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Mark Gregory Tagett

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Robert B. Stephenson
Major professor

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By

Mark Gregory Tagett

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ABSTRACT

THE EFFECTS OF ANGIOTENSIN II-INDUCED HYPERTENSION ON THE BARORECEPTOR REFLEX

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Mark Gregory Tagett

The overall ability of the arterial baroreflex to regulate blood pressure (BP) has not been monitored during the development of chronic hypertension. Furthermore, the relative contributions of sympathetic and parasympathetic mechanisms to baroreflex responses have not been appropriately elucidated in hypertension. In this study, normotensive dogs with intact or denervated aortic depressor nerves were surgically prepared so that the carotid sinus regions could be reversibly isolated from the systemic circulation and exposed to controlled, static pressures. Complete stimulus-response relations were determined for the effects of carotid sinus pressure on BP and heart rate during acute infusions of angiotensin II (AII) (300, 600, 1200 ng/min.), and chronic infusions of AII at 5.0 ng/kg/min. (3-6 weeks). The effects of various autonomic antagonists on the resting level of BP and on the carotid baroreflex stimulus-response relations were determined before and after chronic AII-induced hypertension. The results of this study are significant because they reveal that the changes in the baroreflex which accompany AII-induced hypertension are not time dependent, but rather pressure dependent. The baroreflex rapidly adapts to the elevated BP,

which may in part be caused by AII-induced stimulation of baroreflex-independent pressor pathways. The baroreflex thus maintains its ability to regulate BP on a moment-to-moment basis. Furthermore, in both normotension and hypertension, parasympathetic activation is the predominant mechanism by which the baroreflex decreases BP. Sympathetic mechanisms make a contribution to reflex increases in BP, particularly in aortic-denervated dogs. Thus, although the baroreflex is reset in conjunction with the elevated BP in salt-AII hypertension, the balance between sympathetic and parasympathetic contributions to the baroreflex is unaltered.

Men, in fact, desire from science nothing else but the benefits; not the arguments, but the definitions. Accordingly, our intention in this book is to shorten long-winded discourses and synthesize the various ideas. Our intention also, however, is not to neglect the advice of the ancients.

Ibn Botlan, "the Physician,"
from the preface to the
Tacuinum Sanitatis
(15th century)

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Development of the Experimental Question

Despite numerous studies, the role of the arterial baroreceptor reflex (baroreflex) in the genesis of naturally occuring and experimental hypertension remains an enigma. This dissertation concerns a study of the baroreflex during the development and maintenance of experimental hypertension in dogs, which was brought about by combining a diet high in salt with a continuous infusion of angiotensin II. Two underlying experimental questions were addressed: 1) what is the magnitude and timecourse of baroreflex resetting during the development of salt-AII hypertension, and 2) what are the relative contributions of sympathetic and parasympathetic mechanisms to the support of the hypertensive level of arterial blood pressure and to reflex alterations in that pressure.

The term baroreceptor reflexes is sometimes employed to designate all the reflexes arising from stretch receptors in the cardiovascular system. The arterial baroreceptor reflex, the carotid baroreflex in particular, has been most extensively investigated (Kircheim, 1976); the aortic baroreflex has been relatively neglected, mainly because of the difficulties encountered in the surgical isolation of the aorta. The

term baroreflex, in this text, will be used collectively to represent the aortic depressor reflex and the carotid sinus reflex unless otherwise prefixed.

The arterial baroreflex exerts inhibitory control of tonic sympathetic activity and excitatory control on tonic parasympathetic activity via the cardiovascular centers of the medulla. The French physician Etienne Marey, first described the inverse relationship between imposed changes in arterial blood pressure and the resultant changes in heart rate in 1859. This discovery was soon followed by the first description of the aortic depressor nerves, which are responsible for the bradycardia and diminution of peripheral resistance that results form elevation of pressure in the aortic arch. This depressor phenomenon, originally discovered by Cyon and Ludwig in 1866, and demonstrated to be reflex in origin by Eyster and Hooker in 1908, provided an early example of a negative feedback mechanism (cf. Heymans and Neil, 1958). It was not until 1923 that Hering definitively demonstrated the carotid sinus reflex, which, in conjunction with the aortic depressor reflex, makes up an unusually powerful control system that regulates arterial blood pressure.

The baroreceptor reflex is the predominant regulator of blood pressure under normal circumstances, because it is the only blood pressure regulator with sufficient speed to respond to the moment-to-moment perturbations of blood pressure that result from transient stimuli such as postural changes, emotions, sexual activity, exercise, and eating. The renal and humoral mechanisms which also are involved with blood pressure control are too slow to respond efficiently to these stimuli (Brown, A.M., 1980).

Much of our knowledge concerning the baroreceptor reflex has been gained from experiments in which the reflex arc has been artificially isolated and one component part - the baroreceptor properties, afferent signals, central processing, efferent signals, or effector activity - is identified and examined. This method of analysis has also been almost exclusively utilized in studying the baroreflex under hypertensive conditions.

The Components of the Baroreflex Arc in Normotension and Hypertension

The Baroreceptors

Baroreceptors differ not only among themselves, but baroreceptors in hypertensive animals also differ from those of normotensive animals (McCubbin, 1956). One factor common to naturally occuring hypertension and to the different types of experimental hypertension that have been produced in different species, is baroreceptor resetting. McCubbin (1956) and Kezdi (1967) have used the term resetting to indicate that in renal hypertension the carotid sinus baroreceptors respond over an elevated range of pressure. Subsequent workers confirmed baroreceptor resetting for the rat (Krieger and Marseillan, 1966), rabbit (Aars, 1968a), and dog (Sleight et al.,1975). Adaptation to a sustained stimulus is a property that all peripheral mechanoreceptors display to a certain extent (Landgren, 1952; Mountcastle, 1980). Receptor resetting effectivley alters the set point for the arterial baroreceptor reflex. The exact adaptation rate of receptor resetting with respect to mean arterial pressure changes has not been satisfactorily determined.

Peripheral (baroreceptor) resetting must be distinguished from central resetting, which can ocurr almost instantaneously (Korner, 1971).

It is not clear whether baroreceptor resetting is due to changes in mechanical properties of the arterial wall, to changes in the receptors themselves, or both. Methods to elucidate this question have involved studying baroreceptor resetting under three sets of circumstances: established hypertension (McCubbin et al., 1956; Aars, 1968a), early hypertension (Brown et al., 1976), and following acute, mechanically induced changes in arterial pressure (Krieger, 1970).

In classic experiments on established renal hypertension, McCubbin et al. (1956) used electroneurographic techniques to demonstrate that the relationship between carotid baroreceptor impulse frequency and applied pressure is reset to the higher level, such that the threshold and saturation pressures are both increased. A similar resetting was subsequently confirmed in various models of chronic hypertension (McCubbin, 1958; Kezdi, 1962; Nosaka and Wang, 1972; Angell-James, 1973; Brown et al., 1976; Floral and Jones, 1979). Furthermore, the sensitivity of the baroreceptors to changes of pressure (Aars, 1968a; Angell-James, 1973; Sleight et al., 1975), as well as the maximum firing frequency (Sleight et al., 1975), are both reduced. These changes were shown to occur over days and weeks and to result from the direct effects of higher distending pressure. Resetting was accompanied, in some cases, by structural alterations in the vessel walls. The fact that elevated pressure, and not humoral influences, was responsible for baroreceptor resetting was elegantly shown by Kezdi et al. in 1972. They anastomosed one carotid sinus to the adjacent jugular vein and left the opposite sinus intact. Renal hypertension was then induced by cellophane perinephritis. The anastomosed sinus was exposed to the same

humoral and neurogenic influences as the opposite carotid sinus; yet it was protected from the elevated arterial pressure. After 6 months they measured nerve activity from both carotid sinuses and found that the unprotected sinus had reset, whereas the protected one had not. This experiment indicated clearly that increased distending pressure is involved in the resetting process and excluded a significant contribution of circulating hormones or neurogenic influences. Although the renin-angiotension system has been implicated in various forms of hypertension, a direct action of angiotensin II on the baroreceptors has been refuted (McCubbin et al., 1957; Buckley, 1972; Lumbers et al., 1979; Stein et al., 1984).

It is currently accepted that the elastic properties of the arterial wall are altered in established hypertension. The demonstration of increased sodium and water content in the common carotid arteries of renal hypertensive rats (Tobian and Redleaf, 1958) and the arteries of hypertensive dogs (Jones et al., 1964), led to the suggestion by Jones (1964) and Tobian et al. (1969) that these changes in vascular water and electrolyte balance might stiffen the walls of the baroreceptor areas and thus account for baroreceptor resetting. A decreased compliance of the baroreceptor regions may also be caused by increased deposition of elastin and collagen in the arterial media (Wolinski, 1970).

Kezdi et al. (1972), in the experiment mentioned above, measured the sodium and water content in the walls of the carotid sinuses and found that there was an increased sodium concentration in the sinus exposed to a raised arterial pressure, but not in the protected sinus. However, the hypertensive sinus was found to be more distensible that normal in his experiments. In contrast, Aars (1968b) and Angell-James

(1973) demonstrated that the aortae of hypertensive rabbits were less distensible than their normotensive controls, and that this could account for baroreceptor resetting (Aars, 1969). Many of the experiments on baroreceptor resetting have utilized renal hypertensive models. However, Angell-James (1974a,b) also found impaired receptor activity and reduced vessel distensibilty in rabbits in which pronounced structural changes were induced by vitamin D sclerosis. The high cholesterol diet caused mild hypertension, impaired baroreceptor sensitivity, and degeneration of receptor endings.

The possibility that baroreceptor resetting is produced primarily by damage to the receptor ending in hypertension has been supported by Hilgenberg (1958) and Abraham (1969); however, others have refuted this explanation (Rees et al., 1978; Kraughs et al., 1979). To explore the possibility of baroreceptor damage as a result of elevated pressure, Salgado and Krieger (1973) recorded baroreceptor thresholds in rats with renal hypertension of approximately two months and then removed the clips from the renal arteries. They postulated that receptor damage would not be reversible. Therefore, if a downward resetting could be demonstrated after removal of the renal artery clips, this would imply that no nerve damage had occurred and that resetting was due to changes in the vessel wall. They observed that the pressure range for baroreceptor activation shifted down toward normal within 6 hours. In contrast Kezdi (1973) found downward resetting in only one of five animals 4 to 5 weeks after the cessation of chronic renal hypertension. Similarly, Sleight et al. (1972) reported that downward resetting in dogs' carotid sinuses took longer than four days and appeared to be related to both the level of pressure and the duration of the hypertension. Therefore, it is not yet known whether the resetting

process, in established hypertension, is the result of receptor damage in addition to structural adaptation of the arterial wall. Furthermore, the possibility of uncoupling of the receptor from the vessel wall has not been excluded (Brown, A.M., 1980).

The Role of the Aortic Baroreceptors

The role of the aortic baroreceptors in regulating blood pressure is controversial. It has been evident for over one hundred years that temporary loss of carotid baroreceptor activity produces an elevation in arterial pressure. However, in many species, bilateral section of the aortic depressor nerves causes little change in arterial blood pressure. This fact has led to the assumption that the threshold pressure required to activate aortic baroreflex responses exceeds the normal arterial pressure. Edis (1971) studied the response of anesthetized dogs to hemorrhage and concluded that the aortic baroreflex has little role in normotensive or hypotensive situations and functions primarily in an anti-hypertensive role. Pelletier et al. (1972) narrowed this conclusion to just the aortic baroreceptors themselves.

The carotid sinus and aortic arch baroreceptors also appear to differ with respect to the location of the receptor endings in relation to structural components of the vessel wall. Receptors in the carotid sinus appear to be situated between the collagen fibers of the adventitia parallel to the long axis of the vessel (cf. Ferrario and Takashita, 1983). However, in the aortic arch the receptor endings are parallel to the fibrous elements (Abraham, 1969). A correlation between receptor location and physiological function has yet to be proven.

Most electrical recordings of afferent activity in baroreceptor fibers were performed on the large myelinated fibers (type A) arising

from the carotid sinus and aortic arch. However, unmyelinated C fibers exist in both the carotid sinus nerves and aortic nerves, and in fact prevail in number (Fidone and Sato, 1969). Analysis of both fiber types, in rabbits and rats, has demonstrated that the myelinated fibers have thresholds below ambient arterial pressure and that the unmyelinated fibers only begin to discharge at arterial pressures above normal (Jones and Thoren, 1977; Aars et al., 1978). In chronic renal hypertension the A fibers are fully reset whereas the C fibers are reset to a lesser extent (Jones and Thoren, 1977). Thus, it appears that C fiber afferents only exert a buffering influence during periods of elevated pressure.

The Central Nervous System

Following the mechano-electrical transduction in the baroreceptors the afferent discharge is conducted to the brain stem by way of the carotid sinus nerves and the aortic depressor nerves. The fibers of the primary baroreceptor neurons travel among the other fibers of the IXth and Xth nerves. The somata of the primary afferents are located in the petrosal and nodose ganglia respectively. The primary afferents reach the medulla oblongata laterally at a level close the obex and descend to synapse in both the medial and lateral caudal aspects of the nucleus tractus solitarius (NTS) (Palkovits and Zaborszky, 1977). Beyond this point the neurocircuitry of the baroreflex becomes increasingly unclear. Even the exact identity of the neurotransmitter which is released by the primary baroreceptor afferents is uncertain; although Reis et al. (1980) have suggested that l-glutamate is a likely candidate. Better knowledge of baroreflex cardiovascular control mechanisms requires further neuroanatomical studies.

The neurocircuitry exists within the central nervous system for resetting the baroreflex. The central neural circuitry of the baroreflex can display a great deal of plasticity. Changes in afferent baroreceptor activity have been suggested to alter properties of central neurons by means of ion accumulations and depletions, changes in the electrogenic pump activity (Kruz et al., 1975), as well as by slow synaptic transmission (Spencer, 1970). In fact, resetting of the central components of the baroreflex have been shown to occur within 20 to 90 seconds (Richter et al., 1970).

