THE DEVELOPMENT AND MAINTENANCE OF EXPERIMENTAL ALDOSTERONE HYPERTENSION IN THE RAT: EVIDENCE FOR A MECHANISM OTHER THAN PERIPHERAL VASCULAR AUTOREGULATION FOR THE INCREASED TOTAL PERIPHERAL VASCULAR RESISTANCE

A THESIS

Presented to the

UNIVERSITY OF MANITOBA

In Partial Fulfillment of the Requirements

for the Degree of

MASTER OF SCIENCE

By

CHRISTINA R. CARRIER

January, 1978

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS

My advisory committee consisted of three fine people: Dr. Peter Gaskell, Dr. John McKenzie and Dr. Stefan Carter. Each, in his own way, has added much more to my life than an understanding of cardiovascular physiology, and for this I am grateful.

It is with pleasure that I thank my supervisor, Dr. Gaskell, for providing me with the opportunity to work and learn under his direction. His guidance and patience, with me and with the research project, have been appreciated. I thank Dr. McKenzie for the opportunity to apply to the clinical situation that which I learned in the classroom and laboratory. He showed me that there is more to treating hypertensive patients than just reducing the blood pressure. I thank Dr. Carter for his continuing interest in the progress of my research and for his pertinent questions that have taught me to question things that I once might have taken for granted.

In addition, I would like to thank Mrs. Donna Talbot for her willing technical assistance in the laboratory and Miss Janet Greer for typing this thesis.

ABSTRACT

Peripheral vascular autoregulation at the level of the whole body has been invoked as an explanation for the increased total peripheral resistance (TPR) seen in many forms of volume dependent hypertension. An increased critical opening pressure (COP) has been found in the skin vessels in the tail of the rat made hypertensive with aldosterone. Aldosterone hypertension is believed to be a model of volume dependent hypertension. The COP is a measure of the contraction force of the vascular smooth muscle in the resistance vessels. If autoregulation is responsible for the increased resistance to flow offered by the resistance vessels, then the increase in COP seen in the rat should be part of the autoregulation process.

An experiment was conducted to test the autoregulation theory as an explanation for increased TPR in volume dependent forms of hypertension. An apparatus was designed to apply a continuous, graded increase in external pressure to the skin vessels in the tail of the rat for as long as 4 weeks while the rats became hypertensive from continuous infusion of aldosterone. This increased external pressure was applied in order to prevent increased autoregulatory stimuli (increased transmural pressure and blood flow) from acting on the tail vessels while the rat became hypertensive and went into the chronic stages of the hypertension. Provision was made to keep the tail warm while the increased external pressure was applied.

Test rats received aldosterone (dose rate about 5 µg/100g/d) in a vehicle of 15% alcohol in 5% dextrose in water and had a counterpressure of 25 to 35 mmHg applied to their tails before the hypertension developed. The counterpressure was increased as the hypertension progressed. Control rats received the vehicle only and had a counterpressure of 25-35 mmHg

applied to their tails. All 5 test rats became hypertensive, with a group mean increase in SBP of over 20%. None of the control rats became hypertensive. Their systolic blood pressures and critical opening pressures were essentially unchanged throughout the course of the experiment. It was found that the COP of the tail vessels of the hypertensive rats increased by over 100%, despite application of the increased external pressure to the tail. Elevated values for the SBP and COP in the test rats were also found after administering a ganglion blocking agent.

These results provide no evidence for peripheral vascular autoregulation as an explanation for the increase in COP of the tail vessels in aldosterone hypertension in the rat. These results also suggest that some mechanism other than autoregulation is responsible for the increased TPR in volume dependent hypertension.

The increase in SBP and COP occurs a few days after the start of excess aldosterone administration. In an experiment to investigate the influence of aldosterone dose rate on the delay of onset of increased SBP and COP, it was found that the delay was longer when low aldosterone dose rates were administered. This delay to the onset of increased SBP and COP suggests taht some new event, perhaps the release of a vasoconstrictor hormone, might be involved in the hypertension.

The delayed increase in SBP and COP may be related to renal escape from the influence of aldosterone. Release of a natriuretic hormone that is also a vasoconstrictor may be causing both events.

LIST OF FIGURES

Project 1

Test of the hypothesis of peripheral vascular autoregulation as an explanation for the increased critical opening pressure (COP) in the rat made hypertensive with aldosterone.

Project 2

An experiment to determine the influence of aldosterone dose rate on the delay to onset of increased systolic blood pressure and COP in the rat.

Fig. 17 Results from rat #14, aldosterone dose rate 4.5 μg/100g/d.

Fig. 18 Length of delay to onset of aldosterone hypertension in the rat vs dose rate of aldosterone.

LIST OF TABLES

INTRODUCTION AND LITERATURE REVIEW

The Peripheral Vascular Autoregulation Theory as an Explanation for Increased Total Peripheral Resistance in Volume Dependent forms of Hypertension

Introduction

Hypertension is the term applied to the sustained regulation of the arterial blood pressure at levels above some arbitrarily chosen "normal" value, usually 140-150/90. Maintenance of the blood pressure at hypertensive levels is associated with a greatly increased incidence of vascular damage to the heart, kidneys and brain, which can by itself contribute to the hypertensive condition by causing a further elevation of the blood pressure.

Hypertension itself is not a specific disease entity, it is a sign. In most cases, the pathogenesis of the hypertension is poorly understood. There are some clinical and experimental situations in which the hypertension is secondary to some defined cardiovascular, renovascular or hormonal derangement, but even in these situations, the mechanism of the sustained elevation in arterial pressure is not clear. Most human hypertension falls into the class of essential, or primary hypertension, with no clearly defined derangement save for the elevated blood pressure and an increase in the total peripheral vascular resistance.

Arterial pressure is a function of the cardiac output and the total peripheral resistance offered by the vasculature. Much of the research into hypertension has involved studying possible vasoconstrictor mechanisms and the role of Na^+ and H_2O retention in hypertension.

In some forms of hypertension, the increased TPR can be attributed to high circulating levels of known vasoconstrictors, i.e. angiotensin II. This appears to be the mechanism of the hypertension resulting from stenosis of a renal artery in man, and in the early phases of experimental one and two kidney Goldblatt hypertension. Other forms of hypertension, however, present with a normal or only slightly elevated cardiac output and an increased total peripheral resistance in the absence of high levels of known vasoconstrictors. This includes many examples of essential hypertension, the established phase of one kidney Goldblatt hypertension and the hypertension caused by excess mineralocorticoid administration. The mechanism of the increased TPR in these forms of hypertension is unclear, but an increase in exchangeable Na^+ and/or an increase in ECF volume are believed to be involved.

In this thesis, the term "volume dependent hypertension" refers to those forms of hypertension in which increased retention of Na^+ and H_2O is believed to be involved in the development or maintenance of the hypertension. This includes the following forms of hypertension:

1. that associated with excess mineralocorticoid or glucocorticoid secretion by an abnormally functioning endocrine system, ie Conn's syndrome (excess aldosterone), Cushing's syndrome (excess glucocorticoids).
2. the chronic stage of one kidney Goldblatt hypertension, where an early but transient increase in renin and angiotensin II releases aldosterone, causing the retention of Na^+ and H_2O and in some manner leading to a sustained increase in blood pressure.
3. the hypertension seen sometimes in renal failure, where renin levels appear normal in the presence of an expanded ECF volume.

4. Many examples of essential hypertension. In this broad category of hypertension, it has recently been found that there are low, normal and high renin subtypes. The low renin form of essential hypertension appears to be a volume expanded state, with levels of aldosterone being inappropriately high for the existing low levels of renin.

It is not clearly understood how an increased retention of Na^+ and H_2O can lead to a sustained elevation of arterial pressure.

Concept of Peripheral Vascular Autoregulation

Studies of blood flow in a number of tissues have shown a tendency for flow to return to its previous value, suitable for the needs of the tissue, when the rate of flow is altered by a change in perfusion pressure. This autoregulation of blood flow is independent of the vasomotor nerves.

Two mechanisms have been proposed to account for the ability of tissues to regulate their own blood flow:

1. metabolic hypothesis, whereby an increased blood flow through a tissue causes an increased washout of vasodilator metabolites, with consequent relief of their vasodilator effect and return of blood flow toward normal. No one specific metabolite has been assigned this role.
2. myogenic hypothesis, first suggested by Bayliss (1902), citing the ability of vascular smooth muscle to contract with an increase in stretch and to relax with a decrease in stretch. It is thought now that an increased perfusion pressure at the level of the resistance vessels causes these vessels to be stretched, triggering a myogenic increase in smooth muscle contraction force, resulting in a decrease in vessel lumen and return of flow toward normal, despite the increased perfusion pressure.

It is also possible that increased stretch at the level of the precapillary sphincters increases vasomotion, closing capillary beds more frequently, and reducing flow toward normal.

Whatever the mechanism, most tissues are well able to quickly (seconds to minutes) alter their resistance to blood flow in order to maintain flow at a constant level despite changes in the perfusion pressure.

Autoregulation of blood flow at the level of the whole body has been invoked as an explanation for the increased total peripheral resistance (TPR) seen in many forms of volume dependent hypertension, both human and experimental. I would like here to misquote Pickering (1968) and say that "My difficulty is that the autoregulation hypothesis, as a means to explain the increased TPR, is not one which can easily be refuted; it can always be invoked if other explanations prove wanting."

Support for this Concept as an Explanation for Increased Total Peripheral Resistance in Hypertension in which there appears to have been some Volume Expansion.

Several investigators have championed the idea that autoregulation of the peripheral vessels is a major factor in the pathogenesis of those forms of hypertension in which a high TPR cannot be attributed to high circulating levels of known vasoconstrictors. This includes most chronic forms of hypertension: the experimental and human forms of renovascular and mineralocorticoid hypertension and many essential hypertensions.

In his paper on extrarenal factors involved in the pathogenesis of hypertension, Ledingham (1956) wondered if certain pressor factors may be cardioactive rather than vasoactive. He then referred to Bayliss' (1902) concept of local myogenic activity by which arteriolar smooth muscle can contract in response to an increase in intravascular pressure, and suggested that a more forcible contraction of the heart, ie an increased

cardiac output (CO), might be primary in the genesis of hypertension, with an increase in tone of the resistance vessels occurring secondary to the increased CO, mediated through the local myogenic activity.

Ledingham (1971) has developed this idea further. He reported on a series of studies in which the mean arterial BP, CO, TPR, heart rate and stroke volume were monitored in trained conscious, one-kidney Goldblatt rats as their hypertension progressed from the acute to the chronic (25 days) stages. In these rats it was found that there was a sharp increase in mean arterial BP within 2 hours of operation and a more gradual increase as the hypertension became chronic. The cardiac output of the test rats fell below that of sham operated controls for the first 5 days, then consistently exceeded the cardiac output of the control group for the remainder of the experiment. Calculation of the TPR showed an immediate sharp increase at 2 hours and a gradual subsequent rise as the hypertension progressed. Ledingham stated that at all stages, the increased blood pressure is mainly attributable to the increased resistance. A similar series of studies, in which extracellular fluid (ECF) volume and cardiac output were found to be transiently increased in the early stages of the hypertension, has also been reported (Ledingham and Cohen, 1964). From the hemodynamic changes observed in these studies and with the knowledge that high renin levels are seen in only the first few days of one-kidney Goldblatt hypertension, Ledingham proposed the following sequence of events to explain the increased TPR seen in this experimental model of hypertension:

-increased release of renin and production of angiotensin II following renal artery constriction and removal of the contralateral

kidney.

-peripheral vasoconstriction mediated by angiotensin II, with increase in BP.

-stimulation of aldosterone secretion by angiotensin II, with increased retention of Na^+ and H_2O and an increase in ECF volume and plasma volume.

-increased plasma volume leads to increased atrial filling pressure and increased CO, which contributes to the increased BP.

-the increased CO results in perfusion of the tissues at levels beyond their metabolic needs, causing

-autoregulation of the peripheral vessels, which reduced tissue perfusion and increases the TPR.

-the increased TPR raises the blood pressure and reflexly reduces CO to normal or only slightly elevated levels.

-the increased BP also removes the stimulus for increased renin secretion, so plasma renin, angiotensin II and aldosterone levels return towards normal.

So the hypertension which originally was vasoconstrictor in origin appears, in the chronic phase, to be volume dependent, with increased TPR on the basis of autoregulation.

Guyton and his colleagues have strongly supported the hypothesis that peripheral autoregulation can account for the increased TPR seen in volume dependent hypertensions. An experiment to study total systemic autoregulation in the dog following destruction of the central nervous system was conducted by Granger & Guyton (1969) in order to determine if the whole body has quantitatively significant autoregulatory capabilities. The experiment involved making step changes in the arterial blood pressure and monitoring O_2 consumption and A-V O_2 difference in order to follow

changes in the cardiac output. Arterial blood pressure was controlled by adjusting the height of a blood filled reservoir that had been connected to the femoral artery. Adjusting the BP in this manner changed both the circulating blood volume and the CO. They found, however, that the CO would return toward its previous value and reach a new steady state in a mean of 35 minutes if the pressure increment was large (25-50 mmHg) with less time required if the pressure change was small. Granger and Guyton interpreted this response as a demonstration of whole body autoregulation that requires long periods of time in which to become established, and concluded that whole body autoregulation would significantly increase the TPR following an increase in CO.

There are difficulties in accepting this conclusion on the basis of this experiment. First, the usual autoregulation response that occurs in 1-2 minutes in individual tissues could not be demonstrated. And secondly, good flow regulation was achieved at low pressures, but not at higher, more physiologic pressures. The authors did not address themselves to these problems.

In a later paper (Guyton, Coleman & Norman, 1974), it was again suggested that autoregulation of blood flow, both short term and long term, can account for the increased TPR seen in the hypertensions where expansion of the body fluids and an increase in CO have been early events. Guyton has also speculated that with time, peripheral autoregulation may become increasingly intense, creating a tremendously increased TPR in the presence of a CO that is only slightly elevated (Guyton and Coleman, 1969). His explanation of this long term component of auto-regulation remains vague.

Despite Guyton's belief that some form of autoregulation of the peripheral vessels can account for the increased TPR in volume dependent hypertension, he feels that an increase in TPR is inconsequential as far as longterm pressure control is concerned. His systems analysis of arterial pressure regulation (Guyton and Coleman, 1969) predicts that no factor (ie increased TPR) can cause continued elevation of arterial pressure unless it in some way affects the kidneys and disturbs the body fluid volume control mechanisms. This idea was echoed a few years later by Guyton, Coleman and Norman (1974) and Tobian (1974).

Further support for the concept that some form of autoregulation can account for the increased TPR in volume dependent hypertension comes from a study on blood pressure regulation in anephric man, reported by Coleman et al (1970). They found that salt and water loading in these people, through an appropriate adjustment of the hemodialysis procedure, resulted in an increased BP and TPR and a transiently increased cardiac output. The increase in TPR occurred a few days after the CO increased and persisted when CO returned to normal levels. They believe the increase in TPR was a long-term autoregulatory response of the vessels to overperfusion of the tissues by the increased CO. They postulated that this long-term autoregulation involved either a decrease in average lumen size of the vessels, or a decrease in the total number of open vessels, but gave no mechansims for these processes.

Peer Evaluation of this Proposed Mechanism as an Explanation for Increased TPR in Volume Dependent Hypertension

In a general review, Tobian (1974) proposed a sequence very similar to Ledingham's (1971) to explain the development of a sustained elevation of arterial pressure in conditions in which some early defect results

in an inappropriately high ECF volume and a high "effective" blood volume. In Tobian's scheme, a high effective blood volume would increase venous filling pressure and CO, which would, by itself, elevate arterial pressure. Overperfusion of the tissues by this increased cardiac output is thought to cause an autoregulation of blood flow in many tissues via increased vasoconstriction of the resistance vessels, thereby increasing the TPR. In combination with the elevated cardiac output, the increased TPR raises the arterial blood pressure even more, causing a reflex reduction of the CO to about normal levels. This leaves a hypertensive condition characterized by a high TPR and nearly normal CO. Tobian then pointed out that this hypertension could be sustained only as long as the ECF volume continued to be elevated, presumably through some renal abnormality. He also mentioned that there seems to be some genetic susceptibility required before a high ECF volume can produce this hypertension.

