparations. However, this indirect effect of cocaine was greater in WKY tissues. Webb and Vanhoutte (1982) later reported that the ability of cocaine to release endogenous noradrenaline was most readily demonstrated with a dose of 1 x 10^{-4}M cocaine, even though several other workers have reported a similar result with lower (range of 3 x 10^{-7} to 1 x 10^{-5}M) cocaine doses eg. reviewed in table 1 of Webb and Vanhoutte, 1982. The effect of depolarization of the prejunctional membrane on neuronal uptake of noradrenaline was examined by Webb et al. (1980) who reported that cocaine differentially potentiated the response to low frequency stimulation (and not of high frequency stimulation). Since the period of time between

impulses is longer at low frequencies, the inhibitory effect of cocaine on uptake 1 was evident. Confirmation that uptake 1 was inhibited during nerve depolarization came from the observation that cocaine had no effect on contractions produced by depolarization of the prejunctional membrane with high potassium.

The extraneuronal effects of cocaine remain a contentious issue, since several authors have argued for both a pre- and post-junctional effect of the uptake 1 blocker (Kalsner, 1976, 1977, 1979; Kalsner and Nickerson, 1969; Trendelenburg (1973) and references therein; Maxwell and Eckhardt (1973) and references therein). However, other reports indicate a negligible postsynaptic effect of cocaine in smooth muscle preparations, using a dose range of 1 to 5 x 10^{-5}M (e.g. Wyse, 1974, 1976; Rolewicz et al. 1970; Cohen and Wiley, 1977; Kaiman and Shibata, 1978; O'Connor and Slater, 1981; Cohen et al. 1983). In the present study, as mentioned before, a maximal inhibition of uptake 1 was found to occur when a dose of 4 x 10^{-5}M cocaine was used. Two groups of experiments in this study demonstrate the presence of only minimal postsynaptic cocaine effects. First cocaine did not affect the noradrenaline ED_{50} in the non-innervated aorta (tables 16 to 19, pages 125 to 133), and second, it did not affect the dose-response curves to phenylephrine (which is not a substrate for uptake 1) in any of the tissues studied in > 52 week old animals (tables 8 to 15, pages 109 to 123). The potentiation of the maximal noradrenaline

response observed in some tissues did not show any age or strain selectivity (tables 17 and 20). In fact, Webb and Vanhoutte (1981) have demonstrated a greater indirect effect of cocaine (release of endogenous noradrenaline) in tissues from WKY (than from SHR).

Conceivably, in addition to alterations in uptake 1 other mechanisms exist to influence the dose-response curve to noradrenaline in SHR and WKY tissues (reviewed by Vanhoutte et al, 1980). Cheng and Shibata (1980) have reported a decreased β-adrenoceptor mediated relaxation in aortic strips from SHR, while Webb and Vanhoutte (1979) and Webb et al (1981) suggested an increased extraneuronal uptake of noradrenaline in tail artery strips from SHR. However, these suggestions were speculative, since no experiments were performed, for instance, with an uptake 2 blocker. The results of the present study indicated that, at least for the tail artery strip in the presence of cocaine, propranolol (to antagonize β-adrenoceptor mechanisms) and 17- estradiol (to inhibit uptake 2) had no effect on the noradrenaline dose-response curves in tissues from SHR and WKY (figs. 3 to 6, pages 181 to 187).

The results of Whall et al (1980) also indicated no difference in both the rate and extent of uptake 2 mechanisms in mesenteric arteries of SHR and WKY. Using ^{3}H-noradrenaline they measured both total uptake and uptake in the presence of 1×10^{-4}M cocaine; they found that extraneuronal uptake was 16% of the total uptake from WKY

and 14% from SHR vessels, and that the rates of extraneuronal uptake were similar between WKY and SHR (2.0 and 2.4 fmol/vessel/min.resp.). (table III of Whall et al. 1980). On the other hand, the vessels from SHR had a 44% greater neuronal uptake of ^{3}H-noradrenaline.