Resetting within the central nervous system however, is not necessarily pathogenic but rather the appropriate physiological response under normal circumstances. For example, activation of the hypothalamic "defence area" may reset the reflex to a higher pressure level (Humphreys and Joels, 1972). Central resetting has also been demonstrated during sleep, exercise, arterial hypoxia, and in patients with high cervical cord transections.

Central resetting of the baroreflex imparts flexibility to the blood pressure control system in response to different somatosensory stimuli. However, sustained central resetting may augment sympathetic nervous activity and lead to vascular hypertrophy, a reduced wall to lumen ratio, and an elevated vascular resistance. Ultimately these changes may become independent of the initial stimulus and result in chronic hypertension (Folkow, 1982). Three major lines of evidence suggest that the central nervous system is involved in human essential hypertension: 1) the occurence in some hypertensive patients of elevated levels of circulating catecholamines (DeQuattro and Miura, 1973), 2) the efficacy of certain centrally acting drugs, such as clonidine and alpha-methyldopa, in the treatment of human hypertension (DeJong and

Nijkamp, 1976), and 3) the demonstration in some hypertensives of arterial pressure lability and exaggerated reactivity of arterial pressure to environmental stimuli (Littler et al., 1972). Experimentally, attemps to produce chronic hypertension by manipulating the central nervous system and its reflex mechanisms have involved facilitation of sympathetic drive or withdrawal of sympathetic inhibition. Attempts to produce chronic hypertension by augmenting sympathetic discharge have had limited success. Some of these studies involved chronic, subthreshold electrical stimulation of the posterior or lateral hypothalamus (Folkow and Rubenstein, 1966), chronic brain ischemia (Dickinson, 1965), and chronic emotional stress or classical conditioning (Folkow and Rubenstein, 1966). In general, these experimental protocols created an elevated arterial pressure during the period of stimulation. However, the pressure gradually returned to or towards normal after the stimulation was terminated.

Greater success in the production of sustained hypertension has been obtained by experimental withdrawal of inhibitory input on the sympathetic nervous system. Until recently, the majority of studies have attemped to reduce sympathetic inhibition by chronic denervation of the arterial baroreceptors. The effects of chronic baroreceptor denervation have been studied in rats, rabbits, cats, and dogs for many years. Elevated blood pressure following chronic denervation of baroreceptors was unquestioned until it was observed that the mean level of arterial pressure, averaged over extended periods from continuous recordings, generally was not elevated. Rather arterial blood presure in baroreceptor-denervated dogs exhibited increased lability and

exaggerated reactivity (Cowley et al., 1980). However, Ito and Scher (1981) continue to provide evidence that baroreceptor denervation induces a mild, but real hypertension.

Clearer success in inducing chronic hypertension has been obtained by placing lesions in particular brain regions that participate in tonic sympathoinhibition. Electrolytic destruction of the NTS in rats is characterized, after recovery from anesthesia, by a lethal fulminating hypertension. The increase in blood pressure is the result of an increased total peripheral resistance, which leads to cardiac failure, pulmonary edema, and finally death within four to six hours (Reis et al., 1977). The same lesion in cats results in an acute elevation in blood pressure; however, the majority of the animals survive with average arterial pressure reaching normal values within 24 hours. Nevertheless, cats with NTS lesion exhibit marked pressure lability, exaggerated pressure reactivity, little or no baroreceptor function, sustained tachycardia, and eventual sustained hypertension (Reis, 1980). Similar findings are seen in the anesthetized dog (Laubie and Schmitt, 1979). A more profound elevation in arterial pressure was observed, using a classical conditioning paradigm, in cats with NTS lesion (Nathan et al., 1978). Preservation of the baroreflexes in combination with arterial blood pressure lability has been produced by Reis et al. (1979) following lesions of A2 nerve terminals with 6-OHDA. The neurons of the A2 cell group, located within the NTS caudal to the area postrema, innervates the NTS. Stimulation of the A2 cell group is believed to enhance baroreceptor sympathoinhibition. The effects of the selective lesion of this cell group has led Reis et al. (1979) to hypothesize that for stress to produce hypertension, baroreflex integration must be

impaired, and that further research is warrented concerning the neurobiology of monoamine neurons which regulate blood pressure in the central nervous system.

All the components of the renin-angiotensin system are present in the brain, including in areas that have been proposed to modulate the baroreceptor reflex. It has been demonstrated that isorenin and angiotensin II (AII) are located in some nerve terminals as well as synaptosome fractions of brain homogenates that also contain catecholamines. It has also been observed that there is considerable overlap in the distribution of AII and norepinephrine in the brain (cf. Strahlendorf and Strahlendorf, 1980; Ganong, 1984). Therefore, it has been proposed that a major function of the brain renin-AII system is the adjustment of the activity of monoaminergic baroreflex modulation centers.

Several circumventricular organs are located adjacent to receptors for AII. The area postrema is required for the centrally mediated pressor response to blood-borne AII in the dog, cat, and rabbit. The area postrema is located just rostral to the obex on each side of the fourth ventricle. Afferent fibers are received from NTS and spinal cord, and area postrema efferents have been traced to the medial NTS (Carpenter, 1978). Ferrario et al. (1972) have implicated the area postrema as a site at which subpressor doses of AII, as well as pressor doses administered into the vertebral artery (Fukiyama et al. 1971), evoke elevations in blood pressure that can be sustained.

In the rat, the area postrema is not involved in the central pressor responses to AII. Rather, the AII receptor areas are located in the hypothalamus; specifically in the anteroventral region of the third ventricle (AV3V). A relationship between two circumventricular organs,

the organum vasculosum of the lamina terminalus (OVLT) and the subfornical organ (SFO), has been demonstrated. The pressor effect of intracerebroventricular administration of AII is dependent on access to the AV3V and the integrity of both the AV3V and the OVLT. Furthermore, the AV3V and the SFO mediate the pressor actions of blood-borne AII (Brody et al., 1980). Therefore, AII in the blood stream or in the CSF can modulate central catecholaminergic mechanisms and can effect an increase in blood pressure.

Uncertainty persists as to the mechanism by which AII exerts its central pressor effect. Differences in experimental results can be attributed to species (subspecies) differences, mode of AII administration, the presence or absence of anesthesia, and the type of anesthesia. Independent, but contemporaneous work by two groups of investigators suggested two different mechanisms of action in the same species. Scroop and Lowe (1969) showed that infusion of AII into the vertebral arteries of chloralose-anesthetized greyhounds produced a hypertensive response that was due to withdrawl of parasympathetic tone to the heart. However, Ferrario and co-workers (1970; 1972), applying the same preparation in mongrel dogs, observed that the pressor response was the result of increased peripheral resistance without changes in heart rate or cardiac output. The elevated peripheral resistance was characterized by an increase in preganglionic splanchnic vasomotor discharge and decreased renal nerve activity. The pressor responses could be abolished with sympathetic blockade or spinal cord section at C2. Therefore, these data suggest that AII activates bulbo-spinal vasoconstrictor sympathetic pathways. More recently, direct electrophysiological evidence has been provided by Stein et al. (1984) in support of Ferrario's contention, and by Lumbers et al. (1978) in the

support of Scroop and Lowe. Furthermore, indirect evidence in support of Ferrario's hypothesis has been provided by Johnson et al. (1965) in humans. They showed that "ordinary" pressor concentrations of infused AII exert a hypertensive effect by sympathetic activation. Specifically, the blood level of AII achieved was able to constrict veins in a forearm that was isolated from the circulation; whereas, local blood levels of AII had to be increased by approximately one order of magnitude to elicit a pressor effect in a sympathetically blocked forearm.

McCubbin and Page (1963) reported that AII enhances the responses to carotid occlusion in the perfused superior mesenteric artery, but not in the perfused hindlimb. Consistent with these findings, Sweet and Brody (1970) demonstrated that administration of AII (or reduction of renal perfusion pressure, which would increase endogenous AII) impairs baroreflex-induced hindlimb vasodilation, whereas reflex constrictor activity remains intact. The findings of Sweet and Brody have been further corroborated by others (Goldstein et al., 1974; Marker et al., 1980). Central administration of AII has also been reported to attenuate the parasympathetic component of the baroreflex in the conscious ewe and fetus (Ismay et al., 1979) and chloralose-anesthetized mongrel dogs (Lumbers et al., 1979). It appears that the modification of both sympathetic and parasympathetic activity is due to the effect of AII somewhere along the central interneurons of the baroreflex, since AII does not alter the sensitivity of the peripheral baroreceptors themselves (Stein et al., 1984).

The Effectors

Structural adaptation of the cardiovascular system occurs whenever it is faced with an increased load. The structural alterations of the left ventricle, systemic arteries, and arterioles have been recognized for over one hundred years. The initial assumption was that these changes represented a late and irreversible complication of hypertension. More recently however, it has been revealed that these structural changes appear and regress quite rapidly, so they are now viewed as dynamic participants in the evolution of hypertension.

Cardiac hypertrophy can markedly alter the hemodynamic pattern and progression of hypertension. The heart can also initiate the hypertensive process and maintain it. It has been convincingly demonstrated in both clinical and experimental studies that the progression of many forms of hypertension involves an initial increase in cardiac output followed by an increase in peripheral resistance with normalization of flow. This pattern of hypertension development has been demonstrated in human essential hypertension (Lund-Johansen, 1980), and in experimental renal (Ferrario and Page, 1978), mineralocorticoid (Bravo et al., 1977), and cardiogenic (Liard, 1978) hypertension in dogs. The same pattern has been demonstrated in the SHR (Pfeffer et al., 1976). The sequence from high output to high resistance has been described as "total body autoregulation" by Guyton and co-workers (1974). However, this pattern of hypertension does not encompass all forms of the disease (Tarazi et al., 1973; Ibrahim et al., 1975).

Increased cardiac contractility can initiate an increase in flow; however, two criterion must be met for hypertension to develop: 1) venoconstriction, enhancing central relocation of blood, to maintain the elevated cardiac output and 2) constriction or lack of dilation of the

resistance beds. Increased sympathetic activity, increasing cardiac output as well as vasoconstricting both resistance and capacitance vessels, could cause a hypertensive condition.

The change from a high to lower cardiac output, which often accompanies hypertension has been correlated with cardiac hypertrophy and altered myocardial compliance (Folkow, 1978). Myocardial hypertrophy is the response to increased afterload. However, the concomitant reduction in compliance can functionally reset cardiac mechanoreceptors. This adaptation does not eliminate the autonomic nervous activity that ensures adequate cardiac filling and performance, but acts to maintain rather, than counteract, the hypertensive state.

An increase in blood pressure is a stimulus for structural adaptation in arteries and arterioles, because it elevates the wall tension against which the vascular smooth muscle operates. Cardiac and vascular structural adaptation begins to occur within a few days in rats with experimental renal hypertension (Lundgren et al., 1974), and it is almost complete in less than two weeks. The time course of cardiovascular structural adaptation in rats and rabbits has been demonstrated to be as covert as the increase in arterial pressure (Meerson, 1969; Bevan et al., 1980). The structural precapillary adaptation, in young SHR, follows the increase in blood pressure so closely it is difficult to determine which is the dependent variable (Folkow, 1978). It has been shown, in some models of hypertension, that if the elevated blood pressure lasts only one or two months, complete regression of the abnormal structure of the heart and vessels can occur in two to three weeks (Lundgren et al., 1974). However, the longer the hypertension lasts, the slower and less complete is the reversal of the structural alterations (Lundgren et al., 1974). Structural adaptation

presumably becomes irreversible due to increased collagen deposition which occurs in response to elevated and sustained tension and which regresses slowly if at all in comparison to the reversal of muscle hypertrophy (Wolinsky, 1970; 1972).

Folkow's (1978) theoretical models have demonstrated that thickening of arterial walls causes a reduction in the lumen and an elevated resistance at maximal vasodilation. Furthermore, an enhanced wall thickness to lumen diameter ratio, in resistance vessels of hypertensive subjects, acts to amplify the luminal reduction with muscle contraction. The net result is a pronounced vascular hyperreactivity and proportionally greater vascular resistance without enhanced smooth muscle activity. This hyperreactivity participates as a positive feedback mechanism, along with the initial pressor influence, which theoretically could be slight and intermittent in duration.

The Sum of the Components

"It is clearly teleologically absurd for the [baro]reflex to oppose a rise of arterial pressure where this is physiologically appropriate..." (Pickering and Sleight, 1977); however, the irony occurs with the coexistence of a functional baroreflex and a pathophysiologically elevated arterial blood pressure. Several components of the baroreflex probably contribute to its resetting in hypertension. In order to identify a specific aberation in the neural control of the circulation in hypertension, researchers have almost exclusively utilized a reductionist approach to pinpoint a site, centrally or along the peripheral limbs, as the epicenter for the disease. However, when alterations in homeostatic mechanisms which depend on neurohumoral control occur, it is often difficult to determine

what event triggered the disease and which changes are secondary. The baroreceptors adapt to sustained changes, both functionally and by alterations in the vessel walls in which they are located. The central nervous system and the effector organs of the baroreflex also adapt rapidly to imposed changes in blood pressure. The baroreflex exists as an ever-adapting loop. Therefore, if an abnormality is experimentally observed along the reflex pathway it does not identify that point in the pathway as the key pathological site. "The nervous systems of higher animals and humans are so complex and display such a rich variety of phenomena that any attempt to understand their functioning in purely reductionist terms seems quite hopeless (Capra, 1982)." Therefore, in an attempt to move away from a purely Cartesian approach to experimental design, it must be remembered that it is the baroreflex, and not its components individually or in summation, which is of physiological importance.