It is generally recognized that an alteration of the salt and water balance seems to be involved in the hypertension that sometimes accompanies renal failure in man. These patients frequently show volume expanded characteristics, having a greatly increased exchangeable sodium when compared with those in renal failure who remain normotensive (Ledingham, 1971). In his paper dealing with hypertension in chronic renal failure, Schalekamp et al (1973) mentioned that an increased CO is often found in hypertensive patients in renal failure, and that peripheral resistance is usually increased in such patients as well. Schalekamp is aware of Ledingham's explanation for increased TPR on the basis of autoregulation following an increase in CO, but has reservations about applying it to the situation in man. Schalekamp cited a study by Kim et al (1972) in which

it was found that while patients in end stage renal disease tend to have a significantly elevated cardiac output, some patients remain normotensive and have a normal total peripheral resistance. On this basis, Schalekamp feels that the evidence for peripheral vascular autoregulation operating to increase the peripheral resistance in chronic renal failure in man is not as good as it is in experimental renal hypertension. He thinks instead that the rise in blood pressure in chronic renal failure is due to the vasoconstrictor effects of angiotensin II which circulates at levels inappropriately high for the prevailing exchangeable sodium.

Laragh does not consider autoregulation in his vasoconstrictor-volume analysis of hypertension (1973). He describes pure volume hypertension as being characterized by minimal vasoconstrictor activity (meaning low plasma renin activity) and suggests that the arterioles would be relatively dilated and distended in the presence of high extracellular fluid and plasma volumes. His understanding of volume expanded hypertension is that there is a renal inability to maintain sodium and water balance at lower pressures, so there results an overfilling of the available vascular space up to that pressure at which sodium and water balance can be maintained. He used this concept as an explanation for the hypertension that develops during excess mineralcorticoid administration and for the increased blood pressure seen in the established phase of one-kidney Goldblatt hypertension.

In a recent review, Davis (1977) commented on Ledingham's and Guyton's theory that autoregulation can account for the increased TPR in volume dependent hypertension. He called it an attractive theory lacking in support from a number of other studies, and pointed out that the occurrence of whole body autoregulation over an extended period of time

has not been demonstrated experimentally.

Establishing the hypothesis of whole body autoregulation as an explanation for increased TPR depends on 1) demonstrating that conditions are such that autoregulation is likely to occur, and 2) the exclusion of other vasoconstrictor mechanisms. As understated by Ledingham (1971), "the testing of this hypothesis presents physiologists with a most complex haemodynamic problem."

The Present Investigation: An Approach and Appraisal of the Hypothesis of Whole Body Autoregulation

We have been interested for some time in the cause of the increased TPR seen in volume dependent forms of hypertension. We are particularly interested in factors that might increase the contraction force of the smooth muscle in the resistance vessels. We suspect that there is some other vasoconstrictor mechanism (agent) operating in volume expanded hypertension, and that the increased resistance to flow offered by these vessels is not entirely due to autoregulation of flow.

To study factors that might influence the contraction force of the smooth muscle in the resistance vessels, one first would like to have a fairly direct method of measuring it. Burton (1951) developed the concept of critical closure of small vessels at positive perfusion pressures. The critical closing pressure (CCP) is the maximum transmural pressure against which the unstretched vessel will close by virtue of the force of contraction of the smooth muscle in its wall. The CCP measurement is an index of smooth muscle contraction force when the vessel is unstretched and is a more direct measure of vasomotor tone than the pressure-flow studies that have been used in the past.

Nichol et al (1951) found that vessels would open, as well as close, at the same critical pressure. This was confirmed by Gaskell and Krisman (1958) as they made direct visual measurements of the CCP and critical opening pressure (COP) of the vessels supplying the capillary loops of the nailfold. In practice it has been found more convenient to measure the critical opening pressure. Studies from this laboratory have involved measurements of the COP of vessels in forearm and digital skin and in the skin of the tail of the rat under a number of experimental and pathological circumstances.

As used in this laboratory, measurement of the COP is a convenient, painless, noninvasive technique for obtaining a measure of the contraction force of the smooth muscle in the resistance vessels of the skin. However, it is important to recognize one of the limitations of the COP measurement: the COP that is measured in an area of tissue is that of the vessels with the lowest COP. These vessels may not be those that provide the major proportion of the resistance to flow in that tissue, or indeed, in the whole body. The COP that is measured, then, may not reflect the tension of the smooth muscle in those resistance vessels that are the major determinants of TPR. This was mentioned by Nichol et al (1951) and was shown quite dramatically by Gaskell (1967) when he infused angiotensin II 4 ng/kg/min iv into normotensive subjects and found an increase in both the systemic blood pressure and the digital flow resistance, as expected, but at the same time there was a decrease in the measured COP of the digital skin vessels. With care, however, the COP measurement can be a useful tool in looking at the contraction force of the smooth muscle in the resistance vessels.

We have used the COP measurement to investigate changes in vascular smooth muscle contraction force in a number of what one might think are volume dependent hypertensions. We have found that the COP is elevated in the skin vessels of the tail of the rat in 1) the chronic stage of one-kidney Goldblatt hypertension (Darke, Nair and Gaskell, 1976), 2) the hypertension produced by administration of deoxycorticosterone acetate (DOCA) with 1% NaCl for drinking water (Darke et al, 1976), and 3) the hypertension produced by administration of aldosterone alone (Darke et al, 1977). In all three forms of hypertension, the COP measured after ganglion blockade is greater than normotensive blocked values, so the increase in COP cannot be attributed entirely to neurogenic influences.

The hypertension produced in the rat by administering aldosterone (continuous infusion, dose rate about 5 μg/100g/d) is particularly interesting in that the onset of the increased SBP is delayed, occurring a few days after the start of the infusion. This increase in systolic pressure is accompanied by an abrupt elevation of the COP of the resistance vessels in the skin of the tail. We believe this increase in COP is part of a generalized increase in vascular smooth muscle contraction force.

The development of mineralocorticoid hypertension is believed to involve expansion of the ECF volume. It is well know that the administration of excess aldosterone results in retention of Na^+ and H_2O up to the time that renal escape occurs. Some investigators have studied the effects of prolonged secretion or administration of excess aldosterone on the fluid volumes in man: Dustan, Bravo and Tarazi (1973) found that the plasma

volumes of their patients with the chronic hypertension of primary aldosteronism were not consistently elevated, although the mean plasma volume for the group was slightly but not significantly above normal. On the other hand, August, Nelson and Thorn (1958) found that the acute administration of aldosterone to two normal human subjects, over a number of weeks and in doses similar to those given to rats in our experiments, was accompanied by a weight gain and retention of excess Na^+ and H_2O up to the time that renal escape occurred. Renal escape was characterized by a natriuresis and a diuresis, but at the time aldosterone administration was terminated, there was still a net Na^+ accumulation of over 450 m Eq by each subject. This accumulation of Na^+ probably represented expansion of the ECF space. One might expect that the sequence leading to hypertension in the chronically hypertensive patients by Dustan et al involved early volume expansion as seen in August's subjects, with a subsequent return of plasma volume toward normal values as the circulatory system compensated for the increase in ECF and plasma volume. According to Ledingham and colleagues, and Guyton and colleagues, part of the circulatory adjustments to an increased plasma volume involves peripheral vascular autoregulation leading to an increased total peripheral resistance and hypertension. From this point of view, then, the increased COP that we have observed in aldosterone hypertension in the rat should be part of the autoregulatory process.

My thesis is that the autoregulation theory does not have to be invoked as an explanation for the increased total peripheral resistance seen in volume dependent forms of hypertension. The following evidence from this laboratory suggests that some mechanism other than peripheral

vascular autoregulation is responsible for the increased COP in aldosterone hypertension in the rat:

1. The delayed, abrupt increase in COP seen in our aldosterone treated rats is not suggestive of a slowly developing autoregulatory response. Instead, the nature of this change in COP suggests that some new event has occurred.
2. Darke et al (1977) found that short-term autoregulation mechanisms are not responsible for the increase in COP of the tail vessels in rats made hypertensive with aldosterone.

   To investigate the importance of rapidly acting autoregulatory mechanisms (myogenic or metabolic) in the maintenance of the elevated COP, Darke et al applied an increased extravascular pressure to the surface of the tails of hypertensive ganglion blocked rats for 20-30 minutes and made measurements of the COP at intervals during this period. The increased extravascular pressure was applied to the tail in order to reduce and maintain the transmural pressures and the A-V pressure difference at normal or below normal values. The COP's should have been reduced to normal blocked values if rapidly operating autoregulatory mechanisms were responsible for the increased COP. However, it was found that the COP's were not significantly different from those obtained from blocked hypertensive rats whose tails had not been exposed to this maintained increase in extravascular pressure.
3. Evidence presented in this thesis shows that any more slowly developing autoregulatory mechanisms cannot be wholly responsible for the increased COP in the tail vessels of rats made hypertensive with aldosterone.

Continuous application of increased external pressure to the tails of the rats before and during the development of aldosterone hypertension does not prevent the increase in COP of the tail vessels.

Summary

From this review of the literature, it can be seen that in volume dependent forms of hypertension, the concept of increased TPR on the basis of peripheral vascular autoregulation does have some support. However it can also be seen that there are reasons for both questioning the role of the autoregulation mechanism in chronically increasing the TPR, and for suspecting another mechanism. The experiment described in the next few pages was designed to test the hypothesis that peripheral vascular autoregulation is responsible for increasing the TPR in volume dependent hypertension.

RATIONALE

PROJECT 1

Test of the peripheral vascular autoregulation theory as an explanation for increased total peripheral resistance in experimental aldosterone hypertension in the rat.

Peripheral autoregulation of blood flow has been invoked as an explanation for the increased TPR seen in volume dependent hypertension. The stimulus for autoregulation is thought to be increased transmural pressure at the level of the resistance vessels, leading to an increase in myogenic tone, or increased blood flow, leading to washout of vasodilator metabolites, or both. It would seem that the hypertension produced in the rat by excess aldosterone administration would be an excellent form of hypertension in which to test the autoregulation theory because this form of hypertension is thought to be a volume expanded state, uncomplicated by increased concentrations of known vasoconstrictor hormones.

We have observed a sudden increase in the COP of the skin vessels of the tail of the rat made hypertensive with continuous aldosterone infusion. We believe this increase in COP is part of a generalized increase in vascular smooth muscle contraction force that increases the TPR in volume dependent forms of hypertension by narrowing the lumen of the resistance vessels. If peripheral vascular autoregulation is the explanation for the increased TPR in this form of hypertension, then the increase in COP should be part of the autoregulatory response of the resistance vessels.

To test the autoregulation theory as an explanation for this increase in COP, we designed an apparatus to apply a continuous, graded counter-pressure of 0-50 mm Hg to the surface of the tail of the rat as the rat

became hypertensive from continuous aldosterone infusion. The purpose of the counterpressure was to increase the extravascular pressure on the skin vessels of the tail as the hypertension progressed from the acute to chronic (4 weeks) stages. The counterpressure was to be graded in order to keep transmural pressures in the skin vessels of the tail at normal or slightly low levels, and at the same time govern venous pressures in the tail, keeping blood flow at normal or slightly below normal values. (Poiseuille's law). With the application of counterpressure while the rats became hypertensive, the vessels in the skin of the tail should not experience increased autoregulatory stimuli, and there would be no need for an increased contraction force to develop in the resistance vessels. If an increased contraction force did develop (seen as an increase in COP), it would be fair to say that some mechanism other than peripheral autoregulation was contributing to the increase in vascular smooth muscle contraction force in volume dependent hypertension.

PROJECT 2

Study of the influence of aldosterone dose rate on the delay to onset of hypertension and increased critical opening pressure in the rat.

We have found that the hypertension caused by excess aldosterone administration in the rat is sudden in onset, occurring a few days after the start of the infusion. The increase in SBP is accompanied by an increase in COP of the vessels in the skin of the rat. The sudden increase in contraction force of these vessels is suggestive of a new event occurring.

We are aware that renal escape from the influence of aldosterone also occurs a few days after the start of the excess mineralocorticoid administration. We have wondered if renal escape and the abrupt increase in COP might have a common cause - perhaps the sudden release of a natriuretic hormone. If this is true, the work that has been done on natriuretic hormone will take on new significance, eg. it could be that the natriuretic hormone is also a vasoconstrictor involved in the pathogenesis of some forms of hypertension.

In preparation for investigating such a possibility, we wanted to see if the dose rate of aldosterone influenced the delay to the onset of increased COP and SBP. If this were the case, it would be advantageous to use a lower dose rate of aldosterone to lengthen the delay to the onset of renal escape and increased COP in order to more sharply define the time relationship between these events.

METHODS

Measurement of Systolic Blood Pressure and Critical Opening Pressure

Measurements of SBP and COP were made on the tails of trained conscious rats using an adaptation of the spectroscopic technique used for measuring the COP of vessels in the fingers (Gaskell, 1965). This technique was described in detail previously (Darke, 1974) and will be briefly outlined here: A 3 cm wide blood pressure cuff is applied to the base of the tail and the remainder of the tail is encased in a thin, transparent, air tight vinyl bag. The cuff and bag are connected to a hand bulb and a pressure reservoir and to a system of stopcocks and manometers to allow independent manipulation of air pressure in the bag and cuff. A microscope lamp fitted with both a green filter and a heat filter is used to reflect a focused beam of light off a small area of tail well inside the bag. This reflected light is examined with a hand held Zeiss spectroscope in order to detect the presence or absence of the absorption bands of oxyhemoglobin. The appearance of these absorption bands indicates the presence of blood flow. The COP is measured as the difference between SBP and the maximum extravascular pressure that just allows the arterioles in the skin to open. To make the measurements, blood is first expelled from the skin of the tail by increasing the air pressure in the bag to suprasystolic values. When the oxyhemoglobin absorption bands have disappeared, bag pressure is slowly reduced and the pressure at which the absorption bands suddenly reappear is noted. This is the maximum extravascular pressure that just allows the arterioles in the skin to open and allow blood flow. To obtain the SBP, most of the blood is again first expelled from the tail by inflating

the bag to suprasystolic pressures. Cuff pressure is then increased to suprasystolic and bag pressure is reduced to atmospheric. Once the oxyhemoglobin absorption bands have disappeared, cuff pressure is slowly reduced and the pressure at which flow resumes is noted. This is the SBP. The difference between SBP and the extravascular pressure that just allows blood flow is the COP.

The rats were kept in wire mesh holders in a warm (30°C) darkened box in a quiet room during the pressure measurements and for a half hour relaxation period that preceded the measurements. A heating pad in the platform supporting the tail kept the tail temperature about 34°C.

Six COP determinations were made before and again after ganglion blockade in order to obtain a measure of the vascular smooth muscle tone in the presence and absence of autonomic control. Ganglion blockade was accomplished by administering mecamylamine hydrochloride 10 mg/kg sc or im, in a volume of about 0.2 ml, and waiting a half hour before resuming COP measurements. At least three minutes were allowed between successive COP determinations.

Administration of Continuous Infusions

During these experiments, each rat wore a carefully fitted jacket to which was attached, at the back, a long, hollow aluminum tube (pole) fixed, at its top, to a spring suspended swivel connector (see figure 1). Continuous infusions were administered to the rats through a loop of perforated silastic tubing (ID 0.020", OD 0.037") inserted subcutaneously through a small incision in the loose skin of the back, just over the shoulders. The silastic tubing was taped to the skin in order to keep the cannula in place while the incision healed. The loop was connected to

a length of silastic tubing that passed through a hole in the back of the jacket and up the pole to the swivel connector. The infusate was delivered to the connector through flexible plastic tubing attached to a syringe mounted on a Sage syringe pump, model 341, located some distance from the cage. The infusate was delivered at a rate of 1.5 to 1.7 ml/day.

The rats were infused with a solution of aldosterone in a vehicle of 15% alcohol in 5% dextrose in water or with vehicle only.

Application of the Counterpressure to the Tail of the Rat

A constant, adjustable counterpressure was applied to the external surface of the tail by the apparatus shown in figure 2. The essential features of this apparatus are that the counterpressure was exerted by a column of water and that this pressure was transmitted to the distal 5" of the tail through a thin, vinyl, water filled sleeve that was continuous with the water column. Water is a much better heat conductor than air, so to prevent loss of body heat from the tail to the water surrounding it in the tail sleeve, a heating coil was built into the sleeve. Warm water was circulated through the coil and kept the tail temperature 30 - 34^{o}C as measured by a thermistor positioned between the tail and the vinyl sleeve.