B) Postjunctional sensitivity and uptake of noradrenaline in SHR

The important finding in this part of the study is that no significant differences in the ED_{50} ratio for noradrenaline, an indirect measure of neuronal uptake activity, were noted in non-arterial smooth muscle preparations from 12-16 week old rats from the various hypertensive strains. Since, as Table 1 indicates, the F_1, BC_1(S), and SHR had significantly higher pressures than the WKY, and BC_1(W) group, these findings indicate that the altered uptake 1 and postjunctional sensitivity to noradrenaline at least as determined by the present experimental protocol, are not detectable at this early stage of hypertension, except in the tail artery preparation from the SHR related rats. A correlation between MAP and the ED_{50} ratio was thus only noted for the tail artery preparation (Table 21, page 137), (fig.8, page 191). In contrast, in the > 52 week group, uptake 1 activity, as indicated by the ED_{50} ratio, and the postjunctional sensitivity to noradrenaline shows a closer correlation to

the B.P.: SHR > F_1 > WKY indicating that the altered U_1 activity in arterial and non-arterial smooth muscle occurs only in very old hypertensive animals (Table 21, page 137).

The data from BC_1(S) and BC_1(W) animals of the > 52 week group does not completely fit with the data from the SHR, F_1 and WKY animals. Two explanations may be offered for this discrepancy. Firstly, the data from the > 52 week BC animals was obtained approximately 9 months after the original studies with the SHR, F_1 and WKY were performed, this being necessitated by the breeding program and the difficulties in obtaining sufficient numbers of age-matched animals of each strain at the same time. The differences may represent subtle technical and experimental differences, resulting in the observed greater adrenergic sensitivity of these tissues. In part, the data from the aorta argues against this hypothesis since the noradrenaline ED_{50} for the aorta from the BC animals is not significantly different from the noradrenaline ED_{50} for the SHR, F_1 and WKY rats of the same age group. Furthermore, the reported noradrenaline ED_{50} for the SHR and WKY tail artery strip is similar to that reported by Webb and Vanhoutte (1981) [approximately 9×10^{-8}M] for tissues from 4-6 month old SHR, WKY and Wistar rats. The tissues (except thoracic aorta) from BC rats are thus more sensitive to noradrenaline, having an ED_{50} approximately one tenth of that of tissues from comparable SHR, F_1 and WKY. Secondly, the results with tissue from the BC_1 rats may indicate a separation of adrenergic sensitivity

differences between the SHR and WKY from the differences in MAP, although again it should be noted that noradrenaline ED_{50} before/after cocaine ratio for the $BC_1(S)$ and $BC_1(W)$ rats does, with the exception of the anococcygeus, tend to lie between those of the SHR and F_1 and F_1 and WKY respectively. Further studies with these BC_1 and perhaps BC_2 (i.e. $BC_1(S) \times F_1$, $BC_1(S) \times SHR$, $BC_1(W) \times WKY$, or $BC_1(W) \times F_1$) may help to further elucidate the relationship between blood pressure, tissue uptake 1 activity and smooth muscle sensitivity to adrenergic agents.

Since, according to Vanhoutte (1980) the enhanced α-adrenoceptor sensitivity of smooth muscle in SHR is compensated for by a greater uptake 1 activity, two predictions were tested:- (i) that in SHR tissues lacking adrenergic innervation, there should be a lower ED_{50} for noradrenaline and other α-adrenoceptor agonists. This was not the case in the present (tables 7, 8, 16, 18, 19 and 23) or other (e.g. Clineschmidt et al 1970; Hallback et al 1971) studies, and is discussed later (under "trophic factors"). (ii) The SHR should show an elevated sensitivity to an α-adrenoceptor agonist which is not taken up by uptake 1. This is also not observed in the present studies, where the phenylephrine dose-response curve was similar in aorta, portal vein, tail artery and anococcygeus preparations from > 52 weeks old SHR and WKY (tables 7 to 14, pages 107 to 121). Two explanations can be offered for this. One possibility is that only uptake 1, and not postsynaptic

α-adrenoceptor sensitivity is altered in hypertension. The results from the tail artery preparation (table 18, page 130) would argue against this.

The second possibility concerns the presence of *postsynaptically located α_2-adrenoceptors, stimulated by* noradrenaline and not by phenylephrine (reviewed by McGrath, 1983). So far it has not been possible to clearly pharmacologically characterize these receptors in an in vitro preparation. This α_2-adrenoceptor effect could be *greater in tissues from SHR. Until the presence of these* α_2-adrenoceptors can be clearly demonstrated in vitro, this hypothesis remains to be tested. One can speculate, however, that the altered α-adrenoceptor-operated calcium channels in SHR described by Mulvany and Nyborg (1980) are related to the postsynaptic α_2-adrenoceptor, based on the observation by van Meel et al. (1981) who demonstrated that the tonic component of the vascular response to noradrenaline could be more effectively antagonized by yohimbine-related α_2-adrenoceptor antagonists.