Hypertension and the Baroreflex

Without a doubt, several elements of the baroreceptor reflex become abnormal in chronic hypertension. The baroreceptors themselves adapt or reset to the elevated levels of prevailing pressure, and the sensitivity with which the baroreceptors respond to changes in blood pressure is decreased (Angell-James and George, 1980; Guo et al., 1983; Sleight et al., 1977). Some forms of hypertension involve increased vascular responsiveness to adrenergic stimuli (Webb, 1984), which could potentially offset a decreased sensitivity of the baroreceptors. Complex changes occur within the central and peripheral pathways (Thames et al., 1984, Zimmerman, 1983; Brody et al., 1980). The net effect of

all these changes on the overall ability of the baroreflex to regulate blood pressure is not clear.

Primary Resetting of the Baroreflex

Hering (1927), Koch and Mies (1929), and Volhard (1948) suggested that defective baroreflex buffering of arterial blood pressure might cause hypertension. Although, the validity of this theory has been questioned (Page, 1965) it has not been discredited altogether. Guyton et al. (1970) have proposed that the baroreflex is only of importance in the short-term, moment-to-moment, buffering of changes in arterial pressure. According to Guyton, the relationship between fluid balance and the kidney (the so-called concept of pressure natriuresis) is the most important determinant of arterial blood pressure in the long term (Guyton et al., 1974). If the pressure diuresis hypothesis is accepted, it follows that increased sympathoadrenergic activity, even if sustained, can only induce short-term increases in pressure; long-term pressure increases brought about by the sympathetic nervous system would be corrected by the volume readjustment induced by pressure natriuresis (Zanchetti, 1979).

Theoretically, the renal negative feedback system has an infinite gain; however, many ways have been demonstrated by which renal "long-term barostat function" is reset and has a diminished gain. Some of the factors that alter the renal function curve include enhanced sympathetic renal nerve activity, altered plasma levels of AII and aldosterone, as well as structural adaptation (Guyton et al., 1981), which would adjust both long-term and short-term barostats in parallel.

Guyton's hypothesis does not disqualify the baroreflex from contributing to the onset and maintenance of chronic hypertension,

because the sequence of physiological events leading to increased arterial blood pressure does not necessarily start from the kidney. It is conceivable that a resetting of the baroreflex may be the primary event in the initiation of increased sympathetic activity and/or arterial blood pressure. Evidence for primary baroreflex resetting in hypertension is modest. However, in the SHR, baroreflex resetting, due to changes in the receptors themselves (Brown, A.M., 1976), is evident at ten weeks of age, before the appearence of reduced vessel distensibility and chronic hypertension (Sapru and Krieger, 1979).

A primary role for impairment of the baroreflexes in initiating hypertension has been questioned recently. In particular, Cowley et al. (1981) have reported that the mean level of arterial pressure generally is not elevated in dogs with sinoaortic denervation. However, Ito and Scher (1981) have supported the classical view of blood pressure control (Heymans and Neil, 1958), by showing that chronic denervation of arterial baroreceptors could produce maintained, although mild, hypertension (neurogenic hypertension). Ito and Scher (1981) demonstrated that the magnitude of the chronic hypertension is correlated with the extent of the denervation. Ferarrio et al. (1969) have also demonstrated mild hypertension in dogs following sinoaortic denervation with a profound increase in the lability of heart rate and arterial pressure. Laubie and Schmitt (1979) have also shown chronic hypertension in dogs with denervation.

The debate concerning the relationship between baroreceptor denervation and hypertension is not restricted to dog studies. Neurogenic hypertension has been demonstrated in the rat by Vasquez and Krieger (1980) and by Fink et al. (1980). However, continuous monitoring of arterial pressure by Norman et al. (1981), failed to

indicate hypertension in sinoaortic denervated rats. A different approach at neurogenic hypertension was used by Reis et al. (1977). They produced chronic lability and elevation of arterial pressure by disrupting the integrity of the baroreflex with electrical lesion or 6-hydroxydopamine treatment of the NTS and related brain stem structures.

Complete, or nearly complete, baroreceptor denervation is a rare and traumatic occurence in humans. Furthermore, total loss of baroreflex function is not a probable cause of human essential hypertension, since it is known that human hypertensives can acutely regulate their blood pressure. It has been proposed that if a defective baroreceptor reflex mechanism causes hypertension in man, subjects with mild degrees of blood pressure elevation (borderline hypertension) would express characteristics resembling neurogenic hypertension in animals. In particular, three characteristics should be evident; 1) increased arterial blood pressure lability, 2) increased sympathetic tone, and 3) decreased baroreflex sensitivity (Pickering and Sleight, 1977).

In response to the first prediction, Littler et al. (1978) were not able to show a correlation between the 24 hour level of diastolic pressure and its lability in human hypertensives. As of yet there is no concrete data demonstrating that human essential hypertensives display a labile phase.

Studies using an estimation of plasma catacholamines levels as an index of sympathetic tone have given inconsistent results. Louis et al. (1973) have found that plasma norepinephrine levels are often elevated in established essential hypertension, but not as often in borderline

hypertension. However, increased plasma catecholamines are not necessarily a reliable indication of enhanced sympathetic tone (Sleight et al., 1986).

Bristow et al. (1969) found that baroreflex control of heart rate was depressed in patients with moderate hypertension. Subnormal baroreflex responses were also reported in young men whose average blood pressure was 160/82 mm Hg (Takeshita et al., 1975), but Julius (1976) found normal responses in borderline hypertensive patients whose blood pressures were lower than those studied by Takeshita. Bridging this discrepancy, Eckberg (1979) suggested that a gradation of baroreflex responsiveness exists among patients classified as having borderline hypertension (successive blood pressures above and below 140/90 mm Hg), with subnormal responsiveness in subjects whose resting average systolic arterial pressure was $\geq$ 140 mm Hg. None of these studies allow one to discern whether the malfunction of the baroreflex contributed to, or was the consequence of, the hypertension. Also inferences as to the resetting of the baroreflex as a whole are often made without making the distinction between heart rate and arterial pressure responses to baroreceptor manipulation. Although resetting of both responses is evident in human hypertension, the characteristic readjustments made by each are not identical (Sleight, 1979; Mancia et al., 1978; 1979).

Secondary Resetting of the Baroreflex

It is frequently asserted that the baroreflex in conscious, hypertensive subjects is both reset and has diminished gain. This conclusion is primarily a reflection of studies in which the baroreflexes of hypertensive and normotensive subjects have been measured by the response of heart rate to injections of pressor and

depressor drugs (Sleight, 1979). Studies such as these have shown that (a) heart rate is near normal in hypertension despite an elevated blood pressure (indicative of "resetting") and (b) artificial alterations in blood pressure cause smaller reflex changes in heart rate in hypertensive than normotensive subjects (thus, diminished "gain") (cf. Mancia et al., 1978; Thames et al., 1981; Guo et al., 1983). However, the use of vasoactive drugs to measure baroreflex gain has a practicle limitation that is not often recognized. Specifically, blood pressure is not manipulated over a sufficient range to define the entire, sigmoidal relationship between blood pressure and heart rate, so the distinction between resetting and diminished gain becomes ambiguous. In addition, heart rate is only one of the determinants of blood pressure. Therefore, it may be invalid to assume that the baroreflex regulation of blood pressure is impaired in hypertension simply because the ability of the baroreflex to control heart rate is impaired.

Studies in which blood pressure rather than heart rate has been the measured variable have been equivocal regarding the role of the baroreflex during the development of hypertension. Moment to moment flucuations in blood pressure are generally no greater in hypertensinve than normotensive individuals (Julius and Schork, 1971). This implies that baroreflex control of blood pressure is not impaired in hypertension. However, this conclusion is limited due to the lack of a direct stimulus to the baroreceptors.

Studies in which a direct stimulus was applied to the carotid baroreceptors were done by Rocchini and Barger (1979). They used bilateral carotid occlusion to assess the reflex responsiveness of dogs during the development of renovascular hypertension. The increase in the blood pressure response to bilateral carotid occlusion was found to

be slightly larger in renal hypertensive dogs than in normotensive dogs suggesting, that baroreflex gain is not diminished in hypertension. Furthermore, they reported that arterial baroreceptor resetting was not complete by 14 days. However, two factors hindered their analysis. First, they could not be certain that the stimulus to carotid baroreceptors was standardized in their experiments; carotid occlusion may bring about a larger decrease in carotid sinus pressure in hypertensive dogs than in normotensive dogs. Second, the aortic baroreceptors remained intact, and could buffer reflex-mediated changes in arterial pressure.

Mancia et al. (1978) have described an approach to analyze both heart rate and blood pressure responses in hypertensive and normotensive human subjects. Changes in transmural pressure are imposed on the carotid sinuses by encasing the neck in a chamber that can be either evacuated or pressurized. They found that calculated baroreflex gain was markedly different for responses to increases and decreases in baroreceptor stimulation. In particular, they demonstrated that severely hypertensive subjects had a greater reflex gain than normotensives in response to sinus distension. In contrast, the hypertensives had a smaller gain than the normotensives in response to compression of the sinuses. These data suggested to them that in hypertension the baroreceptor stimulus-response curves shifts to the right with a corresponding depression of the reflex set point. That is, the threshold of the carotid sinus baroreflex is increased in hypertension without substantially altering reflex sensitivity. However, there are many technical limitations of the neck chamber technique. The neck chamber can only offset whatever pulsatile pressure is imposed on the carotid sinuses by the heart, and only limited changes

in distending pressure can be achieved. In using the neck chamber, one must estimate the carotid sinus distending pressure by subtracting chamber pressure from arterial pressure. Correction factors are also needed to account for incomplete transmission of chamber pressure through neck tissue, and different correction factors are needed for increases and decreases in distending pressure.

The behavior of the baroreflex has not been systematically studied throughout the course of development of chronic, experimental hypertension. The baroreflex readily buffers acute changes in arterial pressure, such as those brought about by infusion of pressor agents (Cowley et al., 1974). Furthermore, sinoaortic denervation has been shown to accelerate the rise in arterial pressure in both renal and AII-induced hypertension in conscious dogs (Cowley and Guyton, 1975; Cowley and DeClue, 1976). Specifically, Cowley and DeClue (1976) made inferences as to the time course of baroreflex changes by comparing the development of AII-induced hypertension in conscious dogs with and without intact denervated sinoaortic baroreceptors. They demonstrated that one hour infusions of AII (1.0-100 ng/kg/min) produced twice the pressor effect in the denervated dogs as compared to the intact dogs. During long-term infusions of AII at 5.0 ng/kg/mice the pressor effect in the denervated dogs as compared to the intact dogs. During long-term infusions of AII at 5.0 ng/kg/min blood pressure rose more quickly in baroreceptor-denervated dogs for the first 28 hours. Thereafter, blood pressure was equivalent in the intact and denervated dogs. The authors concluded that about 35% of AII's hypertensive effect was due to its acute pressor action, an additional 35% of the pressure rise was caused by gradual baroreceptor resetting, and the final 30% increase in pressure was the result of an increased cardiac output. These findings

favor the view that the role of the reflex is to buffer short-term changes of arterial pressure. However, studying the effects of the chronic loss of the baroreflex can only provide part of the picture. It remains to be determined how the properties of an intact and functioning baroreflex are altered during the development of hypertension.

Difficulties Incurred in the Assessment of the Baroreflex

Anesthesia

Anesthesia has been an important variable in most previous studies of the baroreflex. It is known for example, that blood pressure and heart rate are higher in cholalose-anesthetized than in conscious dogs (Stephenson and Donald, 1980b). Most studies of baroreflex function have utilized the technique of Moissejeff (1926) for vascularly isolating the carotid baroreceptors from the systemic circulaton. These studies have all been done in anesthetized animals. A number of experiments have been performed to study the effects of various anesthetics on the baroreceptor reflex. It is generally concluded that chloralose elevates the threshold for baroreceptor activation of vagal efferents or eliminates the vagal component of the baroreflex. The sympathetic component of the reflex remains intact or becomes exaggerated (Kirchheim, 1976). Some investigators believe that the baroreflex is preserved (Brown and Hilton, 1956; Barlow and Knott, 1964), or enhanced (Armstrong et al., 1961) under chloralose anesthesia. Cox and Bagshaw (1978) compared the pressor effect of bilateral carotid occlusion in conscious and chloralose anesthetized dogs and observed that the anesthesia slightly decreased the sensitivity of the

baroreflex. In contrast, Stephenson and Donald (1980b) demonstrated that, in vagotomized dogs, the range of the arterial pressure response and the carotid baroreflex gain were enhanced with chloralose anesthesia. Pentobarbital anesthesia has been reported to depress the dog's baroreflex tremendously (Vatner and Braunwald, 1975), moderately (Cox and Bagshaw, 1980), or slightly (Hosoni and Sagawa, 1979). The rabbit is also used in many investigations of the baroreceptor reflex. A comprehensive study has recently been published (Ishikawa et al., 1984) which compared the rabbit carotid sinus reflex under pentobarbital, urethane, and chloralose anesthesia. They found that the blood pressure response range and reflex gain were significantly smaller with chloralose anesthesia than with the other anesthetics. Therefore, although chloralose anesthesia is traditionally used in the dog to obtain the greatest reflex responses, it attenuates the reflex in rabbits. It is therefore evident that the anesthetic utilized as well as the animal species anesthetized contributes to the apparent inconsistencies in various studies of the baroreflex in normotension and hypertension.