Rats involved in the counterpressure experiment received continuous subcutaneous infusions of either aldosterone or its vehicle while they wore the counterpressure apparatus. It was found convenient to combine the infusion and counterpressure systems and to carry the entire weight of the combined apparatus with a large spring suspended swivel connector fixed to the top of the water column. This arrangement allowed the rats reasonable freedom of movement about their cages. To combine the infusion and counterpressure systems, the top of the hollow aluminum pole attached to the

the jacket was joined to the water column with a flexible plastic tube that pierced the wall of the column and extended up inside it, above the water level. The silastic infusion line then passed up the jacket's aluminum pole, through the flexible plastic tube and up through the column to the swivel connector, where it received the infusate delivered from a syringe mounted on a motor driven Syringe pump (Sage model 341). A rigid, spring loaded, telescoping rod was built into the apparatus between the jacket's pole and the water column, about two inches above the rat's body. The joints securing the rod to the pole and column were hinged to allow vertical movement of the pole with respect to the column, but to disallow rotation of one with respect to the other about the horizontal axis of the rod. The telescoping design of this rod, along with the hinge feature, allowed the rats to stand up at will, groom themselves easily and sleep comfortably, but prevented them from rolling over and twisting their tails.

The tail sleeve of the water column was secured to the tail with waterproof adhesive tape and could be removed or replaced quickly. A blood pressure cuff was left on the tail, just proximal to the tail sleeve, for the duration of the experiment and both the cuff and the tape holding the sleeve to the tail were protected by a guard. The cuff was used in the COP and SBP measurements, and was also used to stop blood flow to the tail for 3 or 4 minutes while the tail sleeve and water column were being removed to be replaced by the bag for COP or SBP measurements. Counter-pressure was maintained on the tails at all other times, either by the water column or by increased air pressure in the bag during and between COP measurements, so there was never an opportunity for an increased

transmural pressure or blood flow to act on the vessels.

Training of rats

It can be appreciated that to embark on this study, and for the results to be useful, it was an absolute necessity that the rats be familiar and at ease with all procedures to which they would be exposed. Familiarizing the rats with these procedures and training them to wear the combined infusion and counterpressure apparatus took 2-3 months.

Male Long Evans rats were obtained from the Canadian Breeding Farms and Laboratories Ltd. Quebec, at the age of 4-5 weeks (100-125 g). They were housed initially in groups of 4 or more, then were paired off, and finally separated by the end of the second week in the laboratory. Open ended wire mesh cylinders were placed in the cages for the young rats to play in. This made training the rats to settle quietly in the wire mesh restraining cages (holders) quite easy.

The first few days in the laboratory were devoted to simply handling the animals and allowing them to become familiar with the laboratory staff. One staff member frequently wore gloves while handling the rats (because of allergic reactions) and it was found very important to accustom the rats to being handled with both gloved and ungloved hands. Formal training of the rats began at the end of the first week in the laboratory. It was found that the younger the animals were when this training began, the easier it was for them to learn to accept the procedures. Several aspects of this training were conducted simultaneously, ie, they were being trained to jackets at the same time as being trained to wear something on their tails. Sunflower seeds - a favourite treat - were used to provide incentive for desirable behaviour.

Jackets were designed to cover the neck and thorax of the rats. The jackets had rolled collars, holes for the front legs and velcro fasteners

at the back so they could be adjusted to the girth of the individual animal. At the end of the first week in the laboratory the young rats were fitted into small sized jackets for a half hour. It was important to fasten the jackets loose enough so as not to be uncomfortable, but secure enough that the rat could not wiggle out, because once they had learned how to remove the jacket it was difficult to keep them in it. The length of time in the jackets was gradually increased so that by the end of the 2nd week the rats were in jackets for as much as 6 hours a day. Time in the jackets was thereafter increased to overnight, then to a full day, and then to as much as 5 days at a time by the end of 5 weeks. Larger jackets were used at the rats grew.

By the beginning of the 4th week in the laboratory the rats were quite at ease in the jackets. At this time an aluminium tube (or pole) with a swivel top was attached to the back of each jacket. The swivel was attached by springs to supports located on the cage top. This allowed the rat to move freely about his cage when in the jacket and pole assembly.

Training the rats to wear the counterpressure apparatus was the most time consuming phase of the training because it had to be done very slowly, starting with a very minor intervention, giving the rat time to accept it, and then building on from there. Before the end of the first week in the laboratory, a half inch band of plastic tape was fixed to the base of the tail. If the rat removed the tape, it was replaced. Within a few days the rats had accepted the tape, no longer paying attention to it and washing it as if it was a part of the tail. At this time the length of the tape band was increased by half an inch. Its length was increased daily, half an inch at a time, until it covered almost the entire length of the tail.

Since these were young, rapidly growing rats, it was important to remove the tape occasionally and change its point of attachment in order to avoid constricting the growing tail and to avoid skin trauma from repeatedly removing tape from the same area.

The size and weight of the tail piece was then gradually increased by covering the tail with sections of polyethylene tubing, fixing them to the tape already on the tail. The polyethylene tubing was attached, one section at a time, starting at the base of the tail, until it covered almost the whole length of the tail. At this point it resembled in size and appearance that section of the counterpressure apparatus which was to encase the tail.

By this time the rats were into the jacket and pole assembly. The spring and swivel arrangement was transfered to the top of a rod that had been attached to the tail piece and the top of the jacket's pole was attached by means of a flexible plastic tube to the rod of the tail piece. In order to prevent the rats rolling over and twisting their tails, the pole of the jacket and the rod attached to the tail piece were joined by a rigid telescoping connecting rod. The connectors at either end of this rod were flexible only in the vertical direction. The telescoping design of the connecting rod allowed the animals to groom themselves easily, and sleep comfortably, but prevented them from pulling backwards out of their jackets. It also allowed them to manoeuver fairly easily about their cages.

To train the animals to the restraining cages, the rats were placed frequently in wire mesh cylinders similar to those with which they played in their cages except that these were closed at both ends. In the early stages of their training the rats did struggle for a few minutes to get out, but they soon calmed down. For the first few days they were left for

only a half hour in the cages after they had settled down but the time was extended to 2-3 hours within a few weeks. After the first few days of exposure to the cages, the rats no longer struggled to get out, instead they settled down to eat sunflower seeds and frequently went to sleep.

The final phase of training for the rats involved familiarizing them with the procedure for measuring the COP. From the beginning the rats had been accustomed to having their tails handled. This was extended, after about 5 weeks in the laboratory, to inflating and deflating a BP cuff around the base of the tail while the rat rested in a restraining cage, just to accustom the rat to this sensation. Then about a week later, COP measurements were started, with the rat in a restraining cage and housed in a warm box in quiet, darkened room, as would be the procedure during the experiment. Critical opening pressure measurements were made at this time without administering the ganglion blocking agent. Once the animal was quite at ease with the procedure, the practice of giving the blocking agent was started. Practice COP measurements were made until the readings became stable over several days. At that time the COP measurements were considered acceptable as data.

All experiments were carried out on male Long-Evans rats whose weight at the time of the experiment was usually over 250 grams.

The Autoregulation Experiment

Setting up the infusion and counterpressure was preceded by a control period during which, on several occasions, normal SBP and COP values were obtained from each rat before and after ganglion blockade.

To establish the infusion and start the experiment, each rat was

weighed and then briefly anesthetized with ether. The upper back and shoulders were shaved and the skin was disinfected. The looped cannula was then inserted subcutaneously through a small incision and held in place with tape. The sleeping animal was carefully fitted into a jacket and appropriate connections were made for the immediate infusion of either aldosterone (test rats) or vehicle (control rats). Aldosterone was administered in a dose of approximately 5 µg/100g/d. At the same time, their tails were fitted into the sleeve of the counterpressure apparatus and the counterpressure on their tails was set at 25 or 35 mmHg with the exception of the first rat used in the study. See figure 3.

Control rats were carried through the experiment with counterpressure unchanged from that established at the time of operation. Test rats had their counterpressures advanced at the first sign of increased SBP. The advance of the counterpressure was always greater than the increase in SBP in order to prevent an increased blood flow to the tissues of the tail and to prevent a greater than normal transmural pressure from acting on the vessels in the skin. Infusion of aldosterone or vehicle and maintenance of the appropriately increased counterpressure was continued for up to 32 days. In most cases when aldosterone was discontinued, the counterpressure was reduced gradually over several days as the SBP returned to normal.

Once the infusions were started, measurements of SBP were made every second day, without prior ganglion blockade, until the SBP had increased. Ganglion blockade, with its attendant cardiovascular alterations, was avoided in this period to prevent influencing the events caused by aldosterone. When the SBP did increase, measurements of SBP and COP were made every 2 or 3 days, both with and without ganglion blockade, until

the experiment was terminated.

The rats were fed a diet of standard laboratory rat chow (Wayne Lab Blox F-6) and tap water ad lib throughout the experiment.

Experiment to Determine the Relationship between Dose Rate of Aldosterone and Length of Delay to the Onset of Increased SBP and COP

On several occasions before starting the experiment, SBP and COP measurements were obtained from each rat before and after ganglion blockade with mecamylamine 10 mg/kg given im or sc in a volume of about 0.2 ml.

To establish the infusion and start the experiment, each rat was weighed and then briefly anesthetized with ether. The upper back and shoulders were shaved and disinfected prior to sc insertion of a looped silastic cannula through a small incision. The cannula was held in place until the incision healed by taping the silastic tubing to the skin. The anesthetized animals were carefully fitted into the jacket and pole apparatus and appropriate connections were made for the immediate infusion of aldosterone. Each rat was infused with a constant dose rate of aldosterone ranging from 1.7 to 5.2 µg/100g/d.

Beginning on the second day of infusion, SBP and COP measurements were made every other day before and after ganglion blockade. Unblocked SBP measurements were usually made on the intervening days. Measurements were continued for a few days after SBP and COP had increased.

Throughout the experiment the rats were fed a diet of standard laboratory rat chow (Wayne Lab Blox F-6) and tap water ad lib.

Figure 1

Arrangement for continuous infusion in the rat.

(A) subcutaneous perforated loop of silastic tubing; (D) extension of the silastic tubing, connected at its top to the swivel connector (F). The extension of the silastic infusion tube (D) is protected by a rigid aluminum tube (B) which is secured to a flexible, tightly wound spring (E) which is, in turn, fastened to the jacket (C). The jacket has a rolled collar and is secured by velcro tabs. The swivel connector (F) is held together by a clamp (G) and conducts the infusate through itself to the silastic infusion tube (D). The swivel is suspended at its suspension disc (H) from three springs (I) which take the weight of the swivel and tubing and centre the swivel over the cage. The swivel allows rotation of the aluminum tube (B) and silastic infusion tube (D) about their long axes. (J) is a flexible plastic tube conducting infusate from a syringe mounted on a motor driven syringe pump to the swivel connector.

Fig. 1

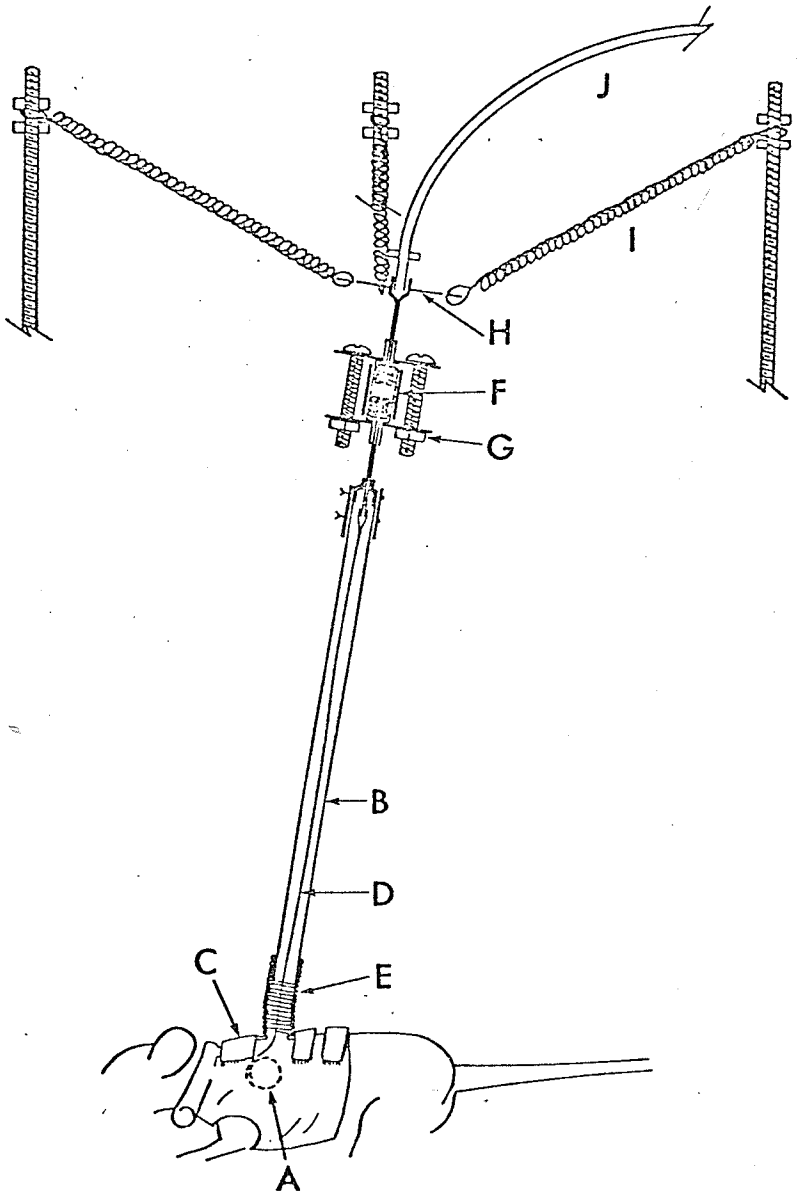
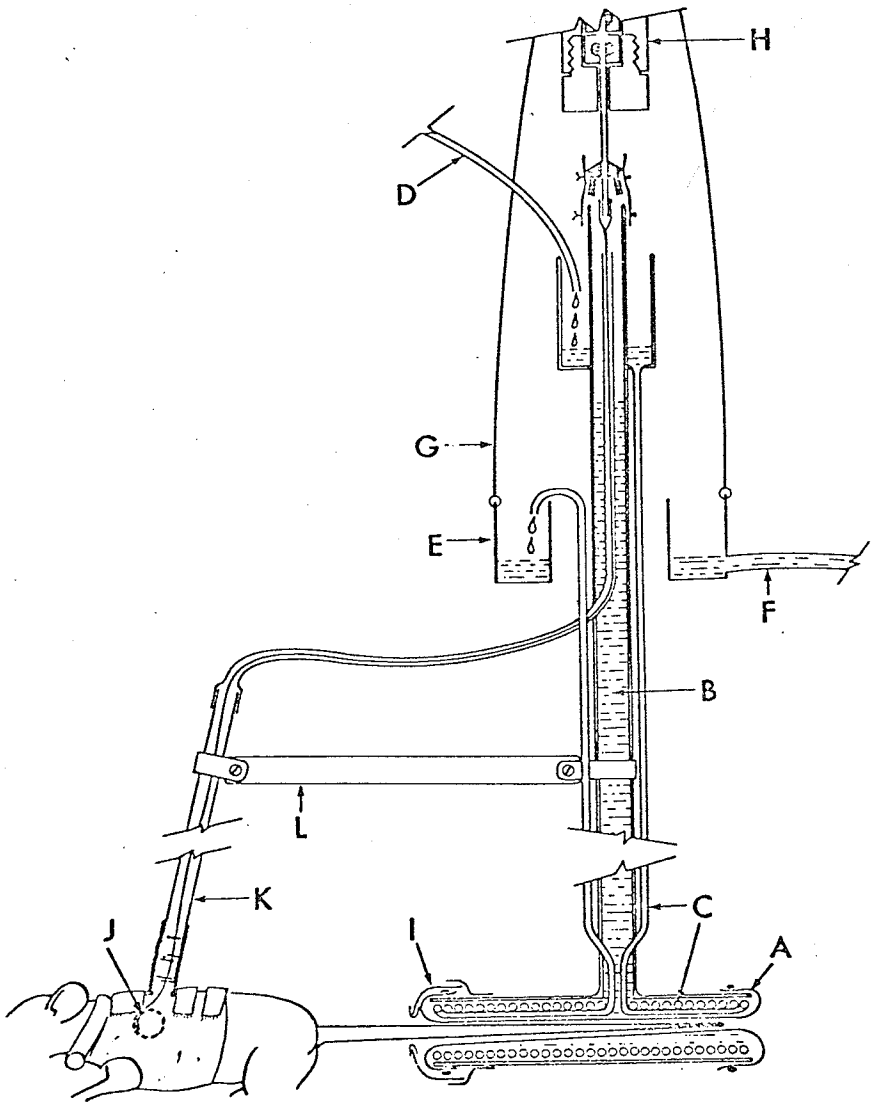


Figure 2

Arrangement for applying counterpressure to the tail of the rat while giving a continuous subcutaneous infusion. (A) is a very thin plastic (Vi-drape) through and through sleeve to transmit the pressure of the water column (B) to the tail; (C) points to a temperature regulating coil and coil supply tube through which water flows at a regulated temperature to warm the water in the tail sleeve and the tail. (D) is the line delivering water to the coil supply tube. In practice, the coil supply tube is insulated against heat loss, as is the cup into which water from the delivery line (D) flows. The insulation is not shown. (E) is a doughnut shaped cup to catch water returned from the temperature regulating coil. This water is channelled via (F) to a pump for return to a reservoir of temperature regulated water. The cup (E) is suspended by wires (G) from the suspension disc of the strong, heavy swivel (H) and does not turn because the suspension disc is attached by 3 three springs to supports outside the cage. The swivel connector performs the same function as in Figure 1. (I) is a hard plastic guard tube protecting the thin plastic sleeve (A). In practice, a longer guard is used in order to protect both the sleeve and a blood pressure cuff that is left on the tail throughout the experiment. (J) is a subcutaneous loop of perforated silastic tubing that extends up through (K), an aluminum tube attached to the back of the rat's jacket, as in Figure 1, and through a section of flexible plastic tubing to pierce the wall of the water column (B) and connect with the swivel connector (H). (L) is a telescoping rod separating the aluminum tube (K) and the water column (B). The joints at either end of the telescoping rod allow flexibility in the vertical direction only.