The results of the present study are in general agreement with those of Webb and Vanhoutte (1979) who, using an in vitro tail artery preparation, have reported that uptake 1 activity and postjunctional noradrenaline sensitivity are only elevated in the tissues from old SHR (> 16 weeks old). Similar conclusions were reached by Collis and Vanhoutte (1977, 1978, 1980) as a result of data obtained from the isolated perfused kidney preparation.

Mulvany et al. (1980b) have reported changes in noradrenaline sensitivity in the mesenteric artery preparation from both young and old SHR but failed to demonstrate changes in noradrenaline sensitivity in the sparsely innervated femoral resistance vessels, whereas, in the presence of cocaine, the noradrenaline sensitivity of the tail artery from SHR was demonstrated to be higher than that from age-matched 14 week old WKY (Mulvany et al. 1982). Mulvany et al. (1980b) have also compared uptake 1 activity and NA sensitivity in the portal vein preparation from SHR and WKY and reported no differences between the two groups, at least for the 12-16 week group. The present results with the portal vein and anococcygeus from the 12-16 week group are thus supportive of Mulvany's work and are also suggestive that elevated uptake 1 changes are not general changes occuring in innervated smooth muscle but are confined to the regions exposed to the elevated B.P.

The present study indicates that the vascular smooth muscle sensitivity is similar in tissues from SHR and WKY when uptake 1 is operational. Therefore the functional nerve-muscle interaction prevents the increased vascular sensitivity of SHR from being expressed. If this were the case with endogenously released noradrenaline in situ, then changes in vascular sensitivity could not contribute to the increased peripheral resistance in SHR. A role for the increased vascular sensitivity to endogenous noradrenaline in affecting peripheral resistance is evident however since

the masking effect of uptake 1 is partially eliminated in vivo. Inhibition of uptake 1 in vivo can occur by two mechanisms. Firstly, uptake 1 may be saturated by high levels of noradrenaline released in both WKY and SHR vessels (a value of 0.1 to 1.0μM at the intimal surface has been suggested by Ljung (1976)). Thus at threshold doses of noradrenaline, uptake 1 would still be operational while at higher concentrations (e.g. at ED_{50} values) neuronal uptake would be saturated and effectively removed. Secondly, based on the observations of Bonaclorsi et al. 1977 and Webb et al. 1981 and discussed earlier in the introduction of the thesis, uptake 1 is inoperational during depolarization of the nerve terminals.

A number of studies have indicated that some aspects of sympathetic activity are elevated in peripheral tissues at an early stage and may be an important initiating factor for increasing B.P. in the SHR. Thus, Nagatsu et al. (1976), using plasma dopamine β-hydroxylase (DBH) as an indicator of noradrenaline release, report that there is an elevation of sympathetic activity in 3 week old SHR, but not in 14 week old SHR when compared to matched WKY; furthermore, the elevated DBH activity was primarily associated with the peripheral blood vessels.

Morphological studies (Ichijima, 1969) report that adrenergic innervation is denser and the varicosities larger around the small jejunal arteries and arterioles of the SHR; however, it is not stated at what age these differences are

detectable. Conceivably, this altered pattern of innervation may explain the elevated uptake 1 activity of the SHR (Hermsmeyer, 1976; Mulvany et al. 1980a, b; Vanhoutte, 1978; Webb and Vanhoutte, 1979; and Whall et al. 1980).

It is argued by Mulvany et al. (1979) that since they detect, after uptake 1 inhibition, an elevated postjunctional sensitivity to noradrenaline in mesenteric vessels from young SHR (6-8 weeks) then this greater intrinsic smooth muscle sensitivity is likely to be a primary factor responsible for the development of hypertension in the SHR. If, as has been suggested (see Vanhoutte et al. 1980; Webb et al. 1981), the elevated uptake 1 activity is a compensatory mechanism in the SHR whereby the nerve terminal attempts to decrease the postjunctional effectiveness of released noradrenaline, then an elevated postjunctional sensitivity to NA in the SHR should be seen in the non-innervated thoracic aorta preparation. It is apparent that this is not the case, suggesting that the presence of the sympathetic innervation may itself play a role in elevating postjunctional sensitivity to NA in the SHR.