Extra Carotid Baroreflexes

Until recently there were three classical approaches an investigator could choose from to study the role of the arterial baroreflexes in the regulation of the cardiovascular system in conscious subjects. One method entails a comparison of the circulatory responses before and after surgical denervation of the carotid sinuses and aortic arch reflexogenic regions (Cowley et al., 1980; Ito and Scher, 1981). However, during the weeks of surgical recovery the cardiovascular system appears to adapt to the the loss of the arterial baroreceptors. Within

a few days after the denervation, arterial pressures return to (or nearly to) normal (Cowley et al., 1973; Walgenbach and Donald, 1983). Apparantly, a significant circulatory adaptation occurs in the sinoaortic-denervated animals immediately subsequent to the denervation. Thus, studies of chronically denervated animals do not reveal simply the effects of the absence of baroreceptors, but the combined effects of absence of baroreceptors plus the body's adaptation to that absence. The second and third approaches are the neck suction technique and bilateral carotid occlusion. Some of the limitations of those two methods have been previously discussed, however they also share a common, and quite significant drawback. These two techniques only affect carotid sinus pressure. Extracarotid baroreceptors continue to be exposed to arterial blood pressure and to buffer changes in blood pressure that are initiated by the carotid barorecptors. For example, the intact aortic and cardiopulmonary receptors substantially blunt the rise in arterial pressure that is initiated by bilateral carotid occlusion (Walgenbach, 1981). In a study on anesthetized rabbits, Angell-James and George (1980) found that the aortic baroreceptors appeared to exert less buffering action on the carotid baroreflex control of blood pressure in hypertension than in normotension. If the same relationship applies to studies of hypertension using bilateral carotid occlusion or the neck suction technique, then the degree to which hypertension affects the gain of the carotid baroreflex would be underestimated. Furthermore, Guo et al. (1983) have demonstrated in anesthetized rabbits that the aortic and carotid baroreceptors interact differently in the control of heart rate and of hindlimb vascular resistance; and that chronic renal hypertension also affects these interactions. It is clearly important to keep in mind the limitations

of the 3 classical approaches to the study of the baroreflex in normotension and hypertension.

Limitations due to Experimental Design

Various forms of experimentally induced renal hypertension have often been utilized by investigators wishing to assess the arterial baroreflexes in hypertension. Characteristics of the baroreflex arc in anesthetized normotensive and renal hypertensive rabbits have been particularly well studied (Guo et al., 1982; Guo et al., 1983; Guo and Thames, 1983; Thames et al., 1984; Guo and Abboud, 1984). The results of these studies indicated that 1) the cardiac component of the baroreflex is impaired by the removal of either aortic or carotid baroreceptor contribution, 2) one set of baroreceptors cannot compensate for the loss of the other with respect to activation of vagal neurons; in contrast, one set of baroreceptors can fully compensate for the absence of the other with respect to sympathetic inhibition, 3) after six weeks of renal hypertension, baroreflex control of lumbar sympathetic nerve activity and hindlimb vascular resistance is maintained, however baroreflex control of heart rate is diminished, 4) the selective impairment of baroreflex control of heart rate in hypertension results from an abnormality in the baroreceptors and not the central nervous system, 5) this abnormality in the afferent limb is not sufficient to impair baroreflex control of lumbar sympathetic nerve activity when all the arterial baroreceptors are intact but is sufficient after partial loss of one set of baroreceptors, and 6) although baroreflex control of lumbar sympathetic nerve activity is preserved after six weeks of hypertension, four months of chronic hypertension is adequate time for an impairment to develop in the

central nervous system mediation of the reflex, resulting in attenuated baroreflex control of both lumbar sympathetic nerve activity and can renal nerve activity. Data obtained from recordings of sympathetic nerve activity may be limited, because the responses of neural effectors are not necessarily predictable from recordings of nerve activity. For example, in some forms of hypertension it has been demonstrated that there is actually augmented responsiveness of the vasculature to adrenergic stimuli (Webb, 1984).

A systematic analysis of the changes in the baroreflex after the initiation of one-kidney, one-wrapped Page hypertension has been made in the conscious dog (Stephenson and Tagett, 1982). Complete stimulus-response relations were determined for the effects of carotid sinus pressure on both arterial blood pressure and heart rate. The results of this study demonstrated that in hypertensive dogs 1) the baroreflex responds over a broadened and elevated range of carotid sinus pressure, 2) the gain of the baroreflex is diminished, 3) a pressor mechanism is evident which maximal stimulation of the baroreceptors cannot oppose and, 4) baroreflex control of heart rate is also reset and has diminished sensitivity. Although the study by Stephenson and Tagett described quantitatively the overall changes in the carotid baroreflex after the development of renal hypertension, technical impracticalities made it impossible to determine the time course of baroreflex changes during the development of the renal hypertension. Thus a rigorous analysis of the time course and magnitude of the baroreflex changes which occur during the development of hypertension has not been performed. Furthermore, their study was also limited by the presence of intact aortic baroreceptors.

Circumventing the Difficulties

Blood Pressure and the Conscious Preparation

In conscious dogs bilateral carotid occlusion has been used to reduce the activity of carotid sinus baroreceptors, and electrical stimulation of Hering's nerve has been used to simulate baroreceptor activation (Kirchheim and Gross, 1971; Vatner et al., 1970). In various studies arterial pressure has been manipulated by injection of vasoactive drugs, by inflation of cuffs on the vena cava or descending aorta, or by acute alterations of blood volume (cf. Kirchheim, 1976). When arterial pressure is the manipulated variable, the analysis of reflex responses is limited to changes in heart rate. None of the techniques used in conscious dogs had allowed pressure at the carotid sinuses to be varied independently of arterial pressure, nor had complete stimulus-response curves relating arterial blood pressure to carotid sinus pressure been obtained until a surgical technique was developed by Stephenson and Donald (1980a) that permits reversible vascular isolation of both carotid sinuses in the conscious dog. This technique allowed two new major modes of study of the carotid sinus baroreceptor reflex in conscious dogs. 1) The sinuses can be isolated and held at a fixed pressure, thus permitting an investigation of the deficits in cardiovascular regulation that result from the acute withdrawal of the buffering influence of the carotid baroreflex. 2) The pressure within the isolated sinuses can be varied over a wide range, thus allowing complete stimulus-response characteristics for the carotid baroreflex to be compared under a variety of experimental circumstances (eg. emotional stress, exercise, and hypertension). The only limitation of this technique is that any intact extracarotid baroreceptors will

buffer reflex changes in blood pressure initiated by the carotid baroreceptors. However, interruption of the aortic baroreflex, when combined with vascular isolation of the carotid sinuses, allows the carotid baroreflex to be studied in a relatively unopposed state in conscious dogs.

Left Vagotomy

The ability of the right carotid sinus baroreceptors to modulate arterial pressure is not different from that of the left (Sagawa and Watanabe, 1965). There is also no difference in the tonic inhibition mediated by cardiopulmonary afferents traveling in the right vagus compared to those in the left vagus (Mancia et al., 1972). However, Walgenbach et al. (1981) have demonstrated that the left aortic depressor nerve in the dog provides 90% of the inhibition of the increase in arterial pressure after bilateral carotid occlusion. The right aortic nerve accounts for only 10% of the inhibition. This study has important consequences for the investigation of baroreflex control of the cardiovascular system in the conscious dog. First, the range and gain of the complete stimulus-response curve after left vagotomy are similar to those after bilateral aortic nerve section. This results from two mechanisms: the removal of almost 90% of the combined inhibition exerted by aortic and cardiopulmonary receptors on the hypertension due to acute inactivation of the carotid sinus baroreceptors and the preservation of vagal slowing, which makes a significant contribution to the hypotension resulting from increased activity of carotid baroreceptors. Left vagotomy does not result in the respiratory and gastrointestinal side effects that accompany bilateral cervical vagotomy. Thus, left cervical vagotomy, with or without

section of the right cervical aortic nerve will yield a preparation in which carotid baroreflex effects will be relatively unopposed by buffering influences of the aortic baroreflexes. In addition, about half of the effects of the vagally mediated cardiopulmonary reflexes will be absent. However, if the minor inhibition exerted by the aortic baroreceptors through an intact right aortic depressor nerve and/or cardiopulmonary receptors through right vagal afferents augments with time, utilization of left vagotomy alone to chronically interupt the aortic baroreflex would be invalid. This possibility was also studied by Walgenbach (1984). The results from her experiment demonstrated that long-term (three weeks) interuption of the aortic baroreflex is achieved by left cervical vagotomy. Thus, when combined with the reversible carotid sinus isolation of Stephenson and Donald, an assessment of the carotid baroreflex is possible without the opposing influence produced by intact aortic baroreceptors operating within a closed loop system, and the cardiovascular adjustment to acute and reversible loss of the carotid baroreflex is made possible.

Primary Angiotensin II-Induced Hypertension

Renal Hypertension and the Renin-Angiotension System

The precise role of the renin-angiotensin system in the etiology of various types of renal hypertension awaits clarification, but the initial rise of blood pressure is probably caused by vasoconstriction due to an increased plasma concentration of angiotensin II. Plasma levels of renin (Bianchi et al., 1972), and angiotensin are increased significantly (Caravaggi et al., 1976). Angiotensin II receptor blockade or the administration of converting enzyme inhibitor restores

normal levels of blood pressure (Masaki et al., 1977; Miller et al., 1975). Although the acute vasoconstrictor action of elevated angiotensin II is not necessarily the only mechanism involved in the initiation of renovascular hypertension, chronic renal hypertension is even less easy to explain. Also among the important components responsible for the initiation and maintenance of renovascular hypertension are the retention of sodium and water (Fitzsimmons, 1972) and the operation of the arterial baroreceptors (Angel-James, 1973). Rocchini and Barger (1979), showed that one-kidney Goldblatt hypertension was due to, and maintained by, an elevated plasma renin activity in sodium-depleted dogs. It appeared that the plasma renin activity and plasma aldosterone rose as quickly as the blood pressure and peaked by one hour and remained there. The more rapid increase in blood pressure which occurs after renal artery constriction in the sodium depleted dogs has been attributed to enhanced renin release by the kidney (Fray et al., 1977) as well as reduced buffering by the arterial baroreceptors (Rocchini et al., 1977). Rocchini and Barger (1979) also showed that the reversal of one-kidney Goldblatt hypertension following deflation of the cuff around the renal artery was more rapid in the sodium-depleted dogs as compared to the sodium-replete ones. Within one hour mean arterial blood pressure, plasma renin activity, and plasma aldosterone levels had decreased significantly; and had returned close to control values by six hours. These studies suggest a close temporal relationship between arterial blood pressure and plasma renin activity in sodium-depleted dogs. Furthermore, when converting enzyme inhibitor was administered as renal artery constriction was removed, blood pressure fell much more drastically. Consonant with this, Gavras et al. (1973) administered saralasin (a

competitive angiotensin II antagonist), so as not to affect the kinin system, to one-kidney Goldblatt rats and observed a precipitous fall in blood pressure in the animals on a sodium-restricted diet. In dogs on a normal salt diet, blood pressure rose more slowly, reaching a plateau after 3-4 days after cuff inflation. Plasma aldosterone and plasma renin activity peaked at 24 to 48 hours and then returned towards control. These results imply that enhanced plasma renin activity is responsible for the initiation of renovascular hypertension in the normal salt state and that the hypertensive condition is maintained by sodium and water retention and an increased body fluid volume. Renovascular hypertension in the low-salt state appears to be initiated and maintained primarily by angiotensin II. As mentioned earlier, they also attempted to describe the time course of changes in the baroreflex of the hypertensive, sodium-depleted dogs, and observed that the baroreflex was not completely reset in 14 days. They generalized that the interaction of the renin-angiotensin system, sodium and water balance, and the reactivity of the baroreceptor reflex determines the rate of rise and sustained level of blood pressure after renal artery constriction in dogs on normal or low-salt intake.

Sodium depletion has been demonstrated to affect the baroreflex in normotensive individuals after blockade of the conversion of angiotensin I to angiotensin II. Samuels and co-workers (1976) showed that the administration of converting enzyme inhibitor produced a persistent decrease in arterial pressure with only a slight increase in heart rate in sodium-depleted dogs. In addition, sodium-depleted human subjects fainted when tilted from a supine to an upright position after the administration of converting enzyme inhibitor (Sancho et al., 1976). These studies imply that the arterial baroreflex is less effective in

regulating arterial pressure in sodium-depleted subjects than in sodium-replete subjects. Rocchini et al. (1977) quantified the blood pressure response to carotid occlusion in conscious dogs maintained on high and low-salt intake. Their experiment showed that the greatly depressed pressor response to bilateral carotid occlusion in the low-salt dogs was not related to changes in plasma renin activity, basal level of angiotensin II, to the degree of carotid hypotension, or to the vascular reaction to infused norepinephrine. However, the dose-response curve of tyramine (an indirect sympathomimetic) to arterial blood pressure was shifted to the right in the sodium-depleted dogs. Therefore, they concluded that chronic sodium depletion results in a reduced response to carotid occlusion, which may be due to a decrease in the responsiveness of the efferent sympathetic nervous system.

The Slow-Pressor Action of Angiotensin II

It is generally agreed that the direct vasoconstrictor effect of angiotensin II plays a role in the maintenance of chronic renal hypertension in the sodium-replete state; however, plasma levels of renin and angiotensin are not high enough to raise blood pressure by acute vasoconstriction alone (Bianchi et al., 1972; Hutchinson et al., 1975; Brown, J.J., et al., 1976, 1977). Angiotensin converting enzyme inhibitors are not very effective in lowering blood pressure (Pals et al., 1971; Thurston and Swales, 1974; MacDonald et al., 1975; Freeman et al., 1977; Masaki et al., 1977). Another pressor mechanism must be present. MacDonald et al. (1975), administered saralasin to Goldblatt rats and concluded that chronic renal hypertension is independent of angiotensin II. However, others contend that chronic renal hypertension is dependent on a slowly developing pressor effect of angiotensin in

conjunction with its direct vasoconstrictor effect (Brown, J.J., et al., 1976, 1977).