Fig. 2



RESULTS

PROJECT 1

Autoregulation Experiment: Test of Peripheral Vascular Autoregulation as an Explanation for Increased Total Peripheral Resistance in Experimental Aldosterone Hypertension in the Rat

It was intended that the counterpressure and infusion should be maintained on each rat for 30 days, but for various reasons, some rats could not be carried through the experiment for this length of time. For some, the experiment was discontinued after about 20 days of infusion and counterpressure because they became uncomfortable or uncooperative. A few rats were lost to the study in the first few days because of technical accidents. Data from these rats has not been included in the study. Individual results for 5 test and 3 control rats are given in Figures 3-10. The pertinent results are summarized in Tables1-4.

Systolic blood pressures and critical opening pressures were fairly uniform in the control period. Ganglion blockade at that time produced a 15-20 mmHg drop in SBP and a 7-10 mmHg drop in COP in both the test group and the control group of rats.

After two weeks of a maintained increase in external pressure, all tails appeared to be thinner and weaker than normal.

Test Rats

Counterpressure and aldosterone infusion were maintained for 30 days on two rats and for 19-20 days on the remaining three rats. In all 5 test rats, there was an increase of at least 10 mmHg (range 10-30 mmHg) in their systolic blood pressures 3-5 days after the start of the

aldosterone infusion. By day 10 or 11 of the infusion, the systolic blood pressure had reached a value 20-35 mmHg above the mean SBP of the control period. This increase was maintained for the duration of the aldosterone infusion and represented an increase in SBP of about 22%.

Pressure measurements under conditions of ganglion blockade were not started until day 10 of the infusion, at the earliest, in order to avoid influencing the early events in the development of aldosterone hypertension. Ganglion blockade reduced the SBP in the infusion period by about 21 mmHg, leaving blocked SBP values that were about 24% greater than ganglion blocked pressures measured during the control period.

Critical opening pressure measurements were started on day 10 or 11. Despite application of the increased external pressure to the tail since the beginning of the aldosterone infusion, the COP was found to be increased to twice the mean value in the control period. Ganglion blockade reduced the COP in the infusion period by about 15 mmHg, leaving blocked COP values that were well over twice the blocked values obtained in the control period.

The SBP and COP were monitored closely in three rats after their aldosterone infusions were discontinued. In all three, SBP and COP decreased gradually, reaching control period values in 7 days or less. The SBP and COP of the remaining two test rats were not followed after the aldosterone infusions were discontinued. When pressure measurements on these rats were resumed some months later, it was found that their systolic blood pressures and critical opening pressures had returned to normotensive levels.

Control Rats

Counterpressure and infusion of the vehicle were maintained for 17, 29 and 32 days on the three control rats. None of these rats became hypertensive. The mean systolic blood pressures and critical opening pressures for the control group changed by no more than 2.2 mmHg during the period of infusion and counterpressure.

Footnote

It was not intended that the control group should be of such a small sample size (n=3). We have recently been stalemated by a disorder among our rats that has forced us to have all rats in the laboratory destroyed. Two consecutive lots of rats, including six rats that were fully trained for the autoregulation experiment, were lost to this disorder. Two more control rats and possibly another test rat will be included in this experiment as the rats became available.

Figure 3

Results of the autoregulation experiment in test rat # 2.

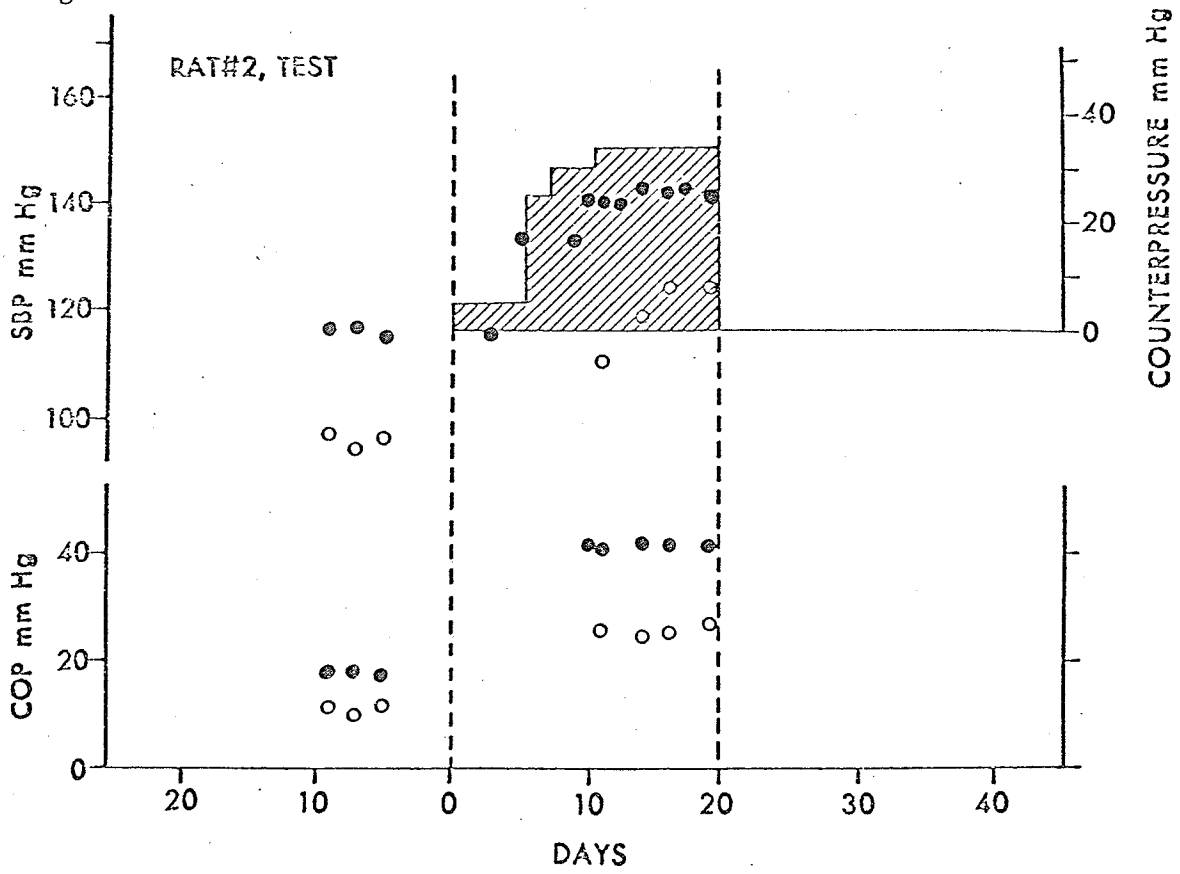
Solid circles represent the mean systolic blood pressure (SBP) and critical opening pressure (COP) values obtained without prior ganglion blockade, while the open circles represent mean values obtained after administering a ganglion blocking agent. Aldosterone was infused in a vehicle at a dose rate of 6.8 µg/100g/d during the period between the two vertical dashed lines. The hatched area represents the level of counterpressure (mmHg) applied to the tail during and after aldosterone infusion. The zero level of the counter-pressure scale is set at the mean SBP obtained, without ganglion blockade, in the control period that preceded the infusion of aldosterone.

Figure 4

Results of the autoregulation experiment in test rat # 7.

Conventions as in Fig. 3. Dose rate of aldosterone was 5.9 µg/100g/d.

Fig. 3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SBP mm Hg
160
140
120
100
COP mm Hg
40
20
0
20
10
0
10
20
30
40
DAYS
COUNTERPRESSURE mm Hg
40
20
0

Fig. 4

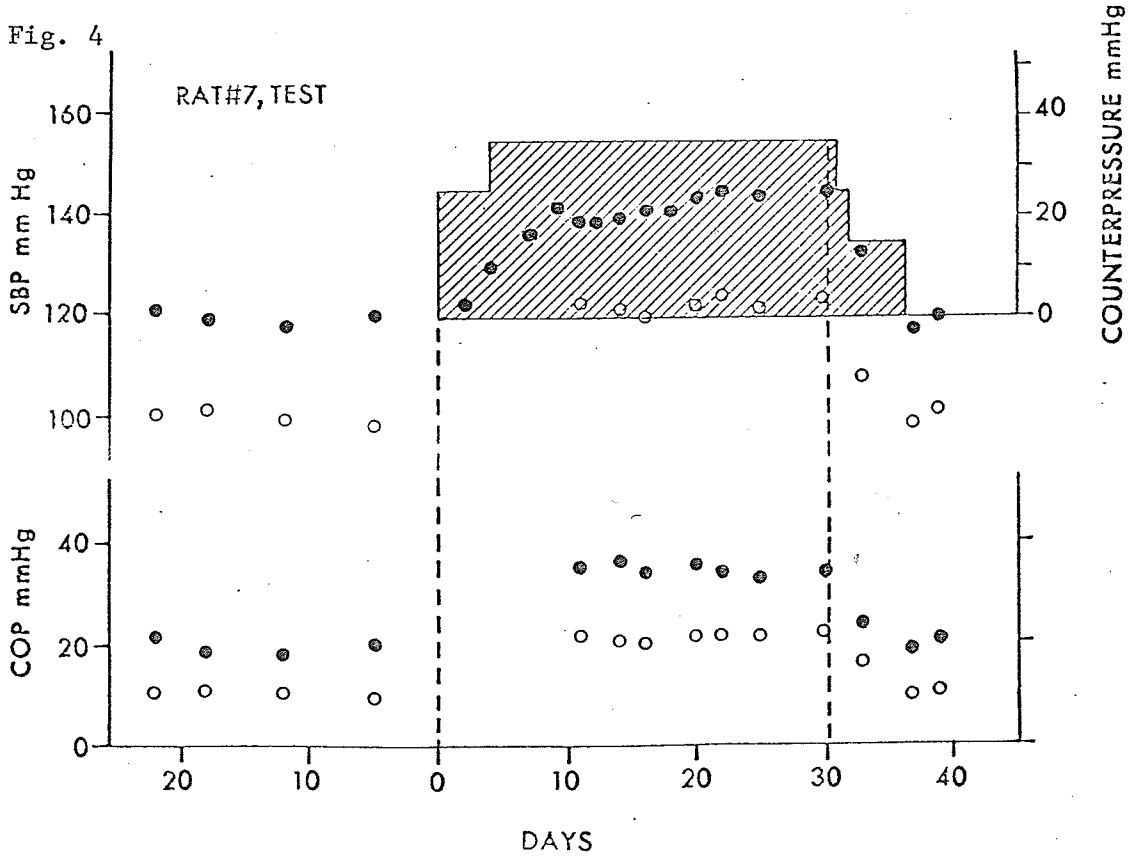

RAT#7, TEST
SBP mm Hg
160
140
120
100
COP mmHg
40
20
0
20
10
0
10
20
30
40
DAYS
COUNTERPRESSURE mmHg
40
20
0

Figure 5

Results of the autoregulation experiment in test rat # 10.

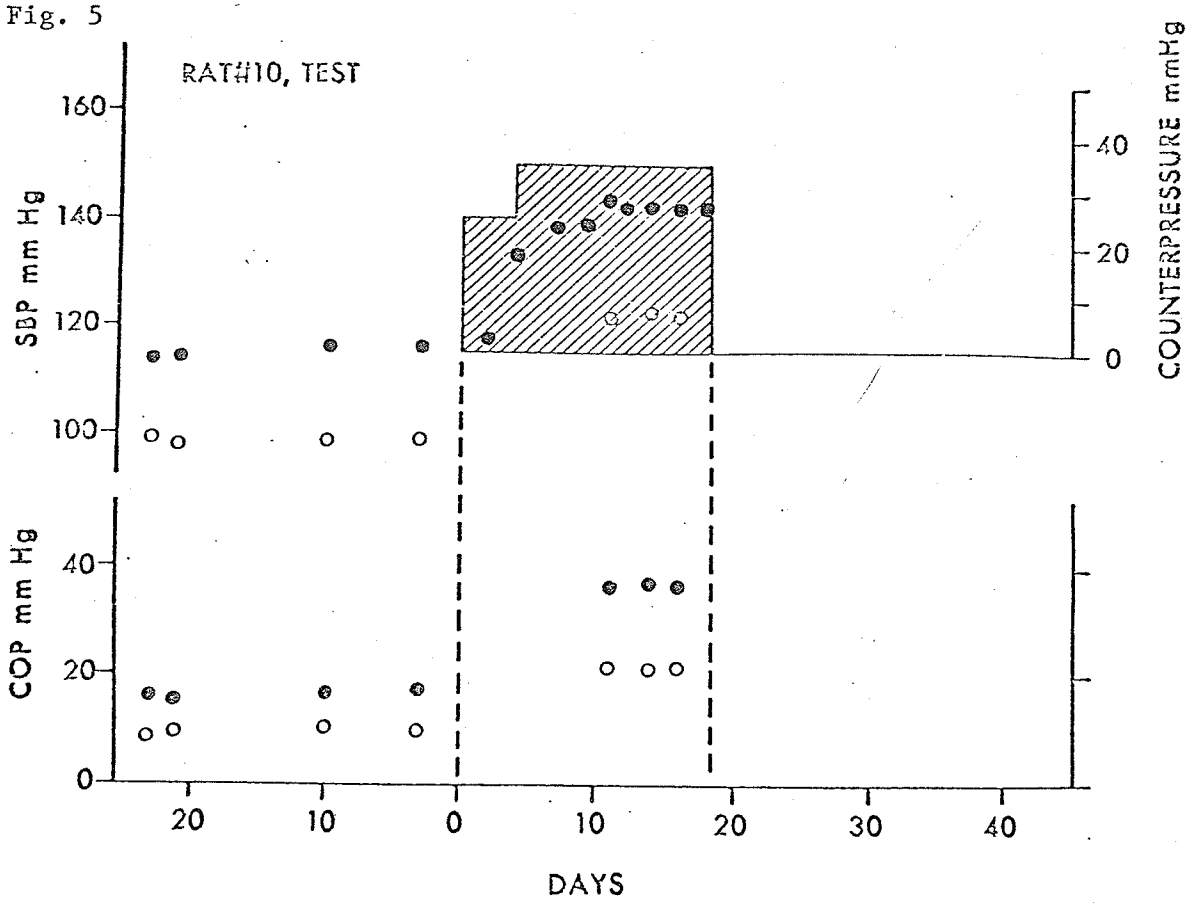
Conventions as in Fig. 3. Dose rate of aldosterone was 7.4 µg/100/d.