TROPHIC INFLUENCES IN SHR

That differences in neuronal influences may affect postjunctional properties in hypertension is supported by

the cross-transplantation experiments, of caudal arteries to the anterior eye chamber, that have been described by Campbell et al. (1981) and Abel and Hermsmeyer (1981). In these studies, tail arteries from 2 week old WKY (or SHR), when transplanted into the eye chamber of 12 - 16 week old SHR (or WKY), developed a vascular membrane potential and noradrenaline sensitivity that is normally measured in host tissues. This was true only if the transplants received sympathetic innervation, suggesting that the sympathetic nervous system exerted a trophic influence on the chemical sensitivity of the smooth muscle cells (Abel and Hermsmeyer, 1981). If, as Abel and Hermsmeyer suggested, a trophic effect of sympathetic nerves regulated postjunctional noradrenaline sensitivity, then a vessel with sparce innervation would show little change in sensitivity. In the present study, this was evident in the results with the aorta, since its sensitivity was not changed at a time when an innervated arterial smooth muscle (tail artery) exhibited enhanced sensitivity (tables 17, 18, page 128 and 130).

To determine if there indeed was an obligatory role for a sympathetic nervous influence possibly via a trophic factor, on regulation of vascular smooth muscle sensitivity in the SHR, the tonic sympathetic discharge to the vasculature was disrupted by breeding animals treated chronically with α-methyldopa.

The results from such a study indicated that while the blood pressure of the SHR was controlled (table 22, page 139

α-methyldopa failed to alter the uptake 1 and ED_{50} characteristics of SHR, F_1 and WKY smooth muscle preparations (tables 23 to 27, pages 142 to 149). These results suggested that the elevated uptake 1 of SHR observed in tail artery strips of 12 - 16 week old rats was possibly the result of genetically determined properties and not secondary to the elevated blood pressure or increased sympathetic activity. A similar finding was reported by Mulvany et al. (1981b) who found that chronic denervation with 6-hydroxydopamine did not affect the increased calcium sensitivity of resistance vessels from SHR.

Since α-methyldopa decreased sympathetic traffic without affecting the uptake abnormality, it may also be concluded that sympathetic activity was not essential to the abnormality. However, other mechanisms could still be operative and have contributed to the hypertensive abnormality. Antihypertensive therapy in the SHR may simply have masked the expression of this abnormality as an increased blood pressure.

Since the changes in smooth muscle preparations are still present in "normotensive" SHR, produced by α-methyldopa treatment or by chemical denervation (Mulvany et al. 1981), they are not clearly directly related to the etiology of the disease but may be unique to the strain of the rat. The noradrenaline sensitivity (ED_{50}) and uptake 1 activity was therefore measured in another strain of genetically hypertensive rats, the Dahl DS and DR rats (study 2).

DAHL RAT STUDIES

There is a dearth of information regarding the role of structural adaptations and changes in calcium handling by vascular smooth muscle in this particular strain of rats, and thus these factors, considered by many as important factors influencing vascular reactivity (see Folkow, 1982 were compared in DS and DR rats.

The present study clearly indicates that the neuronal accumulation of noradrenaline, and the underlying sensitivity of the smooth muscle cells were both identical for vascular (aorta, portal vein, tail artery) and non-vascular (anococcygeus) smooth muscle preparations obtained from DS and DR rats (table 29, page 153); however, there was a trend for uptake 1 activity to be lower in tissues from DS rats.

The chronotropic response to isoprenaline in right atria isolated from DS and DR rat hearts were similar (figure 21, page 217). This contrasts with a reduced β-adrenoceptor responsiveness of cardiac tissues from SHR (summarized by Vanhoutte et al 1980).

Perfused mesenteric vascular beds from DS and DR rats were compared for their responsiveness to noradrenaline, phenylephrine and serotonin. No differences in the characeristics of the dose-response curves were detected, indicating that no alterations in either pharmacological sensitivity or structural parameters had occured in this

vascular bed despite the large increase in blood pressure (fig. 13 to 18, pages 201 to 211). Takashita and Mark (1978) have shown that at maximal vasodilation, the hindquarter perfusion pressures of DS and DR rats are identical. Thus, both the results of this study using the isolated perfused mesenteric bed, and the Takashita and Mark study indicate that structural alterations in the vascular bed are unlikely to be a contributory factor to the elevated peripheral resistance in the DS rat.