Angiotensin II does have a slow pressor effect distinct from its acute pressor action. Hypertension gradually develops over a period of one week when angiotensin is administered continuously in a low dose to dogs (McCubbin et al., 1965; Cowley and DeClue, 1976; Trippodo et al., 1976; Bean et al; 1979), rabbits (Dickinson and Lawrence, 1963), rats (Koletsky et al., 1966), and man (Ames et al., 1965). The hypertension observed under these circumstances has been characterized by only slight elevation in arterial pressure during the first several hours of angiotensin infusion, followed by a gradual increase over the following week to a fixed hypertensive state. Blood pressure can take from 14 to greater than 24 hours to return to normal when infusions of angiotensin are stopped (Cowley and DeClue, 1976; Bean et al., 1979). The slow return of blood pressure to normal may account for the apparant failure of inhibitors of the renin-angiotensin system to restore normal blood pressure in subjects with renal hypertension or primary, angiotensin-induced hypertension.

In many experiments the inhibitors were administered as a bolus injection or infused for two hours at most. Riegger et al. (1977) demonstrated that normal levels of blood pressure could be attained in rats with chronic two-kidney hypertension if saralasin or converting enzyme inhibitor were infused for 11 hours. When greater doses of the inhibitors were infused in the same rats for only two hours, a much reduced reduction in pressure was observed. Consistant with these findings, Miller et al. (1975) prevented the development of one-kidney hypertension in the dog by chronic infusion of converting enzyme inhibitor. Thus the failure of acute administration of inhibitors of

the renin-angiotensin system to reverse renal hypertension is not necessarily a valid arguement for rejecting the role of angiotensin in the pathogenesis of chronic renal hypertension.

Prolonged infusion of angiotensin II gradually produces a hypertensive state in which arterial pressure is higher than can be explained by the acute vasoconstrictor action of angiotensin II. Bean et al. (1979) infused angiotensin II (3 ng/kg/min) into conscious dogs for two weeks, during which blood pressure rose gradually. Before, during, and after the rise in blood pressure, the acute pressor effect of angiotensin was tested by dose-response studies in which additional angiotensin was infused at successive rates of 3, 6, and 12 ng/kg/min, each for one hour. Carotid blood samples were taken at the 60th minute of each of the three rates of angiotensin infusion so that the level of blood pressure could be related to the concurrent plasma angiotensin concentration. Their experiment demonstrated that prolonged infusion of angiotensin can increase the level of arterial blood pressure maintained by a given plasma concentration of angiotensin II. Thus it appears that angiotensin affects an upward shift of its own dose-response curve. These findings are compatible with the hypothesis of a slow pressor effect of angiotensin, but they do not establish its mechanism of action.

Cowley and co-workers have used the slow-pressor action of AII as a working model to assess the function of the baroreflex in hypertension. However, it is well known that AII can bring into play a number of secondary mechanisms such that any conclusion based solely on the affects of AII would be confounded. Therefore, before such studies

could be validated the interaction and possible contribution of AII with such variables as aldosterone, renal tubular sodium reabsorption, and vasopressin had to be investigated.

Aldosterone

The mechanism or mechanisms responsible for the gradual increase in arterial blood pressure during the chronic administration of small doses of angiotensin have not been clearly elucidated. Aldosterone is considered by many to have an important role in the genesis and maintenance of hypertension associated with enhanced activity of the renin-angiotensin-aldosterone system. An increase in plasma aldosterone would lead to sodium retention and a gradual expansion of body fluid volumes. However, it is important to distinguish the suspected hypertensive effect of aldosterone from that of angiotensin. Primary aldosteronism is the best example of the blood pressure-elevating effect of aldosterone. Characteristics of this disease include enhanced mineralocorticoid secretion and mild-to-severe hypertension (Biglieri et al., 1970). However, in both animals and humans, infusions of aldosterone, which produced changes in plasma aldosterone, sodium, and potassium levels comparable to those observed in patients with primary aldosteronism produce little or no change in arterial pressure (August et al., 1958; Lohmeier et al., 1978). Thus, instances of severe hypertension in patients with primary aldosteronism may be due to renovascular lesions caused by more chronic effects of aldosterone (Baer et al., 1970). In fact, it is not uncommon for hypertension to persist after the surgical removal of an aldosterone-secreting adenoma (Baer et al., 1970). It is well known that plasma renin activity decreases with aldosterone treatment, and in patients with primary aldosteronism,

plasma renin activity is suppressed to very low levels. The attenuation of the renin-angiotensin system may be a compensatory mechanism which limits mineralocorticoid hypertension. An approach to elucidate this hypothesis would be to study the effects of aldosterone on blood pressure in which blood levels of angiotensin II are maintained.

The secondary aldosteronism which accompanies chronic angiotensin infusion in experimental animals or primary reninism in humans is sometimes accompanied by severe hypertension (Conn, 1977). However, the role of aldosterone secretion in primary renal hypertension and angiotensin-induced hypertension may have been over emphasized. Muller (1970) has pointed out that hyperaldosteronism is not consistently asssociated with renovascular hypertension in man. Furthermore, Laragh et al. (1966) produced hypertension independent of enhanced aldosterone secretion with small amounts of infused angiotensin; and sustained hypertension has been produced in adrenalectomized rabbits with chronic administration of angiotensin II (Dickinson and Yu, 1967b).

Cowley and McCaa (1976) examined the acute and chronic dose-response relationships between infused angiotensin and the resulting changes in arterial blood pressure and plasma aldosterone concentration at varying levels of salt intake. Angiotensin, infused at 5, 15, and 23 ng/kg/min, was associated with an initial increase of plasma aldosterone. The increase was markedly attenuated after the first 24 hours of infusion. The final level was directly related to the dose of angiotensin and inversely related to sodium intake. The lowest dose of angiotensin infusion produced a sustained level of hypertension without a sustained elevation of plasma aldosterone, and increasing sodium intake from 40 mEq/day to 120 mEq/day resulted in significantly higher levels of hypertension. Chronic stimulatory actions of

angiotensin on aldosterone secretion were only seen at the higher levels of angiotensin infusion. The level of hypertension and plasma aldosterone obtained were dissociated. The plasma aldosterone concentration peaked by six to twelve hours of angiotensin infusion and then declined. However, arterial blood pressure at this time was only slightly elevated and did not reach a maximum steady state level for at least five days. Therefore, Cowley and McCaa concluded that primary, angiotensin-induced hypertension need not be associated with increased levels of plasma aldosterone. These results concurred with a previous study (Cowley and DeClue, 1976) in that the level to which the pressure rises during AII infusion is highly dependent on salt intake.

Lohmeier et al. (1978) studied the importance of aldosterone vs. angiotensin in the maintenance of experimental hypertension caused by chronic angiotensin infusion or primary reninism. They infused aldosterone chronically into both adrenalectomized and intact dogs. Also, high levels of aldosterone were administered both in normal dogs and in dogs receiving angiotensin (5 ng/kg/min). Angiotensin was given to suppress plasma renin activity and thus prevent changes in plasma levels of angiotensin II during the aldosterone infusion. They reasoned that maximal aldosterone-induced hypertension might be observed under conditions where the renin-angiotensin feedback suppression was blunted. They observed that infusion of aldosterone at 9 ug/kg/day (4 times normal), in intact dogs maintained on 75 mEq of sodium per day, increased mean arterial pressure 13 mmHg compared to a greater than 30 mmHg rise seen with angiotensin infusion alone, even though plasma aldosterone concentration only rose two-thirds as much as when aldosterone was infused alone. In contrast to McCaa et al. (1975) they observed that chronic infusion of angiotensin produced a sustained

increase in plasma aldosterone concentration. Although the reported responses of plasma aldosterone concentration to chronic angiotensin infusion vary, it is generally concluded that the aldosteronism associated with a primary increase in angiotensin has no or only a weak hypertensive effect (Cowley and DeClue, 1976; Cowley and McCaa, 1976; Lohmeier et al., 1978; Bean et al., 1979).

Angiotensin II and Sodium Reabsorption

Yeyati et al. (1972), Waugh (1972), and Fagard et al. (1976) demonstrated that infusion of nonpressor doses of angiotensin either intravenously or into the renal artery can cause as much as a 50% decrease in renal sodium and water output. This renal response to angiotensin takes place within minutes, before the possible stimulation of aldosterone secretion can occur. Additionally, Hall et al. (1977) have shown that salt-depleted dogs given appropriate amounts of angiotensin antagonists may increase their sodium output as much as several hundred percent, indicating that intrinsic angiotensin, before its action was blocked, prevented the kidneys from excreting sodium. Therefore, DeClue et al. (1978) tested the hypothesis, that in addition to angiotensin's direct vasoconstrictor effect in various forms of renal hypertension, it might contribute significantly to the hypertension by a direct effect on the kidneys to promote sodium retention. They infused 3.5 liters of isotonic NaCl alone or in combination with angiotensin infusion (5 ng/kg/min) daily for two to eight weeks. The infusion of NaCl alone produced only a 3 mmHg increase in arterial blood pressure whereas the addition of angiotensin increased pressure 39 mmHg. Although the presence or absence of angiotensin infusion did not cause a significant difference in plasma aldosterone concentration at any level

of sodium intake, the urinary output of sodium increased to the same extent. Therefore, the data suggests that angiotensin blocks the normal "pressure natriuresis" often characteristic of large increases in arterial pressure. The authors surmised that since the "normal" relationship between arterial pressure and renal sodium output (Guyton et al., 1974) was shifted to the right with one-tenth the slope, that angiotensin has a direct effect on kidney function to cause sodium retention (Yeyati et al., 1972; Waugh, 1972; Fagard et al., 1976). Therefore, it can be infered that a direct renal sodium-retaining effect also could contribute to the hypertension that results from small and persistent levels of angiotensin in sodium-replete subjects, and thus be a possible mechanism of the slow pressor effect of angiotensin II.

Vasopressin

Although the physiological relationship between circulating angiotensin and vasopressin secretion remains unclear, there are several lines of evidence which link the two. First, it has been demonstrated that enhanced plasma levels of vasopressin within the physiological range can suppress renin secretion (Tagawa et al., 1971). Second, vasopressin is consistently released by intracerebroventricular injections of angiotensin (Mouw et al., 1971). Third, elevated circulating levels of angiotensin have been demonstrated to increase the plasma concentration of vasopressin (Mouw et al., 1971). The evidence is equivocal as to whether or not physiological levels of angiotensin affect vasopressin secretion. Bonjour and Malvin (1970) have concluded that angiotensin is of physiological importance in the control of vasopressin secretion, while Shade and Share (1975) were unable to observe an increase, and others saw an effect only with

supraphysiological amounts of angiotensin (Padfield and Morton, 1977). The inconsistency of these findings may be due to the lack of a sensitive assay procedure for vasopressin, uncontrolled sodium and water intake, and short-term administration of angiotensin. Since renal retention of water is a continuous process and occurs slowly, Cowley et al. (1981) examined the relationship between the chronic maintenance of plasma angiotensin levels and plasma vasopressin concentration to determine if angiotensin plays a significant role in the long-term regulation of vasopressin secretion. However, after continuous infusions of angiotensin (5 and 20 ng/kg/min) for seven days in conscious dogs, they concluded that circulating angiotensin is not directly involved in the long-term control of vasopressin secretion. Furthermore, neither vasopressin nor enhanced drinking contributes significantly to the slow pressor effect of angiotensin.

Water Balance and Cardiac Output

Conscious dogs maintained on a normal sodium intake (2 mEq/kg/day) show no significant change in daily water intake or urine excretion throughout a 14 day period of angiotensin infusion (5 ng/kg/min). In contrast, there was a 128% increase in the water intake in dogs receiving a high sodium intake (6 mEq/kg/day) at the same level of angiotensin infusion. Urine excretion rates, however, only increase by 65% above control during this period. Although hematocrit and plasma osmolality fell initially they returned to control levels after the third day of infusion (Cowley and DeClue, 1976). Sodium and water balance was not determined in a similar study by Bean et al. (1979). An absence of weight gain in their dogs might suggest that there had not been a significant retention of sodium and water, however it has been

demonstrated that angiotensin may also suppress appetite and food intake (McFarland and Rolls, 1972). In the study by Cowley and DeClue, blood volume determined at the fourth or fifth day of infusion was not significantly different from the preinfusion values. Cardiac output was initially depressed and then rose to 40% above control after 4-5 days of angiotensin infusion. Olmstead and Page (1965) also had observed a gradual increase in cardiac output with greater doses (15-150 ng/kg/min) of angiotensin over a period of one month. These hemodynamic results suggest that the rise in cardiac output may be associated with the slow-pressor effect of angiotensin II. Since blood volume was not altered, the observed increases in cardiac output may have been produced by a direct action of angiotensin, indirectly through the nervous system, or by a redistribution of body fluid volumes secondary to changes in vascular compliances. However, the specific mechanism by which cardiac output was enhanced is uncertain.

The Sympathetic Nervous System and the Baroreflex

An increase in sympathetic tone is the most commonly evoked explanation for the gradual increase in blood pressure during continuous infusion of small amounts of angiotensin. Dickinson and Yu (1967a, 1967b) demonstrated that the slow rise in blood pressure during angiotensin infusion in the rabbit is mediated through enhanced sympathetic tone to the vasculature. Their study was based on the use of trimethaphan (a sulfonium ganglionic blocking agent) and sympathetic antagonists (Yu and Dickinson, 1971). A small arterial pressure rise at the onset of angiotensin infusion is most likely a result of arteriolar vasoconstriction, which may be mediated by a direct action of angiotensin, through central nervous system actions of angiotensin

(Ferrario et al., 1972), through actions of angiotensin on the sympathetic ganglia (Lewis and Reit, 1965), through stimulation by angiotensin of the postsynaptic nerve endings (McCubbin et al., 1965), or through the adrenal medullary stimulation by angiotensin (Feldberg and Lewis, 1965). Fukiyama et al. (1971) and Sweet et al. (1971) have demonstrated that long-term infusions of angiotensin into the vertebral artery of conscious dogs have a continuing, nonadapting, stimulatory effect on the sympathetic vasomotor centers. Also, it is plausible that central stimulation of the vasomotor centers and peripheral sensitization of the sympathetic nerve endings could have had an indirect effect in reducing renal excretion of sodium, as observed in the experiment of DeClue et al. (1976).