Figure 6

Results of the autoregulation experiment in test rat # 13.

Conventions as in Fig. 3. Dose rate of aldosterone was 5.0 µg/100g/d.

Fig. 5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140
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100
COP mm Hg
40
20
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COUNTERPRESSURE mmHg
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20
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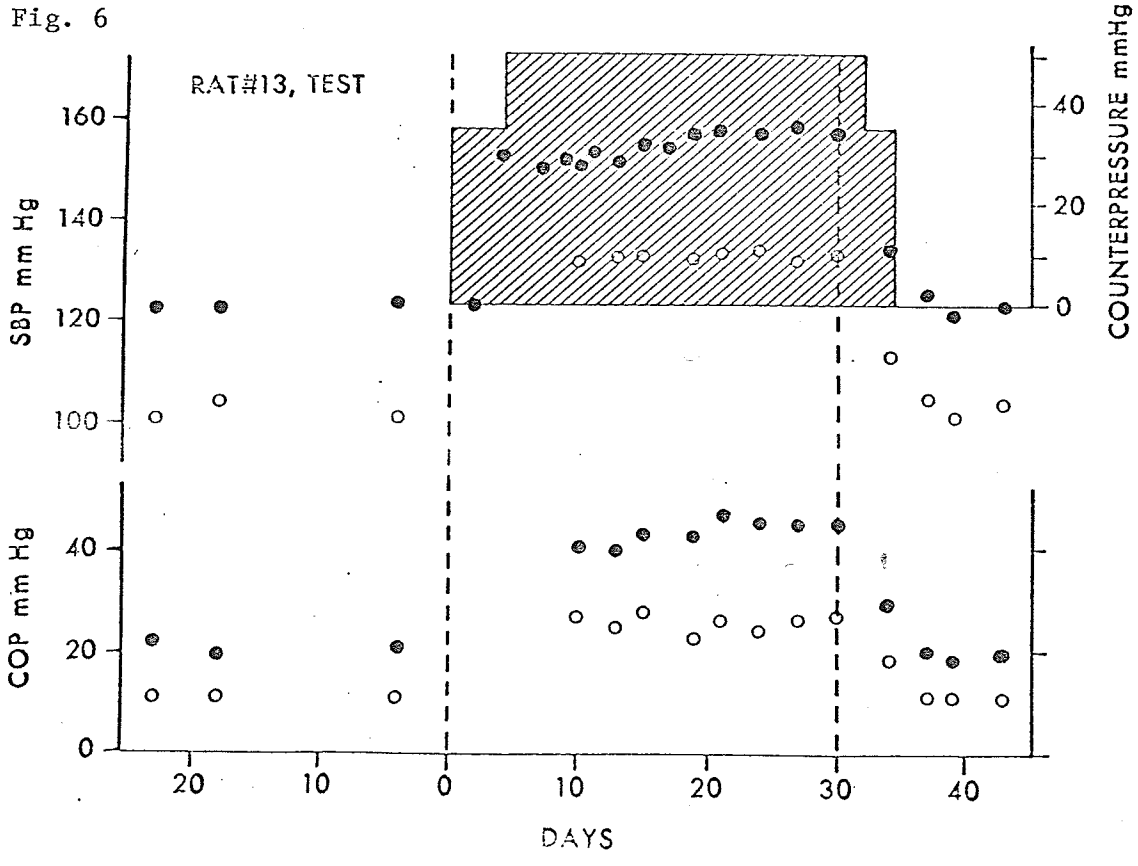
20
10
0
10
20
30
40
DAYS

Fig. 6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SBP mm Hg
160
140
120
100
COP mm Hg
40
20
0
COUNTERPRESSURE mmHg
40
20
0
20
10
0
10
20
30
40
DAYS

Figure 7

Results of the autoregulation experiment in test rat #14.
Conventions as in Fig. 3. Aldosterone dose rate was 5.2 µg/100g/d.

Figure 8

Results of the autoregulation experiment in control rat #9.
Conventions as in Fig. 3 with the exception that aldosterone was not included in the vehicle administered during the period between the two verticle dashed lines. The third estimation of SBP and COP during the infusion period are high because the rat had been disturbed throughout the night preceding the pressure measurements. Water returning from the heating coil had not been properly conducted away, and so over flowed, wetting the rat and the bedding in the cage.

Fig. 7

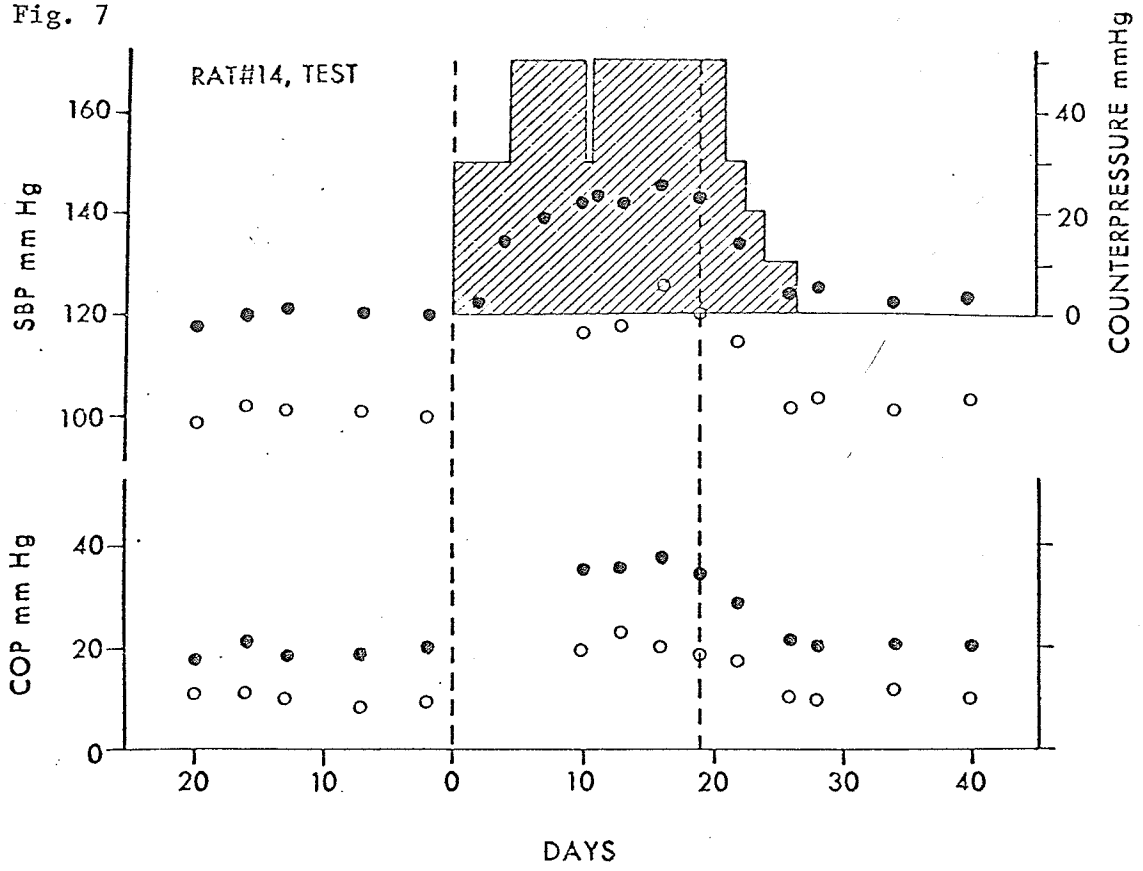


Fig. 8

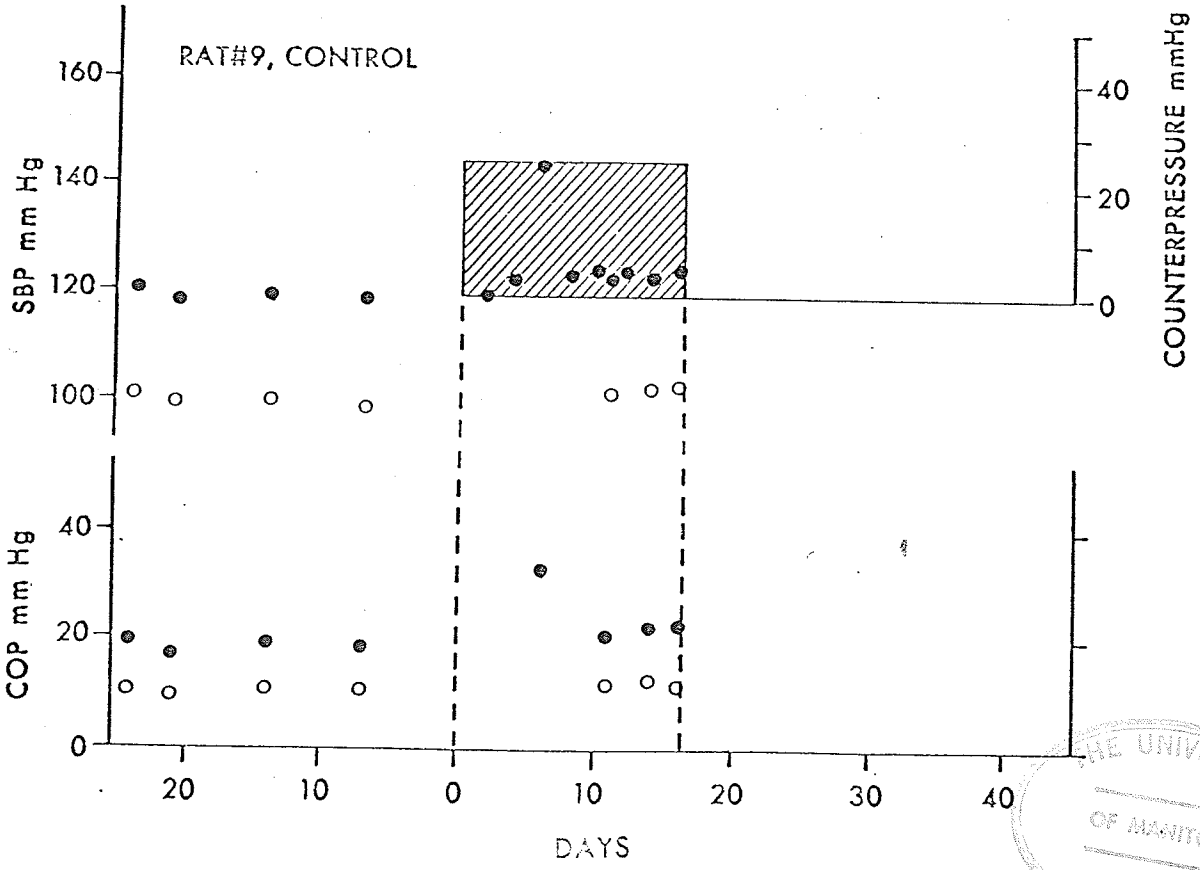


Figure 9

Results of the autoregulation experiment in control rat # 16.

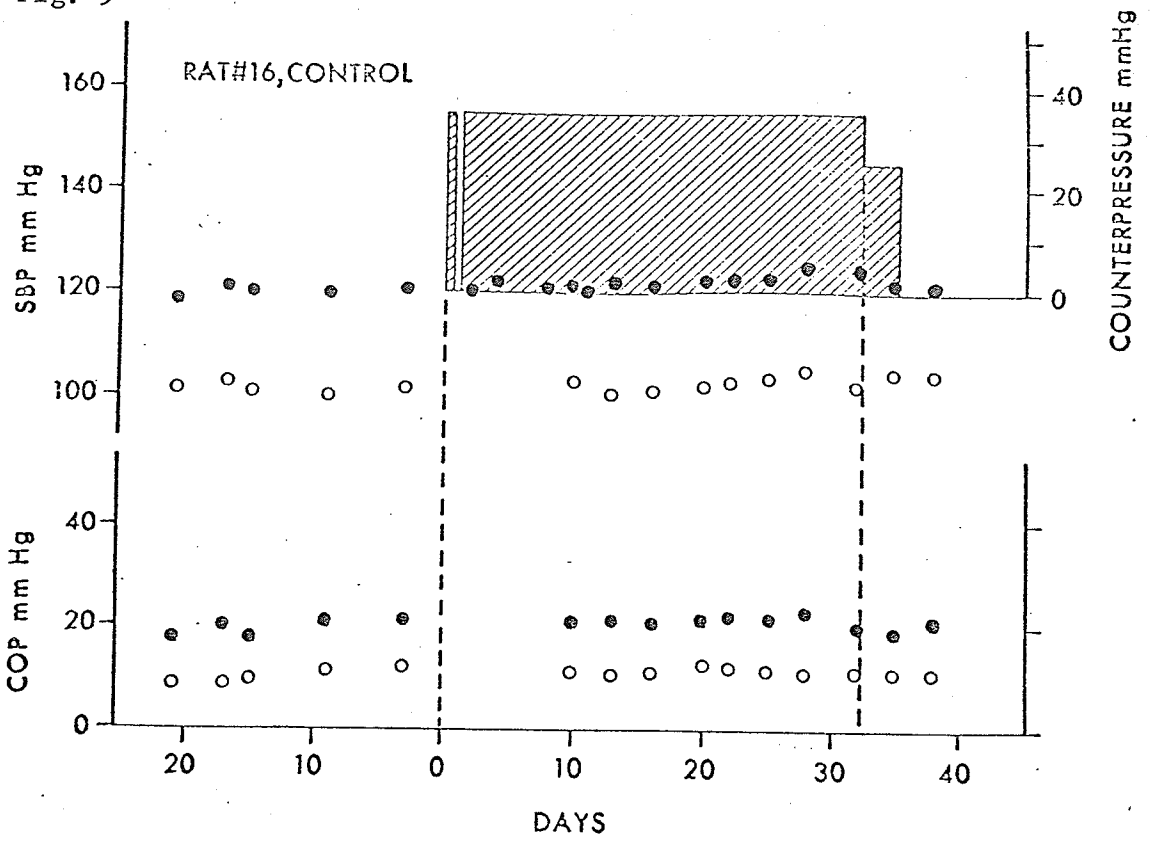
Conventions as in Fig. 8.

Figure 10

Results of the autoregulation in control rat # 18.