Therefore, while the results of study 1 relating uptake 1 and the mean arterial pressure of SHR and genetically related animals lend support to Vanhoutte's suggestion "that the adrenergic neuroeffector interaction undergoes a long *term adaptation in the* blood vessels of hypertensive animals", (Vanhoutte, 1980) the results of the α-methyldopa study in SHR and the Dahl rat study where there was a trend for reduced uptake 1 would indicate that neuronal mechanisms in the SHR are possibly strain, and not blood pressure related effects.

It was also of interest to determine if the elevated <u>in vivo</u> pressor responsiveness of DS rats was related to a reduced capacity to sequester or remove Ca^{2+} from the contractile proteins.

One method of assessing intrinsic differences in vascular smooth muscle from hypertensive and normotensive animals is to compare the ability of precontracted tissues to relax, *either by removal of the stimulus or by using a*

vasocilator. Previous studies in the SHR (Field et al, 1972; Cohen and Berkowitz, 1976) indicated that relaxation rates in the SHR were retarded when compared to normotensive controls, suggesting that there was an abnormality in the ability of vascular smooth muscle from the SHR to sequester or outwardly pump intracellular Ca^{2+}. This hypothesis is supported by the reported decreased activity of vascular plasma membrane calcium pump activity (Daniel and Kwan, 1981). The results of the current study, however, suggest no differences in the ability of aorta from DS and DR rats to relax, and thus it can be inferred that the ability of tissues from both DS and DR to remove calcium from the contractile proteins were similar at least for the thoracic aorta (Fig. 21 to 23, pages 217 to 221).

While there appeared to be little difference in smooth muscle sensitivity from DS and DR, a hypothesis by Blaustein (1977) would argue for alterations in calcium regulation by smooth muscle from DS. The experiments of Tobian et al. (1979b) confirmed the presence of a circulating factor in the plasma of DS rats capable of abolishing the sodium gradient across smooth muscle by acting on the sodium-pump. Blaustein (1977) suggested that when the internal sodium ion concentration was increased (e.g. by pump inhibition in low renin forms of hypertension), the extrusion of calcium (by a Na-Ca exchange) would be retarded. This ultimately would lead to an increased resting tone. The possiblity that the Ca^{2+} permeability of the plasma membrane of the DS rat was

increased is supported by studies demonstrating that the thoracic aortae from the DS rat, but not the DR rats, responded mechanically to La^{3+}, or an increase in extracellular H^+ concentration (table 34, page 163).

Lanthanum (La^{3+}) contractions in aortae

The response to La^{3+} in the aortae from DS rat increased with the level of NaCl in the diet, and hence the B.P., but was absent in young prehypertensive DS rats or adult rats whose B.P. had been reduced or normalized by antihypertensive drug therapy. The response to La^{3+} in tissues from DS rats thus reflected a change that was secondary to the elevated blood pressure. The significance of the response to La^{3+} which presumably reflects alterations in the Ca^{2+} binding/permeability properties of the VSM membrane, to the elevation and maintenance of B.P. in the DS rat has not yet been determined. It is of interest to note the absence of the response to La^{3+} in aortic tissues from the DR rat since the Dahl rats are derived from a Sprague-Dawley source. Aortic tissues from Sprague-Dawley rats also failed to respond to La^{3+} (present study).

A genetic analysis of the responsiveness to cobalt (Co^{2+}) of aortic tissues, from SHR and the DR rat as well as F_1 and F_2 and backcross animals resulting from the mating of the SHR with the DR revealed an autosomal locus that controlled the vascular smooth muscle response to Co^{2+},

exhibiting a partial dominant inheritance, and appeared to be a contributing factor to the increased in B.P. (Rapp, 1982a). The study on the sensitivity to Co^{2+} on tissues from animals with a range of blood pressures from hypertensive to normotensive revealed a similar maximal contractile response to the ion. The responsiveness to low concentrations of Co^{2+} however was higher in tissues from the SHR and F_1 animals than in the DR rat. In our laboratory, we have observed that the response to Co^{2+} in aortic tissues from the SHR is not accompanied by a pH change and that aortic tissues from the DR are unresponsive to either La^{3+} or H^+. Thus the response to Co^{2+} may result from different cellular changes than those that support the response to La^{3+} or H^+.