Cowley and DeClue (1976) examined the response of blood pressure to acute pressor and chronic subpressor infusions of angiotensin in sinoaortic denervated and intact conscious dogs. They observed that, although pressure rose more quickly in the denervated dogs, the pressure increases in the intact and denervated dogs were the same after the 28th hour of infusion. They concluded that the apparent withdrawal of sympathetic activity seen by Dickinson and Yu (1967b) during the first day of angiotensin infusion was a reflection of the baroreflex attempting to restrain the pressor effect of angiotensin, and that the baroreceptors no longer opposed the development of hypertension thereafter. In fact, they claimed that 35% of the gradual increase in arterial pressure is the result of baroreceptor resetting. Therefore, it appears that baroreflex resetting may be responsible for a portion of the slow pressor effect or "increased sensitivity" to angiotensin.

Purpose of the Experiment

Specific Aim

The ability of the baroreflex to regulate blood pressure and heart rate was compared before and during acute and chronic, angiotensin II-induced hypertension in conscious dogs. The following experimental questions were specifically addressed:

1. How does slowly developing, chronic, AII-induced hypertension affect (a) the open-loop gain of the baroreflex, (b) the range over which the baroreflex can increase blood pressure above or decrease it below its prevailing level, and (c) the range of carotid sinus pressure over which reflex responses occur?

2. In what way is the baroreflex different during (a) the slowly developing phase of AII-induced hypertension, (b) the subsequent plateau phase of chronic hypertension, and (c) the reversal of the chronic hypertension?

3. How does baroreflex function in AII-induced chronic hypertension, differ from baroreflex function in acute, AII-induced hypertension?

4. How are the sympathetic and parasympathetic components of the baroreflex affected by chronic AII-induced hypertension?

5. How does aortic denervation affect questions 1-3?

6. How does aortic denervation affect the balance between sympathetic and parasympathetic systems in mediating baroreflex responses during normotension and during chronic salt-AII hypertension?

The data obtained are presented in the form of two papers prepared for submission to American Journal of Physiology. Paper number one, entitled "**TIME COURSE AND MAGNITUDE OF BAROREFLEX CHANGES DURING ACUTE AND CHRONIC ANGIOTENSIN-INDUCED HYPERTENSION**", specifically addresses questions 1., 2., 3., and 5. Paper number two, entitled "**SYMPATHETIC AND PARASYMPATHETIC CONTRIBUTIONS TO THE CAROTID BAROREFLEX IN ANGIOTENSIN-INDUCED HYPERTENSION**", addresses question 4., and 6.

TIME COURSE AND MAGNITUDE OF BAROREFLEX CHANGES DURING ACUTE AND CHRONIC ANGIOTENSIN-INDUCED HYPERTENSION

INTRODUCTION

In various forms of experimental hypertension, the arterial baroreceptors become reset so that they respond over an elevated pressure range (McCubbin et al, 1956, Krieger and Marseillan, 1966, Aars, 1968a, Sleight et al, 1975). Resetting of the baroreceptors can begin after only a few minutes' exposure to sustained, abnormally high pressure (Krieger, 1970; Salgado and Krieger, 1978; Coleridge et al, 1981; Kunze, 1981). However, Krieger (1986) has shown that 48 hours are required for baroreceptor resetting to become 90% complete following imposition of a sustained hypertension. The properties of the baroreceptor reflex in hypertension reflect not only the abnormalities of the baroreceptors, but also changes in the central and effector elements of the reflex arc. Only a few studies have addressed the timecourse for resetting of the whole baroreflex. After days or weeks of sustained hypertension, heart rate is near normal despite an elevated blood pressure (Bristow et al., 1969; Gribben et al., 1971; West and Korner, 1974; Korner et al., 1974; Takeshita et al., 1975; Thames et al., 1981), which implies that the baroreflex has been completely or nearly completely reset. Kunze (1981) showed some resetting in baroreflex control of blood pressure after the isolated carotid sinuses had been exposed to elevated pressure for only 5 minutes.

Chronic hypertension can be induced in several species by combining a diet high in sodium with a continuous infusion of initially subpressor amounts of angiotensin II (Koletsky et al., 1966; Dickinson and Lawrence, 1963; McCubbin et al., 1965; Ames et al., 1965). Cowley and DeClue (1976) compared the rate of development of salt-AII hypertension in dogs with and without intact baroreceptor afferents. They found that blood pressure rose more slowly in dogs with intact baroreceptor afferents than in baroreceptor-denervated dogs for the first 28 hours of AII infusion. Thereafter, the blood pressure levels were similar. These results imply that, although the baroreflex may rapidly begin to reset at the onset of hypertension, an intact baroreflex can buffer increases in blood pressure for at least one day.

Our first purpose in the present study was to assess, by a more direct means than baroreceptor denervation, the time course and magnitude of baroreflex resetting during the development of salt-AII hypertension. If the baroreflex requires on the order of 28 hours to adapt to an elevated pressure, then baroreflex resetting should be more pronounced during the development of chronic salt-AII hypertension than during equivalent, acute elevations of blood pressure brought about by infusion of pressor doses of angiotensin or norepinephrine. Therefore, we compared baroreflex characteristics during the development of chronic, salt-AII hypertension and during acute elevations of blood pressure brought about by angiotensin and norepinephrine. In addition, since the relative roles of the aortic and carotid baroreflexes in the regulation of blood pressure are controversial (Pelletier et al., 1972, McRitchie et al., 1976, Ito and Scher, 1978), the carotid baroreflexes were studied both with and without intact aortic baroreceptors.

The apparent failure of the baroreflex to buffer the development of salt-AII hypertension beyond 28 hours could result from decreased baroreflex gain, instead of, or in addition to, baroreflex resetting. Baroreflex sensitivity appears to be impaired in human essential hypertension and in experimental renal hypertension, as judged from the finding that artificial elevations in blood pressure cause less reflex cardiac slowing in hypertensive than normotensive subjects (Bristow et al., 1969; Gribben et al., 1971; West and Korner, 1974; Korner et al., 1974; Takeshita et al., 1975; Thames et al., 1981). However, blood pressure, not heart rate is the regulated variable of greatest importance. Recent studies on anesthetized rabbits with renal hypertension have shown that baroreflex control of peripheral vascular resistance and blood pressure can be normal or even enhanced at a time when baroreflex control of heart rate is impaired (Angell-James and George, 1980; Guo et al., 1983). The gain of baroreflex control of blood pressure has not been assessed in chronic salt-AII hypertension.

The second purpose of our study was to determine the timecourse and magnitude of changes in carotid baroreflex gain during the development of chronic salt-AII hypertension in aortic-intact and aortic-denervated, conscious dogs. To more clearly distinguish the influence of duration of hypertension from the influence of blood pressure per se, we also measured baroreflex gain during acute infusions of pressor doses of angiotensin and norepinephrine.

METHODS

Diet

Twelve healthy, mongrel dogs, weighing 20-35 kg were maintained on a dietary sodium intake of 6 mEq Na^+/kg/day. The high sodium diet was prepared by adding salt tablets (Lilly) to low sodium chow (Prescription Diet, k/d, Hills). The salted food was divided between morning and evening feedings. Fresh drinking water was available ad libitum.

Surgical Preparation

Anesthesia was induced with sodium thiamylal (Biotal, Bio-Ceutic, 20 mg/kg, i.v.) and maintained with halothane and nitrous oxide in oxygen. The carotid sinus regions of each dog were surgically prepared for subsequent, reversible isolation from the systemic circulation by the method previously reported (Stephenson and Donald, 1980). Briefly, both carotid arteries were approached through a midline incision in the neck. The thyroid, lingual, occipital, internal carotid, and ascending pharyngeal arteries were ligated, which left the common carotid and external carotid arteries as the only pathways for blood flow. On these vessels were placed inflatable occlusion cuffs. When these cuffs were deflated, the carotid sinuses communicated freely with the systemic circulation; inflation of the cuffs isolated the carotid sinuses. To permit the imposition of known pressures on the isolated carotid sinuses, non-occlusive catheters (Tygon Microbore, 0.040" ID x 0.070" OD, Norton) were placed bilaterally into the carotid arteries between the common carotid occluders and the carotid sinuses. The occluder tubes and catheters were exteriorized on the lateral aspects of the neck.

In 7 dogs the cervical vagosympathetic sheaths were isolated bilaterally. Identification of specific aortic depressor nerves was attempted by gentle dissection within the sheath and confirmed if nerve activity, as recorded with a platinum bipolar electrode, was synchronized with the cardiac cycle (Edis and Shepherd, 1971). Positively identified nerves were sectioned. If identification of the aortic depressor nerves was uncertain, the left cervical vagosympathetic trunk was sectioned as was the right cervical sympathetic tract (Walgenbach et al., 1981). These 7 dogs were designated "aortic-denervated dogs" as opposed to the 5 "aortic-intact dogs".

Seven to 10 days after the surgical preparation of the carotid sinuses, each dog was anesthetized again and equipped with an arterial catheter for measurement of blood pressure and a venous catheter for administration of drugs. For this purpose, silicone rubber tubes (Silastic, 0.065" ID x 0.125" OD, Dow Corning) were inserted in the right femoral artery and vein and advanced into the abdominal aorta and vena cava. An additional catheter (Tygon Microbore, 0.046" ID x 0.070"OD, Norton) was inserted into the left external jugular vein and advanced toward the right atrium; this catheter was used for the chronic infusion of angiotensin II. The distal ends of the catheters were routed subcutaneously and exteriorized at the mid-scapular region. An analgesic (Nubain, Endo Pharmaceuticals) and antibiotics (Combiotic, Pfizer; 2.5 ml, i.m.) were given following surgeries.

Derivation of Complete Stimulus-Response Relations

All experiments were carried out with the dogs lying quietly in a conscious state. To obtain stimulus-response curves for the effects of carotid sinus pressure on arterial blood pressure and heart rate, the

carotid catheters were attached to an external, pressurized reservoir that had been filled with Lactated Ringers, equilibrated with 95% O_2-5% CO_2, and brought to pH 7.4 by addition of $NaHCO_3$. The occluders on the common and external carotid arteries were inflated, which isolated the sinuses from the systemic circulation. The isolated sinuses were exposed to increments of static pressure (25 mm Hg steps) beginning at 50 and ending with 225-300 mm Hg. The goal was to achieve saturation of the reflex response, and the sinus pressure required to reach saturation was higher when the dogs were hypertensive than when they were normotensive. Each level of carotid sinus pressure was maintained long enough (40-120 sec) to allow a steady-state response of blood pressure and heart rate to develop. A definite reflex saturation was not reached in some of the aortic-denervated, hypertensive dogs, because behavioral excitation occurred in these dogs at carotid sinus pressures above 250 mm Hg. We have previously shown that behavioral excitation results from low systemic blood pressure and not from high carotid sinus pressure per se (Stephenson and Donald, 1980). Strain gauges (Statham Intruments, Model P23Db) were used to monitor left and right carotid sinus pressure and systemic arterial blood pressure. These pressures were displayed on an oscillograph (Grass Instruments, Model 7D). Mean blood pressure was derived by electronic damping (0.5 Hz half amplitude point). Heart rate was derived from the phasic blood pressure signal via a cardiotachometer.

For each level of imposed carotid sinus pressure, the steady-state responses of mean blood pressure and heart rate were read from the oscillograph record and plotted as functions of carotid sinus pressure. Smooth curves were fitted to the resulting points. The natural values

of blood pressure and heart rate were determined during periods when the sinuses were not isolated before and after the derivation of each stimulus-response relation. These readings were averaged and plotted as horizontal lines (control values) on the same graphs as the stimulus-response relationships (Figs. 1-7). The following parameters were evaluated for each curve: amount by which the carotid baroreflex can increase blood pressure (or heart rate) above control, amount by which the carotid baroreflex can decrease blood pressure (or heart rate) below control, carotid sinus pressure at threshold for a response, and carotid sinus pressure that leads to saturation of the reflex response. Upper limit is the blood pressure or heart rate in response to subthreshold carotid sinus pressure. Likewise, lower limit is the response obtained at maximal carotid sinus pressure. Range is the difference between the upper limit and the lower limit. The slope of the blood pressure response curve is taken as a measure of the open loop baroreflex gain. In the case of heart rate responses, the slope of the curve provides a measure of the sensitivity of the cardiac component of the baroreflex.

Acute Norepinephrine Infusion

Blood pressure was elevated acutely in 6 normotensive, aortic-intact dogs by intravenous infusion of norepinephrine (Levophed, Winthrop) at 10 and 20 ug/min. Stimulus-response relations for the baroreflex were determined during infusion at each rate and also during no infusion. The group average stimulus-response curves are presented as Figure 5 and the corresponding baroreflex parameters are shown in Table 3.

Acute Angiotensin II Infusion

Blood pressure was elevated acutely in 5 normotensive, aortic-intact dogs and 6 normotensive, aortic-denervated dogs by intravenous infusion of angiotensin II (CIBA) at 300, 600, and 1200 ng/min. Stimulus-response relations for the baroreflex were determined during infusion at each rate and also during no infusion. The group average stimulus-response curves are presented in Figures 2 and 4 and the corresponding baroreflex parameters are shown in Table 2. For both norepinephrine and angiotensin infusion, blood pressure typically reached a stable level within 5 minutes after the start of infusion, and 15-20 additional minutes were required in order to derive a stimulus-response relation and to determine post-isolation control values for blood pressure and heart rate.

Chronic Administration of AII

Chronic hypertension was produced in 5 aortic-intact dogs and 7 aortic-denervated dogs by the continuous intravenous administration of angiotension II (5 ng/kg/min) while the high salt diet continued. Salt-AII hypertension has been well characterized in rats, rabbits, dogs, and man (Koletsky et al., 1966; Dickinson and Lawrence, 1963; McCubbin et al., 1965; Ames et al., 1965). The severity of the hypertension created is directly related to sodium intake (Cowley and McCaa, 1976; Cowley and DeClue, 1976).