Conventions as in Fig. 8

Fig. 9


RAT#16,CONTROL
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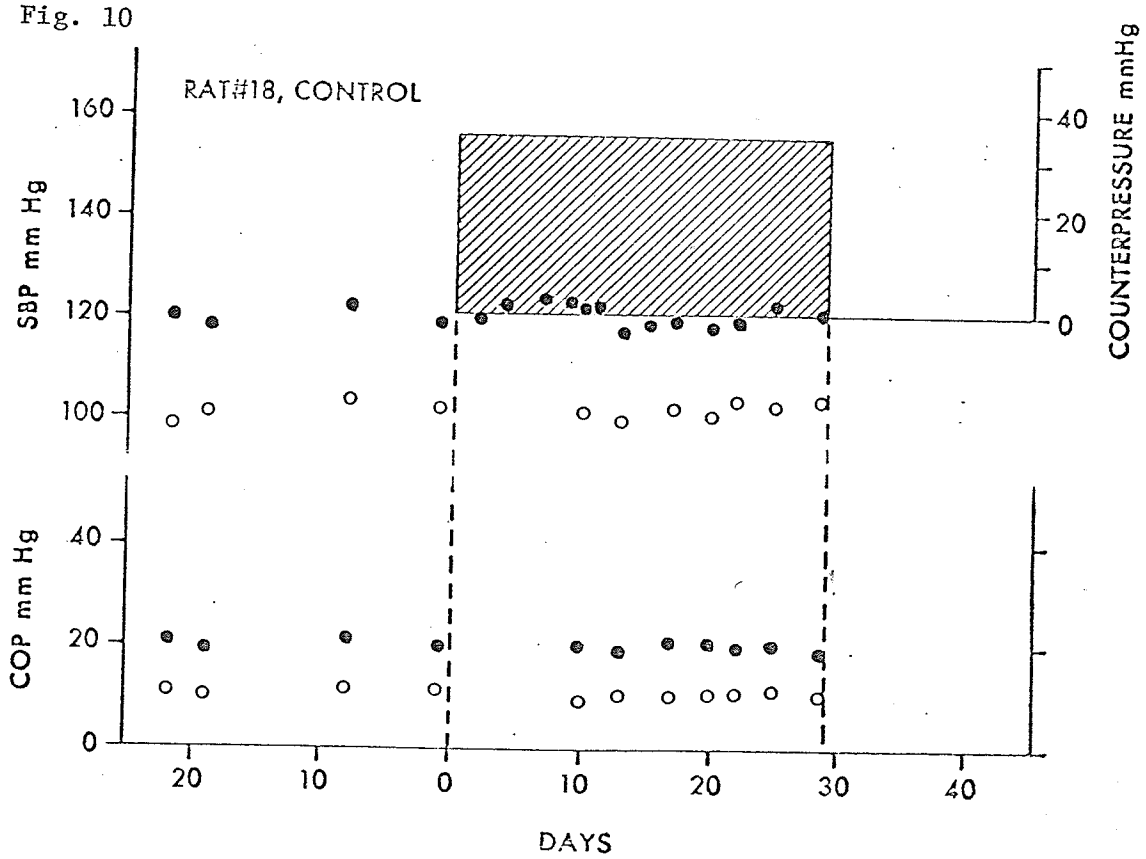
160
140
120
100
COP mm Hg
40
20
0
COUNTERPRESSURE mmHg
40
20
0
20
10
0
10
20
30
40
DAYS

Fig. 10


RAT#18, CONTROL
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160
140
120
100
COP mm Hg
40
20
0
COUNTERPRESSURE mmHg
40
20
0
20
10
0
10
20
30
40
DAYS

Tables 1 and 2

Values in Tables 1 and 2 were obtained in the following manner:

1. the MEAN CONTROL value for the SBP or COP for each rat is the mean of all respective values obtained during the control period and used in Figures 3-10. For the tables, mean systolic blood pressures have been rounded off to the nearest mmHg.
2. the mean value of the SBP and COP during the period of infusion, from day 10 on, was calculated for each rat using values represented in the figures.
3. the MEAN INCREASE in SBP or COP for each rat is the difference between (2) and (1) above and has been expressed as mmHg and as % control. Mean increases in SBP have been rounded off to the nearest whole number.
4. group means were calculated before rounding off and have been entered in the tables as MEAN ± SEM.

Table 1: The effect of continuous subcutaneous infusion of aldosterone (about 5µg/100g/d) on systolic blood pressure in the rat.

TEST RATS

RAT	Intact Systolic Blood Pressure			With GBA* Systolic Blood Pressure		
	Mean Control mmHg	Mean Increase mmHg	Mean Increase %	Mean Control mmHg	Mean Increase mmHg	Mean Increase %
2	116	25	22	96	24	25
7	119	22	19	100	22	22
10	115	27	24	99	23	24
13	123	30	24	102	31	30
14	120	23	19	101	19	19
MEAN ± SEM	118.7 ± 1.43	25.6 ± 1.43	21.6 ± 1.12	99.4 ± 1.06	23.7 ± 1.86	24.0 ± 1.82

CONTROL RATS

Rat	Intact Systolic Blood Pressure			Ganglion Blocked Systolic Blood Pressure		
	Mean Control mmHg	Mean Increase mmHg	Mean Increase %	Mean Control mmHg	Mean Increase mmHg	Mean Increase %
9	119	4	3	100	2	2
16	120	2	2	101	1	1
18	120	0	0	102	1	1
MEAN ± SEM	119.8 ± 0.35	2.2 ± 1.13	1.7 ± 0.82	100.8 ± 0.67	1.2 ± 0.47	1.2 ± 0.44

*GBA: ganglion blocking agent

Table 2: The effect of continuous subcutaneous infusion of aldosterone (about 5µg/100g/d) on the COP of small vessels in the tail of the rat.

TEST RATS

	Intact Critical Opening Pressure			With GBA* Critical Opening Pressure		
	Mean Control	Mean Increase		Mean Control	Mean Increase	
RAT	mmHg	mmHg	%	mmHg	mmHg	%
2	17.8	23.6	133	10.8	14.6	135
7	19.8	15.1	76	10.2	11.1	109
10	16.8	20.6	123	9.7	12.0	124
13	20.8	20.6	99	10.8	15.6	144
14	19.3	16.7	87	9.8	10.5	107
MEAN ± SEM	18.90 ± 0.71	19.32 ± 1.52	103.6 ± 10.7	10.26 ± 0.24	12.76 ± 1.00	123.8 ± 7.2

CONTROL RATS

	Intact Critical Opening Pressure			Ganglion Blocked Critical Opening Pressure		
	Mean Control	Mean Increase		Mean Control	Mean Increase	
RAT	mmHg	mmHg	%	mmHg	mmHg	%
9	18.9	3.1	16	10.3	1.4	14
16	19.3	1.8	9	10.1	1.2	12
18	20.8	-0.5	-2	11.3	-0.7	-6
MEAN ± SEM	19.67 ± 0.58	1.47 ± 1.05	7.7 ± 5.2	10.57 ± 0.37	0.63 ± 0.67	6.7 ± 6.4

*GBA: ganglion blocking agent

Tables 3 and 4

Values in Tables 3 and 4 were obtained in the following manner:

1. for each rat, the MEAN INTACT SBP or COP in the control period and again in the infusion period (from day 10 on) has been calculated from those values represented in Figures 3 - 10 and obtained without ganglion blockade. For the tables, mean systolic blood pressures have been rounded off to the nearest mmHg.
2. the corresponding mean values obtained after ganglion blockade were calculated.
3. the MEAN DECREASE WITH GBA (ganglion blocking agent) in the SBP and COP of each rat is the difference between (1) and (2) above. For the tables, the individual mean decreases in SBP have been rounded off the nearest mmHg.
4. group means were calculated before rounding off and have been entered in the tables as MEAN ± SEM.

Table 3: Comparison between the reduction in SBP caused by ganglion blockade before and during aldosterone hypertension in the rat.

TEST RATS

	Control Period		Infusion Period (from day 10)	
	Mean SBP Intact	Mean Decrease With GBA*	Mean SBP Intact	Mean Decrease With GBA*
RAT	mmHg	mmHg	mmHg	mmHg
2	116	20	141	22
7	119	20	142	20
10	115	16	142	20
13	123	21	153	21
14	120	19	143	23
MEAN ± SEM	118.7 ± 1.43	19.3 ± 0.82	144.3 ± 2.22	21.2 ± 0.60

CONTROL RATS

	Control Period		Infusion Period (from day 10)	
	Mean SBP Intact	Mean Decrease With GBA	Mean SBP Intact	Mean Decrease With GBA
RAT	mmHg	mmHg	mmHg	mmHg
9	119	20	123	22
16	120	19	123	20
18	120	18	120	18
MEAN ± SEM	119.8 ± 0.35	19.0 ± 0.35	122.0 ± 0.87	20.0 ± 1.02

*GBA: ganglion blocking agent

Table 4: Comparison between the reduction in COP of the small vessels in the tail of the rat caused by ganglion blockade before and during aldosterone hypertension.

TEST RATS

	Control Period		Infusion Period (from day 10)	
	Mean COP Intact	Mean Decrease With GBA*	Mean COP Intact	Mean Decrease With GBA
RAT	mmHg	mmHg	mmHg	mmHg
2	17.8	7.0	41.4	16.0
7	19.8	9.6	34.9	13.6
10	16.8	7.1	37.4	15.7
13	20.8	10.0	41.4	15.0
14	19.3	9.5	36.0	15.7
MEAN ± SEM	18.90 ± 0.71	8.64 ± 0.65	38.22 ± 1.36	15.20 ± 0.43

CONTROL RATS

	Control Period		Infusion Period (from day 10)	
	Mean COP Intact	Mean Decrease With GBA	Mean COP Intact	Mean Decrease With GBA
RAT	mmHg	mmHg	mmHg	mmHg
9	18.9	8.6	22.0	10.3
16	19.3	9.2	21.1	9.8
18	20.8	9.5	20.3	9.7
MEAN ± SEM	19.67 ± 0.58	9.10 ± 0.26	21.13 ± 0.49	9.93 ± 0.19

*GBA: ganglion blocking agent

PROJECT 2

Influence of Aldosterone Dose Rate on the Delay to Onset of Hypertension and Increased Critical Opening Pressure in Experimental Aldosterone Hypertension in the Rat.

This experiment was run in three groups of 3, 2 and 2 rats, and involved collecting data from 6 rats. Two sets of results were obtained from one particular rat by including this rat in two groups and administering different doses of aldosterone each time. Within each group the animals were handled similarly and received aldosterone diluted from the same stock solution. The only differences within each group could be the dose rate of aldosterone and the individual responsiveness of the rats.

Figures 11 through 17 show the individual results obtained from each of the rats as they were infused with known doses of aldosterone ranging from 1.7 to 5.2 µg/100g/d. The day of onset of hypertension and increased COP is indicated by an arrow on each figure. These results are summarized by the points in Figure 18, which relate the dose rate of aldosterone to the day of onset of increased SBP and COP. The lines in this figure connect data obtained from rats in the same group and emphasize the influence the dose rate of aldosterone had on the delay to onset of hypertension and increased COP. It is evident from this figure that more time is required for the development of hypertension when low dose rates of aldosterone are used. To illustrate: the lowest dose rates of 1.7 and 1.8 µg/100g/d required 6 and 8 days, respectively, to produce hypertension, while the highest dose rates of 4.5 and 5.2 µg/100g/d produced an increased SBP and COP in only 3 and 4 days, respectively.

Figure 11

Results from rat # 1 in an experiment to investigate the influence of aldosterone dose rate on the delay to onset of increased SBP and COP in the rat. Solid circles represent mean SBP and COP values obtained without administering a ganglion blocking agent (GBA), while open circles represent mean values obtained with GBA. The start of the aldosterone infusion is indicated by the verticle dashed line. The day of onset of hypertension is indicated by an arrow. Aldosterone dose rate was 1.8 µg/100g/d.

Figure 12

Results from rat # 4, aldosterone dose rate 5.2 µg/100g/d.

Conventions as in Fig. 11.

Fig. 11

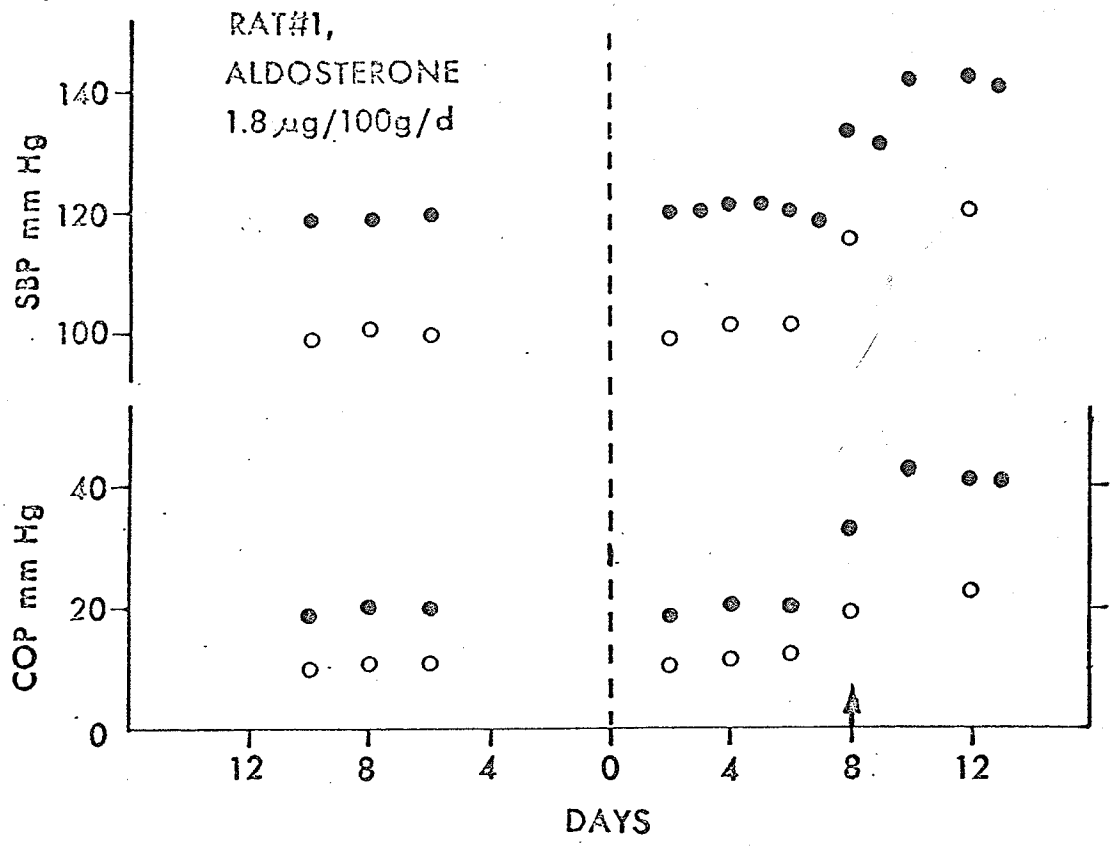

RAT#1,
ALDOSTERONE
1.8 µg/100g/d
SBP mm Hg
140
120
100
COP mm Hg
40
20
0
12
8
4
0
4
8
12
DAYS

Fig. 12

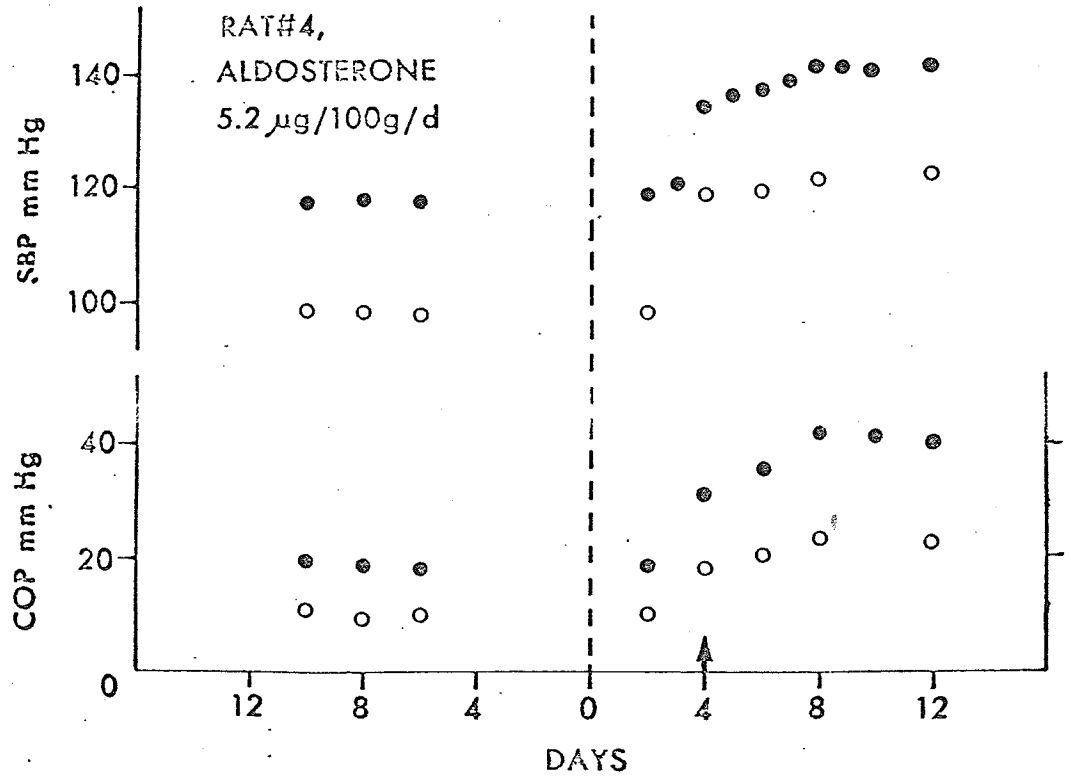

RAT#4,
ALDOSTERONE
5.2 µg/100g/d
SBP mm Hg
140
120
100
COP mm Hg
40
20
0
12
8
4
0
4
8
12
DAYS

Figure 13

Results of rat # 2, aldosterone dose rate 3.1 µg/100g/d.

Conventions as in Fig. 11.

Figure 14

Results from rat # 4, aldosterone dose rate 3.1 µg/100g/d.

Conventions as in Fig. 11.