Since the response to La^{3+} was absent in prehypertensive and normotensive DS rats it may be concluded that this phenomenon is secondary to the rise in blood pressure. Rapp (1982a) suggested a correlation between the blood pressure the altered cellular mechanisms which resulted in mechanical responses to non-physiological ions such as Co^{2+} and La^{3+}. However, Rapp's observations of a linear correlation between the two parameters were derived from experiments inwhich the normotensive control for the SHR and F_1 rats was the DR, a Sprague-Dawley derived species shown in the present study not to respond to La^{3+}. Another successful attempt to correlate a physiological parameter to the SHR blood pressure also used Wistar-Lewis strain as a

control (Judy et al, 1979). When the genetically appropriate WKY strain was used no correlation was observed (Hendley et al, 1983).

It is conceivable that the relationship between the La^{3+} response and blood pressure in the SHR may reflect a similar situation and may be highly dependent on the choice of the strain of the control normotensive rat.

The analysis of the response to La^{3+} indicates the *presence of a blood pressure independent response, as* indicated by the significant tension development recorded in the WKY of all three age groups, and a response which increased as the mean blood pressure of the SHR group increased with age (table 34, page 163). The response to La^{3+} observed in the F_1, F_2 and WKY animals also increased with age and there was a non-significant trend for the response to be greater in the F_1 and F_2 rats than in the WKY rats. However, the response to La^{3+} in the $BC_1(S)$ and $BC_1(W)$ rats was not significantly different from WKY rats. A comparison of tissues from male and female SHR, WKY, F_1 and F_2 at both 6 - 8 and 12 - 16 weeks indicated that the magnitude of the response to La^{3+} was not sex-linked. Chronic antihypertensive therapy with α-methyldopa reduced blood pressure of SHR, F_1 and WKY but did not affect the La^{3+} response in tissues from these rats. Other investigations in our laboratory also indicated that chronic timolol treatment from conception (Goldberg and Triggle, 1977) or hydrochlorothizide treatment (Corbett and Triggle,

unpublished) did not affect the response to La^{3+} in SHR and WKY. Clearly the response to La^{3+} cannot be considered to be a distinquishing feature of the SHR (Shibata et al. 1973; Bohr, 1974b), since the WKY also have the genetic characteristics determining the response.

When the maximum tension developing capacity of the tissues from the various groups of rats was compared, the response to La^{3+}, expressed as mg tension/mg wet weight of tissue, was not significantly different between the groups, indicating that it was the maximum noradrenaline response of the tissue that decreased with the increase in B.P. of the animals (fig 30, page 235). The decreased contractility of SHR vasculature has been discussed in the introduction section of the thesis (page 10).

Since Sprague-Dawley rats, DR and Wistar rats did not show a response to La^{3+}, then inclusion of these rats in F_1, F_2 etc. and backcross breeding experiments would be expected to improve the correlation between the response to La^{3+} and blood pressure in SHR related animals. An explanation for this is that in the SHR and WKY derived crosses, blood pressure is not the sole determining factor in the response to La^{3+} since other genetic factors independent of blood pressure clearly play a major role in determining the responsiveness to La^{3+} in the rats used in the present study. Similar conclusions were reported by Tanase et al. (1982) who were unable to segregate left ventricular hypertrophy and elevated blood pressure in SHR and WKY derived rats.

In summary the study of the sensitivity of aortic tissues to lanthanum demonstrates that tissues from DS, but not DR, rats made hypertensive with salt diets develop a paradoxical responsiveness to La^{3+}. This response to La^{3+} is secondary to the development of the hypertension and the response can be prevented by controlling the development of the hypertension with either hydrochlorothiazide or MK421. An apparent elevated response to La^{3+} in SHR, when related to the maximal tissue response to noradrenaline in genetically related animals, has been shown to reflect a blood pressure dependent decreased responsiveness to noradrenaline. The magnitude of the noradrenaline responsiveness is correlated negatively and significantly as an inverse relationship to the elevated blood pressure of the rat and is unaffected by partially controlling the development of hypertension with α-methyldopa therapy. This implies that decreased noradrenaline responsiveness represents a primary genetically determined defect of VSM from the hypertensive rats. It is apparent that the choice of the control normotensive strain of rat will greatly influence the interpretation of the results and, hence, the significance of the findings to the etiology of hypertension in the SHR.

CONCLUSION

When SHR and WKY are compared, many differences, including a blood pressure difference, are noted. In this thesis, three well defined differences between SHR and WKY were studied in relation to hypertension (see objectives of the thesis). Three approaches were taken to examine these changes:- a) by designing a breeding program to produce animals with a spectrum of blood pressures (ranging between SHR and WKY levels) and then relating selected observations to the mean arterial pressure, b) by studying the phenomena in another model of genetic hypertension, the Dahl strain of salt-sensitive rats and c) by producing "normotensive" SHR and Dahl rats by treatment with antihypertensive drugs.