AII was diluted to a concentration of 1.0 ug/ul in 0.9% saline. Heparin (500 u/ml) was added and the solution was infused from a calibrated ambulatory infusion pump (Cormed, Model ML-6-4). The pump, as well as the exteriorized catheters, were protected by a fitted canvas vest. Stimulus-response relations for the baroreflex were determined

immediately before the AII infusion and at 4 hours, 1 day, 2-3 days, 4-6 days, and 7-10 days, and 11-30 days following the initiation of the infusion. When stimulus-response relations and their corresponding baroreflex parameters were determined more than once within one of these time periods, the replicate determinations were averaged together to derive a single stimulus-response relation for each dog. A second averaging step yielded group mean stimulus-response relations for each time period (Figures 1 and 3) and group mean baroreflex parameters (Table 1).

Following 2-8 weeks of hypertension, the chronic AII infusion was stopped (high sodium diet maintained). Blood pressure returned toward normotensive levels. Stimulus-response relations were obtained for 3 aortic-intact dogs and 4 aortic-denervated dogs at blood pressures which closely resembled the pre-AII infusion blood pressures (Figures 6 and 7). The carotid sinus preparations did not remain functional long enough to allow all of the dogs to be studied as they returned to the normotensive state.

Statistical Analysis

Changes in baroreflex parameters during acute norepinephrine infusion, acute AII infusion, and chronic AII infusion were analyzed by a randomized block analysis of variance followed by the least significant difference test. Comparisons between aortic-denervated and aortic-intact dogs were made by the Wilcoxin Rank-Sum Test. Baroreflex characteristics during acute and chronic hypertensive states were compared by calculating linear regressions for the relationships between various baroreflex parameters and control blood pressure. Slopes of

these linear regressions were compared by a sign rank test. In all cases, significance was assigned at the .05 level.

RESULTS

Chronic Administration of AII

The effects of continuous AII infusion on the stimulus-response characteristics for the baroreflex are shown in Figures 1 and 3 and in Table 1. The level of control blood pressure prior to AII infusion was 106±2 mm Hg in the aortic-denervated group and 91±3 mm Hg in the aortic-intact group, the difference being significant. In both groups, control blood pressure was significantly elevated after 4 hours of continuous AII infusion. One day after the start of AII infusion, blood pressure in the aortic-intact dogs had risen 25±2 mm Hg, which corresponded to 58% of the eventual increase in blood pressure after 11-30 days of continuous AII infusion. By contrast, a plateau of hypertension was reached within 1 day in the aortic-denervated dogs. Over the course of AII infusion, blood pressure increased 43±3 mm Hg in the aortic-intact group and 34±5 mm Hg in the denervated group. The difference was significant, both in absolute and fractional terms.

A rightward shift of the stimulus-response curves, as indicated by a significant increase in both threshold and saturation levels of carotid sinus pressure, was evident after 1 day of AII infusion in the aortic-intact dogs, and after 4 hours in the aortic-denervated dogs. In both groups, the increase in saturation carotid sinus pressure was significantly greater than the increase in threshold pressure. Thus, the baroreflex responded over a broadened and elevated range of carotid sinus pressure in hypertension.

By 4 hours of continuous AII infusion the stimulus-response curves had shifted upward significantly. In the aortic-intact group, the left and right-hand ends of the curves had risen 13±5 mm Hg and 10±4 mm Hg respectively. After 11-30 days of AII infusion, the upward shifts for the left and right-hand ends were 61±4 mm Hg and 48±6 mm Hg. Although the upward shift was not as great in the aortic-denervated dogs, the left-hand end of the curve was significantly elevated after 1 day of continuous AII infusion, as well as at each subsequent time period. The right-hand end of the curve was not significantly elevated. However, there were no significant differences between the upward shifts of the two ends of the curves in either group. As a result, the range of the blood pressure responses was not significantly altered during the development of hypertension in either group. The maximal slope of the blood pressure response curves was not significantly altered at any point during the development or plateau phase of salt-AII hypertension in either aortic-intact or aortic-denervated dogs. That is, there was no evident impairment in the gain or range of baroreflex control of blood pressure in salt-AII hypertension.

In the aortic-intact dogs, the ability of the baroreflex to increase blood pressure above control blood pressure was significantly elevated by 1 day and for the remainder of the AII infusion. By contrast, the aortic-denervated dogs displayed an enhanced ability to decrease blood pressure below its control level at 1 day of AII infusion, as well as all subsequent time periods.

In aortic-intact dogs, the control levels of heart rate were decreased from the second through the tenth day of AII infusion but not thereafter. In the aortic-denervated group, control heart rate decreased significantly on days 7-10 of AII infusion and remained low throughout the remainder of AII infusion. The development of hypertension caused the heart rate curves in each group to shift rightward, but not significantly upward. Neither the range nor the maximal slope of the heart rate response curves was significantly altered during the development of hypertension. That is, there was no evidence that the ability of the carotid baroreflex to control heart rate was impaired during salt-AII hypertension.

Acute AII Infusion

When blood pressure in normotensive dogs was elevated acutely by intravenous infusions of AII, the blood pressure response curves shifted upward and rightward in much the same fashion as they did during chronic infusion of subpressor doses of AII (Figures 2 and 4 and Table 2). Control blood pressure in the 5 aortic-intact dogs was elevated 27, 40, and 53 mm Hg by 300, 600, and 1200 ng/min of AII. The corresponding elevations in the aortic-denervated dogs (29, 41, and 45 mm Hg) were not significantly different from the elevations in the aortic-intact dogs. Threshold and saturation levels of carotid sinus pressure for both

aortic-intact and denervated dogs were significantly elevated, as reflected in the rightward shift in the stimulus-response curves at all levels of AII infusion. As in the case of chronic AII infusion, the saturation levels of carotid sinus pressure increased significantly more than the threshold levels, so that the baroreflex responded over a broadened and elevated range of carotid sinus pressure. The left and right-hand ends of the blood pressure response curves were shifted significantly upward by AII infusion. Reflex gain was not significantly affected by AII infusion in the aortic-denervated dogs, but was significantly reduced during the infusion of 600 and 1200 ng/min of AII in the aortic-intact dogs.

Acute AII infusion did not significantly affect control heart rate in either aortic-intact or aortic-denervated dogs. However, both the range and the maximal slope (sensitivity) of the heart rate response curves were significantly increased by AII infusion in the aortic-intact dogs. In the aortic-denervated dogs, the range but not the slope of heart rate responses was increased.

Table 4 shows a standardized comparison of the effects of acute and chronic AII infusion on the various baroreflex parameters. For equivalent elevations of control blood pressure, acute and chronic AII infusion brought about very similar changes in the baroreflex parameters for the control of blood pressure. This similarity in the effects of acute and chronic AII was evident both for the aortic-intact dogs and the aortic-denervated dogs. Acute and chronic AII infusion had less uniform effects on the heart rate parameters of the baroreflex. The

differences in the effects of acute and chronic AII on control heart rate and on minimum heart rate were statistically significant for the aortic-denervated dogs.

The far right-hand columns of Table 4 provide a basis for comparing the effects of chronic AII infusion in aortic-intact verses aortic-denervated dogs (P**) and for comparing the effects of acute AII infusion in aortic-intact vs. aortic-denervated dogs (P+). For equivalent increases in control blood pressure brought about by either chronic or acute AII infusion, the upward shifts of the blood pressure curves (reflected in ΔBP_{max} and ΔBP_{min}) were significantly greater for the aortic-intact dogs than for the aortic denervated dogs. An analysis of the gain data indicated a significantly stronger tendency for chronic AII infusion to steepen the blood pressure response curves in the aortic-denervated dogs than in the aortic-intact dogs.

Acute Norepinephrine Infusion

Acute intravenous infusions of norepinephrine in normotensive, aortic-intact dogs caused the blood pressure response curves to shift upward (Figure 5 and Table 3). Control blood pressure was elevated 15 and 30 mm Hg by 10 and 20 ug/min norepinephrine. Norepinephrine infusion did not significantly alter the threshold or saturation levels of carotid sinus pressure and the gain of the reflex was not changed. During norepinephrine infusion, there was an augmentaion of the amount by which the baroreflex could increase blood pressure above its control value, although the total range of blood pressure responses was not significantly altered. Control heart rate was decreased and shifted

relatively lower on the heart rate response curve during norepinephrine infusion. The sensitivity of the cardiac component of the baroreflex remained unchanged.

Acute norepinephrine infusion and acute AII infusion had very similar effects on baroreflex control of blood pressure. Although acute AII infusion caused a significant rightward shift of the blood pressure response curves (ie., significant increase in threshold and saturation carotid sinus pressure) and norepinephrine infusion did not, the effects of AII and norepinephrine on threshold and saturation were not significantly different when standardized for equivalent increases in control pressure. Likewise, the effects of norepinephrine and AII on baroreflex range and gain were not significantly different.

Reversal of AII Hypertension

When the continuous infusion of AII was stopped, the control levels of blood pressure and the baroreflex characteristics both reverted toward their normotensive values. As indicated in Figure 6, the control pressure of 3 aortic-intact dogs returned 70 $\pm$ 3% of the way toward the original normotensive value. This occured within 1 week after cessation of AII infusion. The upward and rightward shifts of the blood pressure response curves were reversed to an equal or greater degree than was control pressure. The rightward shift of the heart rate curve was also reversed after cessation of AII. The other parameters of the heart rate response were not significantly changed either during or after AII infusion. As indicated in Figure 7, the control blood pressure of 4 aortic-denervated dogs returned 99$\pm$9% of the way toward the original normotensive value within 3 days after cessation of AII infusion. The reversal of the rightward shift in the blood pressure response curve was

nearly complete. In these 4 dogs the upward shift of the blood pressure response curve during AII infusion was not significant. However, the graph suggests a tendency for an upward shift during AII infusion and also for its reversal following cessation of AII infusion.

Table 1. Effect of continuous intravenous infusion of angiotensin II (5 ng/kg/min.) on baroreflex characteristics of conscious dogs. Baroreflex parameters are defined in text. Values in table are mean ± S.E.M. **Significant treatment effect indicated by ANOVA. *Significantly different from time zero (No infusion) value.

Parameter	Units	No Infusion	Time Since Beginning Angiotensin Infusion				
			4 hours	1 day	2-3 Days	4-6 Days	7-10 Days	11-30 Days
AORTIC DEPRESSOR NERVES INTACT (n=5)								
Blood Pressure Parameters								
Control Level	mm Hg	91±3	104±5*	116±3*	122±4*	123±4*	130±4*	134±1*
Threshold CSP	mm Hg	92±5	101±3	112±4*	111±4*	110±4*	115±3*	124±5*
Saturation CSP	mm Hg	190±8	201±2	220±7*	230±10*	230±6*	233±11*	251±10*
ΔCSP (Saturation-Threshold)	mm Hg	98±8	101±4	108±4*	120±8*	119±7*	119±9*	128±6*
Increase	mm Hg	23±4	24±4	32±5*	31±7*	32±5*	35±8*	43±10*
Decrease	mm Hg	41±5	43±5	41±3	43±2	37±2	41±1	35±5
Range (Increase+Decrease)	mm Hg	65±8	67±8	73±6	74±7	69±7	76±8	77±10
Gain (maximum)	dimensionless	.82±.10	.78±.12	.79±.06	.78±.14	.68±.10	.77±.11	.67±.10
Heart Rate Parameters								
Control Level	bpm	75±10	74±8	67±6	64±10*	61±11*	63±9*	68±10
Increase	bpm	4±3	5±2	18±4*	13±6	11±3	15±5*	17±5*
Decrease	bpm	27±6	26±7	19±4	16±4*	13±2*	12±3*	12±3*
Range (Increase+Decrease)	bpm	31±4	31±6	37±6	29±7	24±2	28±4	29±3
Sensitivity (maximum)	bpm/mm Hg	.37±.02	.33±.07	.44±.05	.33±.08	.29±.06	.32±.07	.26±.02
AORTIC DEPRESSOR NERVES SECTIONED (n=7)								
Blood Pressure Parameters								
Control Level	mm Hg	106±2	121±3*	141±4*	137±4*	139±4*	139±2*	140±4*
Threshold CSP	mm Hg	115±8	127±6*	140±10*	137±8*	134±8*	143±9*	148±11*
Saturation CSP	mm Hg	176±6	193±9*	218±12*	208±7*	225±5*	225±8*	225±4*
ΔCSP (Saturation-Threshold)	mm Hg	61±3	66±6	78±5*	71±7	91±7*	82±9*	79±8*
Increase	mm Hg	121±11	109±15	102±12	102±14	111±13	105±14	112±9
Decrease	mm Hg	52±2	61±4	77±5*	76±6*	79±4*	78±3*	82±4*
Range (Increase+Decrease)	mm Hg	173±12	169±15	179±14	178±18	190±15	183±16	194±11
Gain (maximum)	dimensionless	3.46±.35	3.33±.32	2.95±.42	2.93±.37	2.57±.38	2.86±.41	2.81±.35
Heart Rate Parameters								
Control Level	bpm	97±5	94±5	91±6	92±7	92±11	80±10*	80±10*
Increase	bpm	88±12	82±11	92±9	94±11	92±11	104±10	105±9
Decrease	bpm	32±4	42±2	59±11	44±8	51±8	37±6	41±3
Range (Increase+Decrease)	bpm	120±13	124±11	142±12	138±15	143±11	140±13	146±11
Sensitivity (maximum)	bpm/mm Hg	1.86±.12	2.31±.25	2.28±.20	2.31±.37	1.89±.31	2.11±.35	2.17±.24

Table 2. Effect of acute intravenous infusion of angiotensin II on carotid baroreflex characteristics of conscious, normotensive dogs. Baroreflex parameters are defined in the text. Values in table are mean ± S.E.M. **Significant *Significantly different from baseline (0 ng/min.) value.