Fig. 13

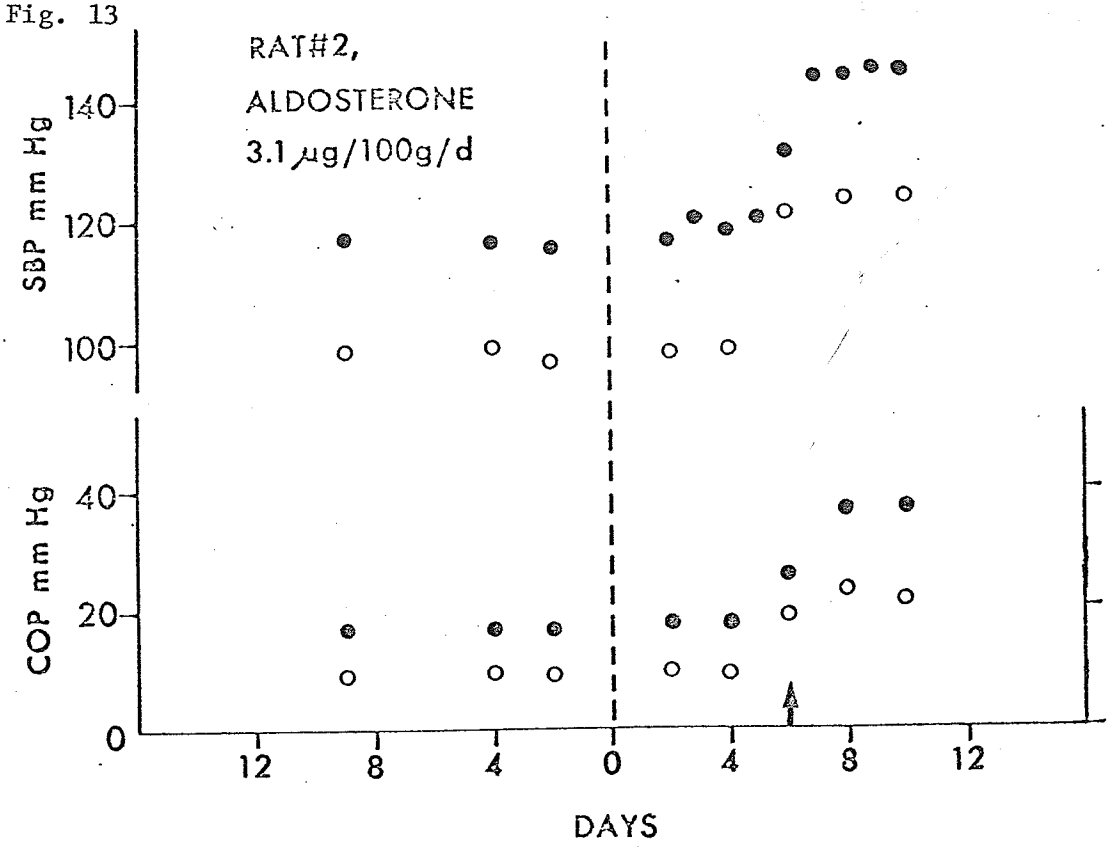

RAT#2,
ALDOSTERONE
3.1 µg/100g/d
SBP mm Hg
140
120
100
COP mm Hg
40
20
0
12
8
4
0
4
8
12
DAYS

Fig. 14

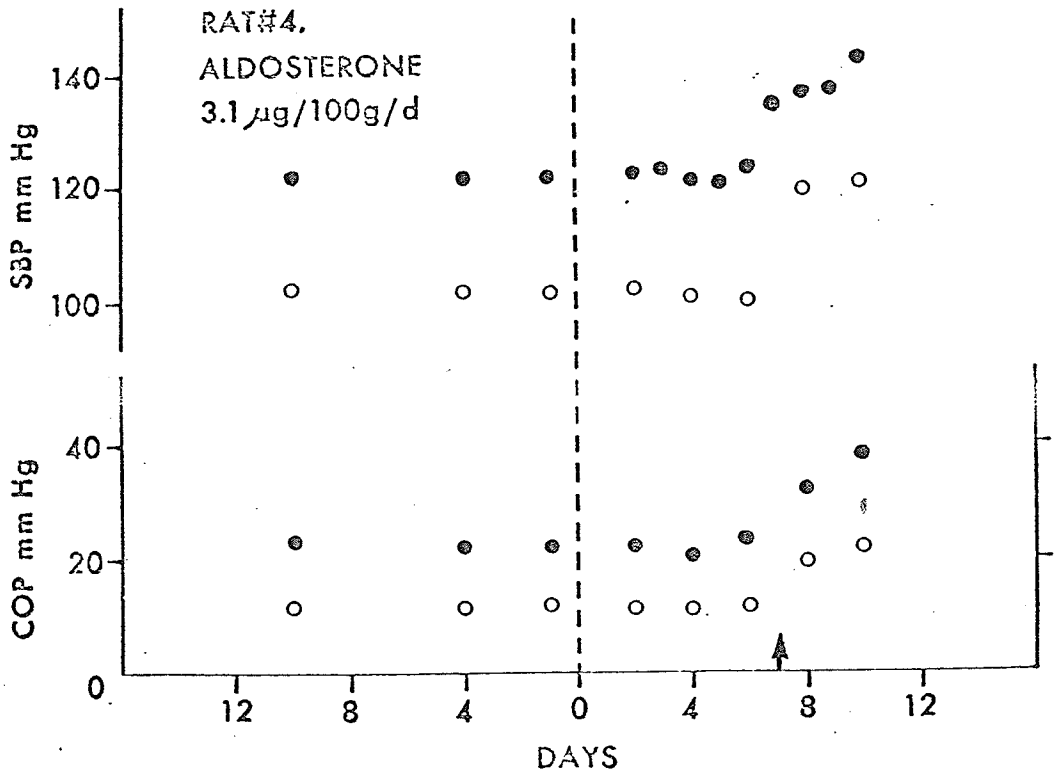

RAT#4,
ALDOSTERONE
3.1 µg/100g/d
SBP mm Hg
140
120
100
COP mm Hg
40
20
0
12
8
4
0
4
8
12
DAYS

Figure 15

Results from rat # 7, aldosterone dose rate 1.7 µg/100g/d.

Conventions as in Fig. 11.

Figure 16

Results from rat #10, aldosterone dose rate 3.8 µg/100g/d.

Conventions as in Fig. 11.

Fig. 15

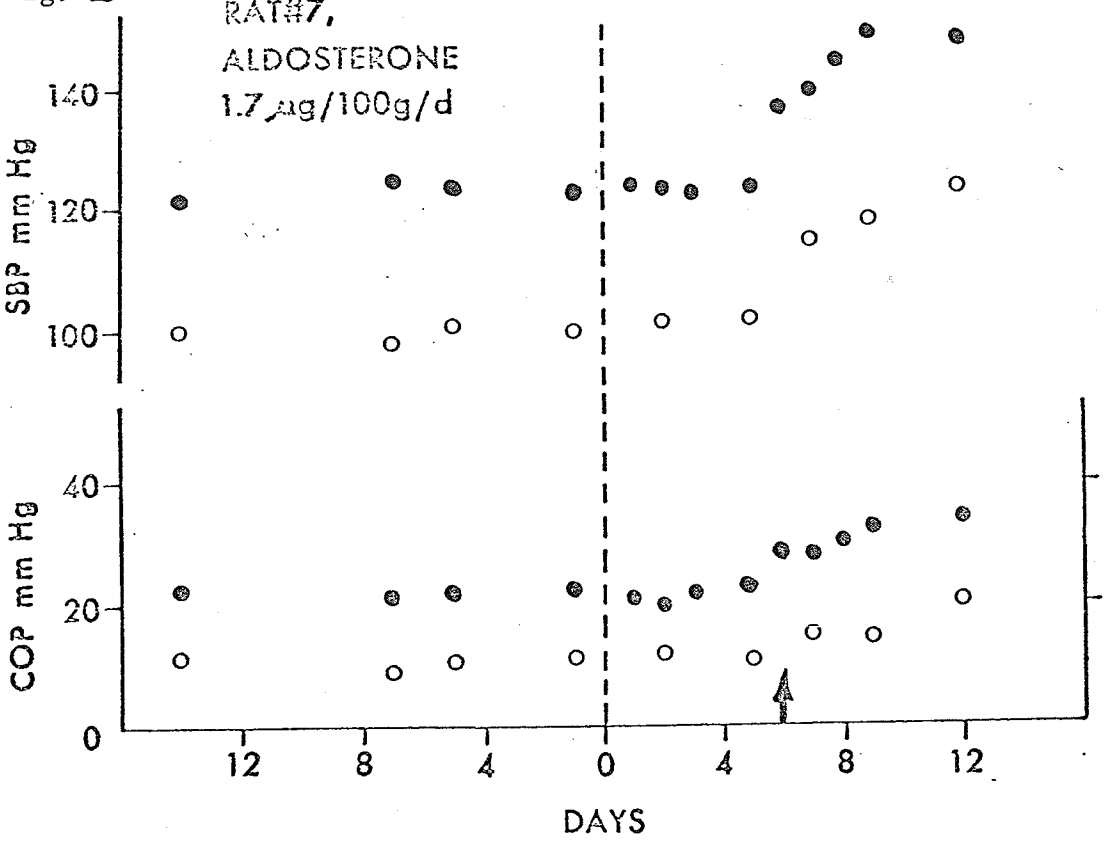

RAT#7,
ALDOSTERONE
1.7 µg/100g/d
SBP mm Hg
140
120
100
COP mm Hg
40
20
0
12
8
4
0
4
8
12
DAYS

Fig. 16

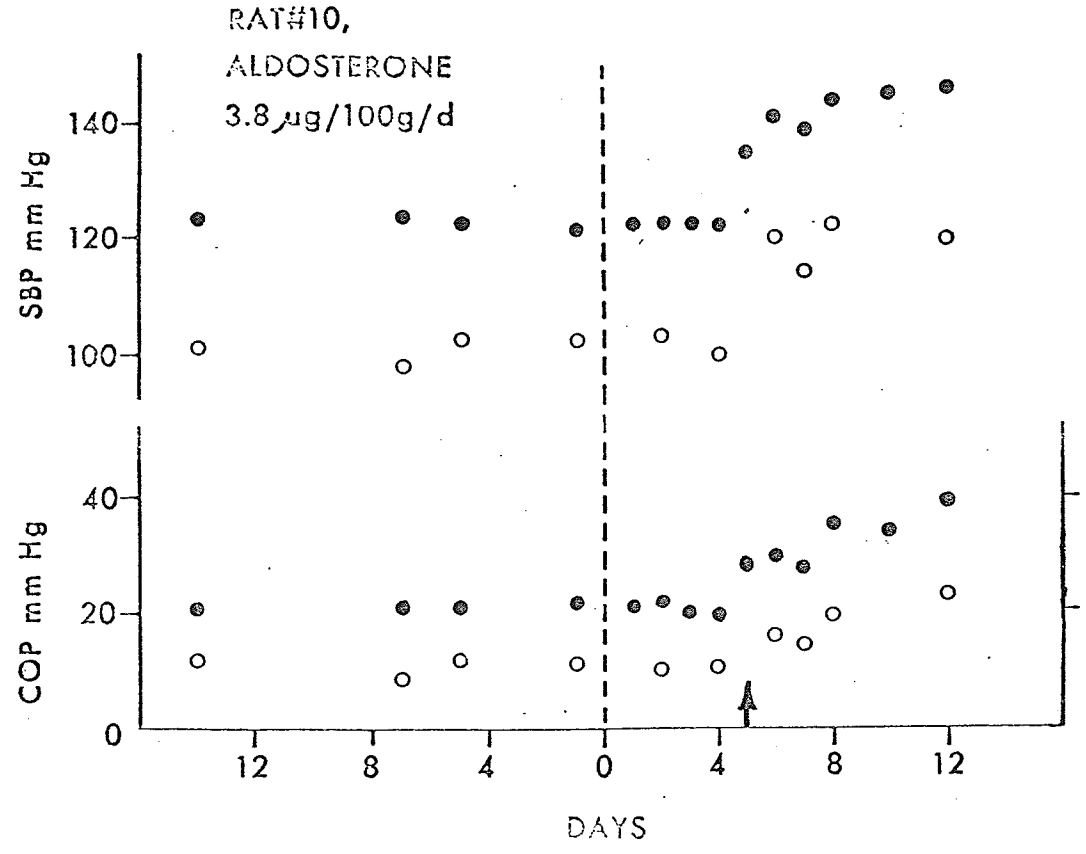

RAT#10,
ALDOSTERONE
3.8 µg/100g/d
SBP mm Hg
140
120
100
COP mm Hg
40
20
0
12
8
4
0
4
8
12
DAYS

Figure 17

Results from rat # 14, aldosterone dose rate 4.5 µg/100g/d.

Conventions as in Fig. 11.

Figure 18

Length of delay to onset of aldosterone hypertension in the rat versus dose rate of aldosterone. A composite graph to illustrate the results seen individually in Figures 11-17. The lines connect values obtained from rats that were carried through the experiment simultaneously with other rats in the same group.

Fig. 17

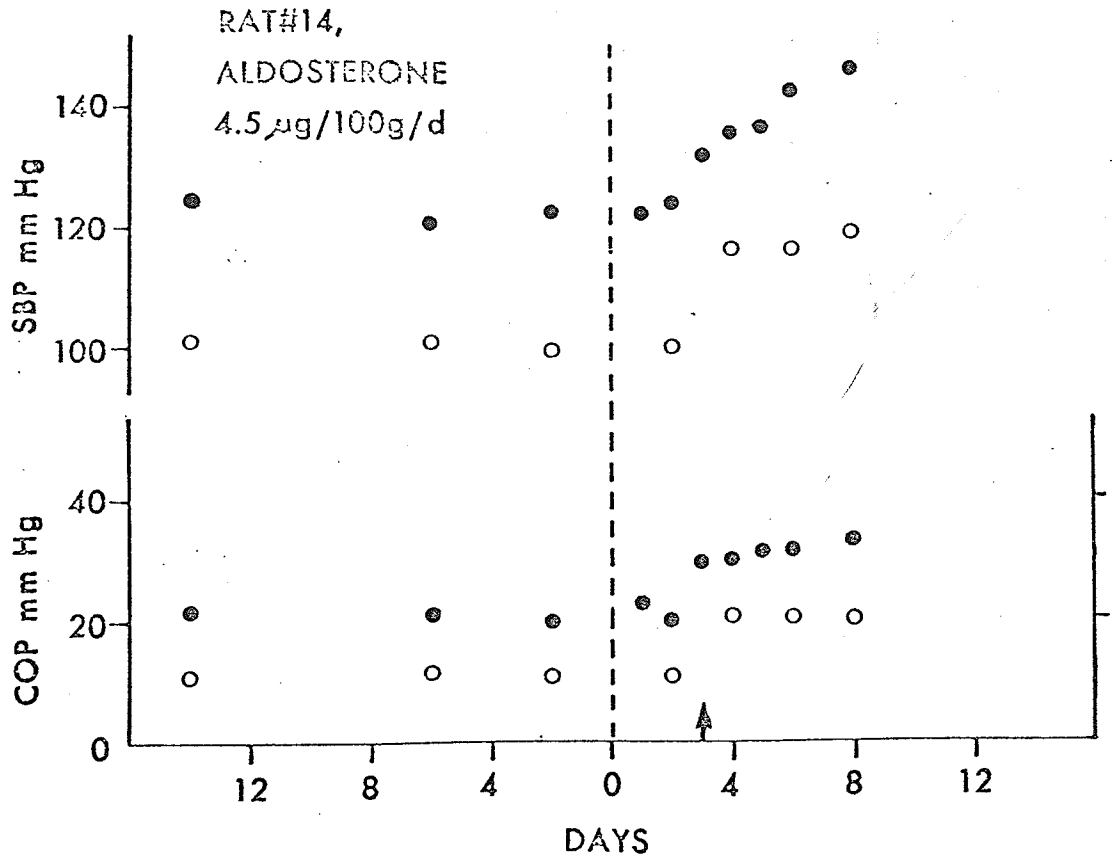
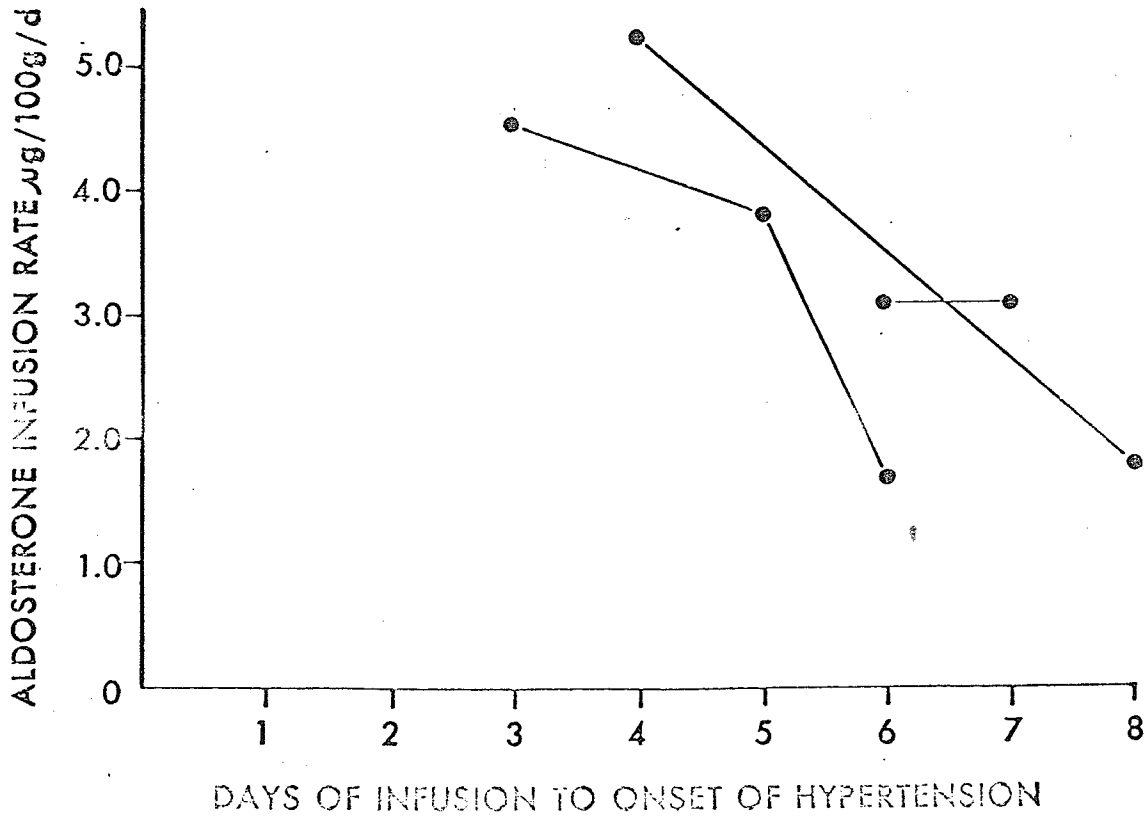