It has been suggested that alteration in blood vessel wall thickness plays a primary role in hypertension (Folkow, 1982). While it is accepted that this change occurs in the SHR, the present study demonstrates that the increased reactivity and contractility observed in perfused vascular beds of SHR were not present in age-matched Dahl rats fed either 0.3% or 8.0% dietary NaCl. Therefore, medial thickening as indicated by the slope and maxima of dose-response curves from perfused vascular beds is indicated in only the one (SHR) model of genetic hypertension, and cannot explain the increased peripheral resistance of Dahl rats.

Another possible explanation for the increased peripheral resistance in SHR is an increased sensitivity of

blood vessels to noradrenaline. This increased sensitivity of blood vessels from SHR can only be shown in vitro when the influence of uptake 1 is eliminated. Similar studies in Dahl rats showed no differences in uptake 1 or noradrenaline sensitivity were noted when DS and DR were compared. Clearly, alterations in vascular α-adrenoceptor sensitivity do not occur in the Dahl model of hypertension, and cannot be responsible for the difference in blood pressure (resting or stimulated) between DS and DR. On the other hand, it was evidently easier to correlate the mean arterial pressure of SHR and related animals to uptake 1 rather than to differences in post-synaptic α-adrenoceptor sensitivity. However, this tendency for SHR and related animals to have an increased neuronal uptake ability appeared to be present regardless of the blood pressure, since it was unaffected by antihypertensive treatment with α-methyldopa.

Another mechanism thought to be present in vessels from hypertensive animals is an increased sensitivity to intracellular calcium. This was studied by examining the response of aortae from SHR (and related animals) and Dahl rats to the mechanical response to lanthanum. La^{3+} has been suggested to produce a contractile response by displacing membrane bound Ca^{2+}, which then interacts with the cellular contractile machinery. This response to La^{3+} is greater in tissues from SHR either because tissues from SHR have an increased membrane permeability to Ca^{2+} or a reduced ability to remove Ca^{2+} from the contractile proteins. In this

study, it was shown indirectly that the ability to sequester intracellular Ca^{2+} was similar in aortae from DS and DR, while an increased membrane permeability to Ca^{2+} occured secondary to feeding DS (and not DR) with diets rich in sodium. However, in a comparison of SHR to WKY rats the response to La^{3+} per se is not increased in SHR, as has been suggested by other workers. Rather, it results from a reduced noradrenaline activated tension generating ability such that when the response to La^{3+} is normalized using the noradrenaline response as a standard, a correlation exists between increased blood pressure and the response to lanthanum. The reduced noradrenaline response of aortae from SHR, and the response to La^{3+} were not affected by antihypertensive therapy. The results of the study also suggested that the WKY rat, while normotensive, also possessed the genetic material regulating the response to La^{3+} and that other normotensive strains (Wistar and Sprague-Dawley) lacked this response to La^{3+}, therefore suggesting caution when choosing the normotensive control whenever attempts are made to correlate any parameter to blood pressure in SHR and related animals.

SUMMARY

Experiments were designed to answer the questions raised earlier in the discussion of the objectives of the thesis. A summary of the observations follows:

A. The noradrenaline ED_{50} ratio, a reflection of uptake 1, increased with blood pressure and age. Increased postsynaptic sensitivity was evident in only arterial smooth muscle of very old SHR.

B. Uptake 1 activity was increased in arterial smooth muscle of SHR at 6-8, 12-16 and > 52 weeks of age. In other smooth muscle (venous and non-vascular) uptake 1 was increased only in very old SHR.

C. Rats with blood pressures between SHR and WKY levels were bred. The correlation between arterial pressure and uptake 1 in the tail artery was present in the three age groups studied. For the portal vein and anococygeus, the correlatign was significant only in the > 52 week age group.

D. Experiments with α-methyldopa suggested that the increased uptake 1 activity in the SHR and related animals was not related to the increased tonic sympathetic-discharge in SHR.

E. The changes in neuronal uptake and sensitivity to noradrenaline in SHR were not present in another mode of genetic hypertension, the Dahl DS and DR rats.

F. The La^{3+}-response was found not to be a distinguishing feature of the SHR, and was thus most likely a strain-related characteristic in Kyoto-Wistar derived rats.

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