RAT#14,
ALDOSTERONE
4.5 µg/100g/d
SBP mm Hg
140
120
100
COP mm Hg
40
20
0
12
8
4
0
4
8
12
DAYS

Fig. 18


ALDOSTERONE INFUSION RATE µg/100g/d
5.0
4.0
3.0
2.0
1.0
0
1
2
3
4
5
6
7
8
DAYS OF INFUSION TO ONSET OF HYPERTENSION

DISCUSSION

Peripheral Vascular Autoregulation as an Explanation for Increased COP in the Tail Vessels of the Rat with Aldosterone Hypertension.

Peripheral vascular autoregulation has been invoked by some (Ledingham, 1971; Granger and Guyton, 1969; Guyton et al, 1974; Coleman et al, 1974), as an explanation for the increased total peripheral resistance to flow in the volume hypertensions where high circulating levels of vasoconstrictors are not found. The stimulus for peripheral autoregulation is believed to be an increased transmural pressure at the level of the resistance vessels, leading to a myogenic vasoconstriction, or an increased blood flow to the tissues, causing washout of vasodilator metabolites, or both. In these volumes hypertensions, (chronic renovascular, mineralocorticoid, some essential hypertensions) an increase in the ECF volume and cardiac output appear to be early events in the hypertension, lending support to the hypothesis of increased TPR on the basis of autoregulation.

In this laboratory we are involved in investigating factors that might increase the TPR in various forms of hypertension, particularly factors that can increase the contraction force of the vascular smooth muscle in the resistance vessels. We use the COP measurement as an index of vascular smooth muscle contraction force. An increased COPwas found in the resistance vessels in the skin of the tail of the rat made hypertensive with aldosterone. The hypertension produced by aldoterone is considered to be a volume hypertension, and if peripheral autoregulation of blood flow is responsible for the hypertension, through increasing the TPR, then the increased COP observed in the rat should be part of the autoregulation process.

In the present investigation, an experiment was conducted in order to test the autoregulation theory as an explanation for the increased TPR seen in volume hypertensions. The experiment was designed to allow for a continuous, graded increase in external pressure to be applied to the skin vessels in the tail of the rat as the rat became hypertensive from continuous subcutaneous infusion of aldosterone. The increased counterpressure was to be applied for up to one month in order to cover both acute and chronic phases of the hypertension, and was graded so as to keep transmural pressures and A-V pressure differences at normal or slightly low values. The rationale for applying this counterpressure was that if the increase in COP observed in those vessels was due to peripheral autoregulation, then preventing the development of increased autoregulatory stimuli should also prevent the increase in COP of those vessels. If, however, an increased COP did develop, then one would be forced to consider some other mechanism to explain the increased force of contraction in the smooth muscle of those vessels.

In this investigation, it was found that the COP of the skin vessels in the tail of the rat did increase, despite application of the increased external pressure to the tail as the aldosterone hypertension developed. If one could be assured that this increased extravascular pressure did keep transmural pressures and blood flow in the tail vessels at normal or slightly low values, then one would be forced to consider some other mechanism as an explanation for the increased COP.

A number of investigators have dealt with the effects of increased extravascular pressure on transmural pressures and blood flow through tissues.

Effects of Increased extravascular pressure on transmural pressures: Burton and Yamada (1951) pointed out that the absolute levels of pressure within a vessel can affect that vessel only through a change in the transmural pressure. As an example, they illustrated that the transmural pressure of a vessel with an intravascular pressure of 60 mmHg and 0 external pressure was the same as a vessel with a 100 mmHg intravascular pressure and a 40 mmHg extravascular pressure. In addition, Guyton has discussed the role of total tissue pressure (the extravascular pressure) in determining blood vessel compression (Guyton, 1971). More recently Brace and Guyton (1977) illustrated that the total tissue pressure in the subcutaneous space of the hind limb of the dog would change by exactly the amount of pressure applied to the limb with a plethysmograph. This direct pressure transmission was confirmed by Clayton, Hayes and Barnes (1977) who showed that muscle compartment pressure in the hind limb of the rabbit correlated extremely well ($r = 0.99$) with an externally applied counterpressure.

Effects of increased extravascular pressure on blood flow: Application of an increased extravascular pressure to a part will result in an increase in venous outflow pressure up to and perhaps just beyond that extravascular pressure that has been applied to the part. This equilibration of pressures will occur as long as the increased external pressure does not excede the arterial inflow pressure. By applying an increased extravascular pressure to a part, then, it is possible to keep A-V pressure differences at normal levels while allowing the arterial inflow pressure to reach hypertensive values. Since the A-V pressure difference is involved in determining blood flow, it should also be possible to keep blood flows

through a part at normal levels while the arterial pressure increases in hypertension. A very clear demonstration of the effect of increased extravascular pressure on blood flow in a part is seen in the work by Clayton et al (1977), mentioned earlier. They found that the application of an external pressure of 60 mmHg with a plethysmograph would reduce muscle blood flow by as much as 80%.

There seems little doubt, then, that the process of applying an increased extravascular pressure to the tail of the rat as the animal became hypertensive would keep transmural pressures and blood flow from increasing above resting normotensive values. This discounts peripheral vascular autoregulation as the explanation for the increase in COP of the tail vessels in the skin of the rat made hypertensive with aldosterone. It also suggests that some mechanism other than autoregulation is involved in increasing the total peripheral resistance in other volume dependent forms of hypertension.

The Possibility that a Hormonal Mechanism may be Involved in Increasing The Smooth Muscle Contraction Force in Resistance Vessels in Volume Dependent Hypertension

In the experiments that have been done on aldosterone hypertension in the rat, it has always been found that there is a delay of some days before there is an increase in the COP of the skin vessels in the tail. This delayed increase in COP suggests that some new event might have occurred to increase the vascular smooth muscle contraction force. The nature of the new event, and the trigger for its occurrence, are not yet understood. In this laboratory we suspect that a hormonal mechanism is involved in increasing the COP of the resistance vessels.

This hormonal mechanism for increasing the vascular smooth muscle contraction force is not likely to be a direct effect of aldosterone on enhancing sodium transport into the vascular smooth muscle cell. This statement is made became aldosterone is believed to exert its influence on sodium transport by stimulating mRNA and protein synthesis, a process that is known to require only a few hours. One would suspect that if aldosterone increased the vascular smooth muscle contraction force by enhancing vascular smooth muscle Na^+ transport into the cell, then an increased contraction force in the vascular smooth muscle should be seen in a matter of hours, not days.

Similarly, it is not likely that aldosteorne is increasing the tone of the vascular smooth muscle indirectly by changing the ionic milieu of the vascular smooth muscle cell. Aldosterone's action on the kidney tubule has a latency period of just hours. If the altered handling of electrolytes by the kidney is considered to be responsible for changing the ionic milieu of the smooth muscle and for increasing the vascular smooth muscle contraction force, one would expect the increased contraction force to develop within a few hours of beginning the administration of excess aldosterone. This was never observed in the development of aldosterone hypertension in our rats.

We suspect that the trigger for the hormonal mechanism is an expansion of the extracellular fluid volume or an increase in exchangeable Na^+ up to a particular level that causes the release of a new vasoconstrictor hormone. One would think that the timing of the release of this hormone would depend on the time required to increase the ECF volume and exchangeable Na^+ values up to that particular level. If this mechanism does exist, then it would

be expected that in this present investigation, the delay before the release of the vasoconstrictor should depend on the dose rate of aldosterone. This has been confirmed by the results of Project II which was conducted in order to investigate the influence of the dose rate of aldosterone on the delay to the onset of hypertension and increased COP. It was found that this delay tended to be long (ie a week) when low dose rates (about 2 μg/100g/d) were administered, but was much shorter when higher dose rates were used. Supporting evidence for the influence of aldosterone dose rate on the time of onset of hypertension comes from the autoregulation experiment where aldosterone dose rates of 5.0 μg/100g/d all produced hypertension in 3-4 days.

The elaboration of such a vasoconstrictor would account for the increase in COP in the autoregulation experiment where it was found that preventing the development of increased autoregulatory stimuli in the tail vessels did not prevent the increase in COP.

It is known that renal escape from the Na^+ retaining effects of excess mineralocorticoid administration occurs some days after starting the mineralocorticoid treatment. One wonders if the two events, the onset of renal escape and the delayed increase in COP in aldosterone hypertension in the rat, might be related.

Renal Na^+ escape is believed to be mediated by a natriuretic hormone. A natriuretic fraction recovered from the kidneys of volume expanded rats, but not from those of hydropenic rats, was found to be an in vitro inhibitor of both transepithelial Na^+ transport in the frog skin and $Na^+ - K^+$ - ATPase activity in the normal rat kidney (Hillyard, Lu and Gonick, 1976). This fraction was also found to induce a natriuresis and a diuresis when

administered iv into normal rats. Haddy and Overbeck (1976) have extrapolated from these and similar results and suggested that in volume expanded hypertension, there might be "a circulating agent that suppresses cardiovascular membrane $Na^+ - K^+$ - ATPase, resulting in reduced activity of the $Na^+ - K^+$ pump and hence increased contractility of heart, arteries and veins."

Whatever such a humoral substance might be, it does seem that some individuals are more susceptible than others to the hypertensive effects of volume expansion, either in terms of producing such an agent or responding with an increase in TPR if it is released. This was suggested by the work of Onesti et al (1975) when they expanded the ECF volumes of anephric patients by dietary salt loading and an appropriate adjustment of the hemodialysis procedure. Previously hypertensive patients showed an elevation of arterial pressure and an increase in TPR upon expansion of the ECF volume in this manner. Previously normotensive patients, however, showed only minor elevation of arterial pressure and inconsistent changes in TPR.

Possibility of a Neurogenic Component in the Increased COP in Aldosterone Hypertension

In aldosterone hypertension in the rat, it has been found that the increased COP cannot be explained on the basis of autoregulation. The nature of the increase in COP suggests a humoral mechanism for increasing the vascular smooth muscle contraction force in the resistance vessels. In addition, there seems to be a neurogenic component to the increase in COP. Administration of a ganglion blocking agent (GBA) before the rats became hypertensive resulted in a mean decrease of about 9 mmHg in the COP, but in the hypertensive condition the mean COP was reduced by about

15 mmHg by the GBA. The increased neurogenic component of the COP could have been due to 1) increased reactivity to norepinephrine (NE) released from the vasomotor nerves, or 2) increased activity of the vasomotor nerves, causing the release of more NE from the nerve terminal. The first consideration, that of the possibility of an increased reactivity of the vascular smooth muscle to NE released from the vasomotor nerves is not supported by the work of Darke et al (1977) which involved administering NE iv to hypertensive rats. They found no increased reactivity to NE in the tail vessels of rats made hypertensive with aldosterone and 1% NaCl for drinking water. Reactivity was assessed by the change in COP of the tail vessels in response to NE. Reactivity to NE in the hypertensive rats was compared to that seen in normotensive controls, after both groups of rats had received a ganglion blocking agent. This leaves the second possibility, that of an increased activity of the vasomotor nerves to the resistance vessels, as being part of the mechanism of increased COP in aldosterone hypertension and possibly other volume hypertensions. The mechanism of this increased neurogenic activity is not known.

In contrast to the changes in COP obtained with a GBA before and during the hypertension, it was found that the SBP in both the normotensive and hypertensive states were reduced by about 20 mmHg. This is not inconsistent with the increased neurogenic component of the COP because the SBP is the end result of a number of controlling mechanism which will tend to keep the SBP as low as possible.

Structural Alterations in the Resistance Vessels as a Mechanism for Increasing the COP in Aldosterone Hypertension in the Rat.

There is no doubt that medial hypertrophy of the smooth muscle in the resistance vessels does occur in hypertension and that it does contribute to an increased TPR by narrowing the lumen of the vessels. Medial hypertrophy would result in an apparent increase in smooth muscle contraction force and an increase in COP. It is thought by most, however, that such structural alterations occur in response to an existing hypertensive state and are not by themselves responsible for the increase in TPR (Bohr and Berecek, 1976).

Folkow believes that such vascular restructuring on a long term basis is responsible for the sustained increase in TPR that is seen in hypertensions where there has been a prolonged increase in the transmural pressures, including volume dependent forms of hypertension (Folkow and Neil, 1971; Folkow and Silvertsson, 1968). In the present investigation, however, transmural pressures in the tail vessels were not allowed to increase, so adaptive medial hypertrophy could not have occurred, yet there was still an increase in COP. This suggests that structural alterations were not important in increasing the COP of the tail vessels.

Folkow believes that the increased TPR in spontaneously hypertensive rats and many human essential hypertensions is due to such vascular restructuring. In the development of human essential hypertension, he cites repeated arousal of the defence reaction, with its cardiovascular sequelae (i.e. repeated increases in transmural pressures) as being important in causing hypertrophy of the smooth muscle in the resistance vessels.

This may or may not be involved in the development of these hypertensions. It is interesting to note, however, that in the hormonal events of the defence reaction, there are many hormones released, some of which have mineralocorticoid activity, including aldosterone. It could be that expansion of the ECF volume has occurred in these hypertensions, triggering the release of vasoconstrictor hormone.

CONCLUSIONS

1. Aldosterone hypertension in the rat is characterized by an increase in systolic blood pressure (SBP) and an increase in the critical opening pressure (COP) of the resistance vessels in the skin of the tail.
2. This increase in COP cannot be explained on the basis of peripheral vascular autoregulation in volume dependent hypertension.
3. The increase in SBP and COP is delayed in onset, with the length of delay influenced by the dose rate of aldosterone.
4. The nature of this increase in COP suggests that some new event might have occurred, perhaps the release of a vasoconstrictor hormone.

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