AORTIC DEPRESSOR NERVES INTACT, n=5

Parameter	Units	Infusion Rate (ng/min) 0	300	600	1200	P
Blood Pressure Parameters						
Control Level	mm Hg	94±2	121±5*	134±6*	147±5*	**
Threshold CSP	mm Hg	95±4	112±7*	108±5*	116±5*	**
Saturation CSP	mm Hg	193±8	237±8*	239±8*	246±12*	**
ΔCSP (Saturation-Threshold)	mm Hg	98±7	125±5*	131±5*	130±10*	**
Increase	mm Hg	18±3	28±3*	29±2*	30±5*	**
Decrease	mm Hg	39±2	36±3	31±5	29±5	NS
Range (Increase+Decrease)	mm Hg	57±5	64±5	60±7	60±6	NS
Gain (maximum)	dimensionless	.63±.03	.58±.05	.49±.06*	.48±.05*	**
Heart Rate Parameters						
Control Level	bpm	78±9	74±9	72±11	86±11	NS
Increase	bpm	3±2	16±4	34±8*	43±13*	**
Decrease	bpm	24±4	23±6	11±2	22±4	NS
Range (Increase+Decrease)	bpm	26±4	39±8	46±9*	65±13*	**
Sensitivity (maximum)	bpm/mm Hg	.28±.08	.46±.07*	.50±.11*	.63±.14*	**

AORTIC DEPRESSOR NERVES SECTIONED, n=6

Blood Pressure Parameters						
Control Level	mm Hg	105±3	134±4*	146±5*	150±3*	**
Threshold CSP	mm Hg	110±8	129±8*	133±8*	137±9*	**
Saturation CSP	mm Hg	174±6	211±10*	232±14*	230±11*	**
ΔCSP (Saturation-Threshold)	mm Hg	64±6	82±6	99±9*	92±9*	**
Increase	mm Hg	109±10	107±8	105±10	106±8	NS
Decrease	mm Hg	54±4	79±3*	89±3*	88±4*	**
Range (Increase+Decrease)	mm Hg	164±7	186±8*	194±9*	193±9*	**
Gain (maximum)	dimensionless	3.35±.58	2.40±.25	2.23±.33	2.44±.39	NS
Heart Rate Parameters						
Control Level	bpm	94±5	90±8	95±7	95±10	NS
Increase	bpm	58±9	74±6	66±7	62±7	NS
Decrease	bpm	40±5	50±9	56±4	57±10	NS
Range (Increase+Decrease)	bpm	98±10	123±11*	122±9*	118±13*	**
Sensitivity (maximum)	bpm/mm Hg	1.42±.22	1.82±.27	1.65±.22	1.56±.13	NS

Table 3. Effect of acute intravenous infusions of norepinephrine on carotid baroreflex characteristics of conscious, normotensive dogs. Baroreflex parameters are defined in the text. Values in table are mean ± S.E.M. (n=6). **Significant treatment indicated by ANOVA. *Significanlty different from baseline (0 ug/min.) value.

Parameter	Units	Infusion Rate (ug/min)			P
		0	10	20	
Blood Pressure Parameters					
Control Level	mm Hg	102±5	117±5*	132±7*	**
Increase	mm Hg	20±4	42±7*	41±8*	**
Decrease	mm Hg	35±5	24±7	26±6	NS
Range (Increase+Decrease)	mm Hg	55±7	66±2	67±7	NS
Threshold CSP	mm Hg	99±7	109±8	117±11	NS
Saturation CSP	mm Hg	202±11	225±9	226±11	NS
ΔCSP (Saturation-Threshold)	mm Hg	119±11	116±9	109±10	NS
Gain (maximum)	dimensionless	.79±.18	.82±.21	.85±.23	NS
Heart Rate Parameters					
Control Level	bpm	80±7	57±5*	60±5*	**
Increase	bpm	1±1	10±4	14±6*	**
Decrease	bpm	19±3	9±3	9±4	NS
Range (Increase+Decrease)	bpm	20±2	19±2	23±3	NS
Sensitivity (maximum)	bpm/mm Hg	.26±.07	.29±.06	.30±.06	NS

Table 4. Comparison of baroreflex changes during acute and chronic AII infusion --Table entries are derived from linear regression analysis and changes in baroreflex parameters associated with each 10 mm Hg elevation in control blood pressure.
P* Chronic AII vs. Acute AII, paired comparisons
P** Intact vs. Denervated -- Chronic AII, unpaired
P+ Intact vs. Denervated -- Acute AII, unpaired

Parameter	Aortic Nerves Intact (n=5)			Aortic Nerves Denervated (n=6)				
	Chronic AII	Acute AII	P*	Chronic AII	Acute AII	P*	P**	P+
Δ Threshold	6.7±1.5	3.6±0.6	NS	8.9±1.9	6.7±1.3	NS	NS	NS
Δ Saturation	12.7±1.9	11.6±1.1	NS	12.4±1.2	15.0±2.7	NS	NS	NS
Δ BP max	13.5±1.2	13.1±0.9	NS	5.1±3.9	9.3±1.8	NS	*	*
Δ BP min	10.8±1.4	11.5±0.7	NS	2.1±0.2	4.9±2.2	NS	*	*
Δ Increase	3.6±1.3	2.8±0.8	NS	2.7±4.1	0.7±1.9	NS	NS	*
Δ Decrease	-1.0±1.5	-1.6±0.6	NS	2.7±3.8	4.2±2.3	NS	NS	NS
Δ Gain	-0.03±0.02	-0.03±0.01	NS	-0.12±0.08	-0.32±0.16	NS	*	NS
Δ HR control	-2.8±0.9	-0.4±1.6	NS	-3.6±0.6	0.1±1.3	*	NS	NS
Δ HR max	0.6±1.6	8.2±1.6	NS	-0.2±5.9	3.5±2.6	NS	NS	NS
Δ HR min	0.8±0.5	0.8±1.6	NS	-5.7±1.1	-2.6±1.0	*	*	NS
Δ Increase	3.3±1.4	6.8±0.8	NS	3.4±1.4	2.8±3.2	NS	NS	NS
Δ Decrease	-3.7±1.5	-1.0±0.8	NS	2.0±1.3	2.3±1.8	NS	*	NS
Δ Sensitivity	0.00±0.02	0.05±0.02	NS	0.15±0.08	0.02±0.07	NS	NS	NS

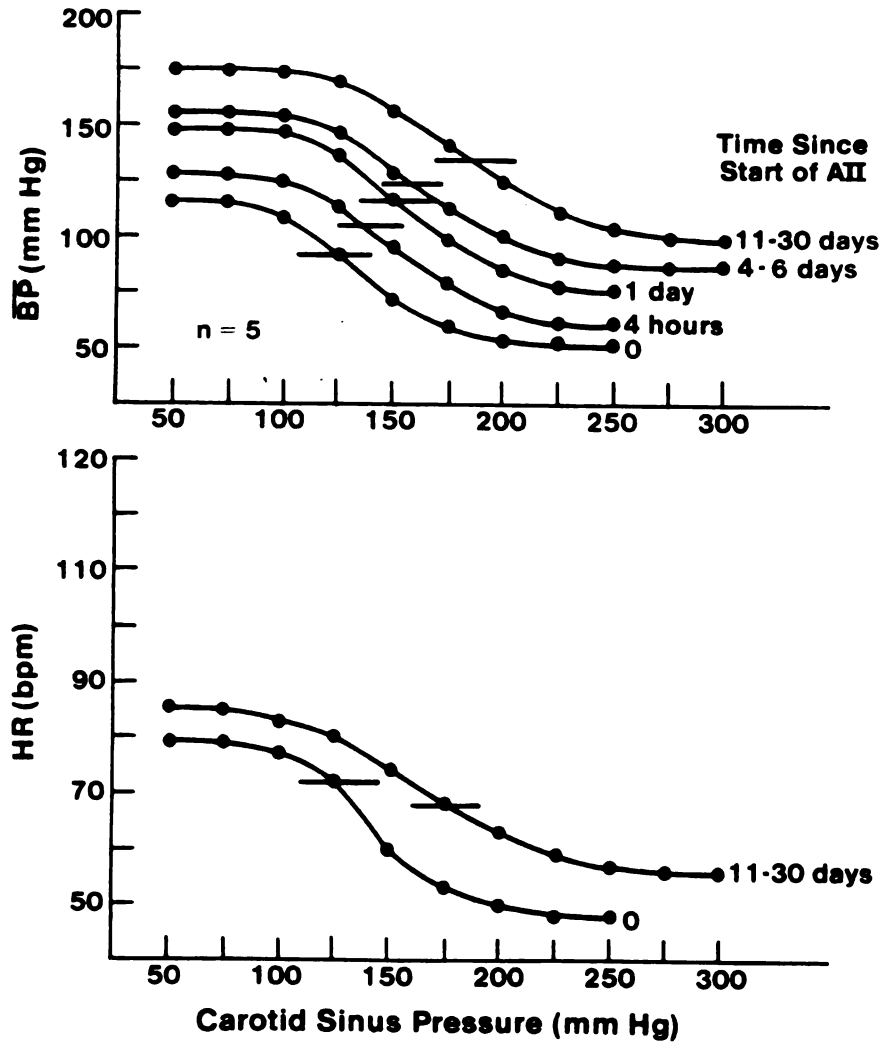

Figure 1. Development of chronic salt-AII hypertension in aortic-intact dogs. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated.

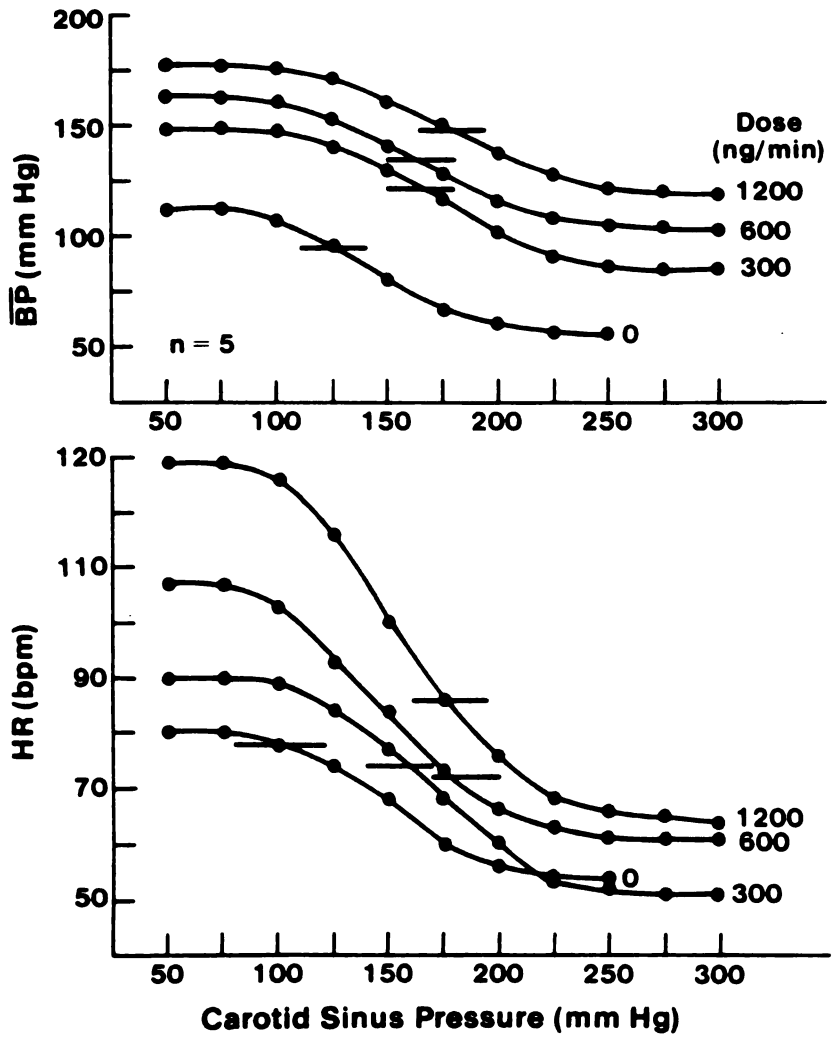

Figure 2. Acute, intravenous infusion of AII in normotensive, aortic-intact dogs. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated.

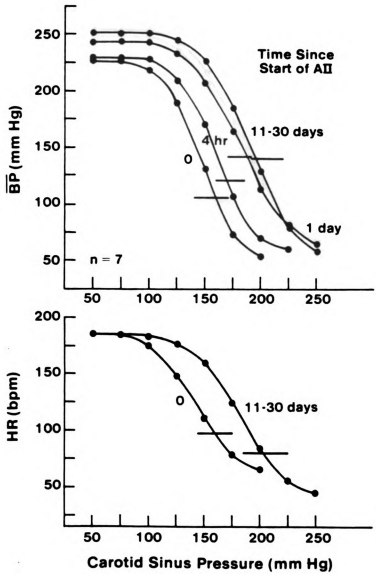

Figure 3. Development of salt-AII hypertension in aortic-denervated dogs. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated.

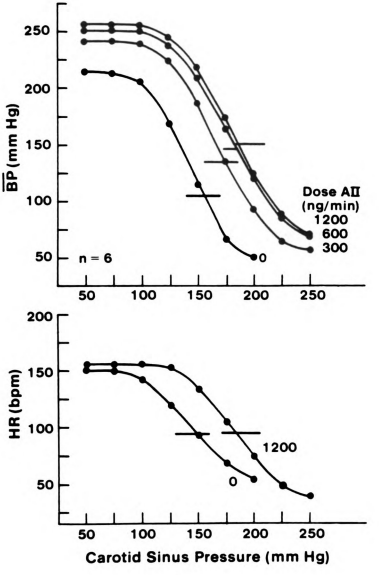

Figure 4. Acute, intravenous infusion of AII in aortic-denervated dogs. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated.

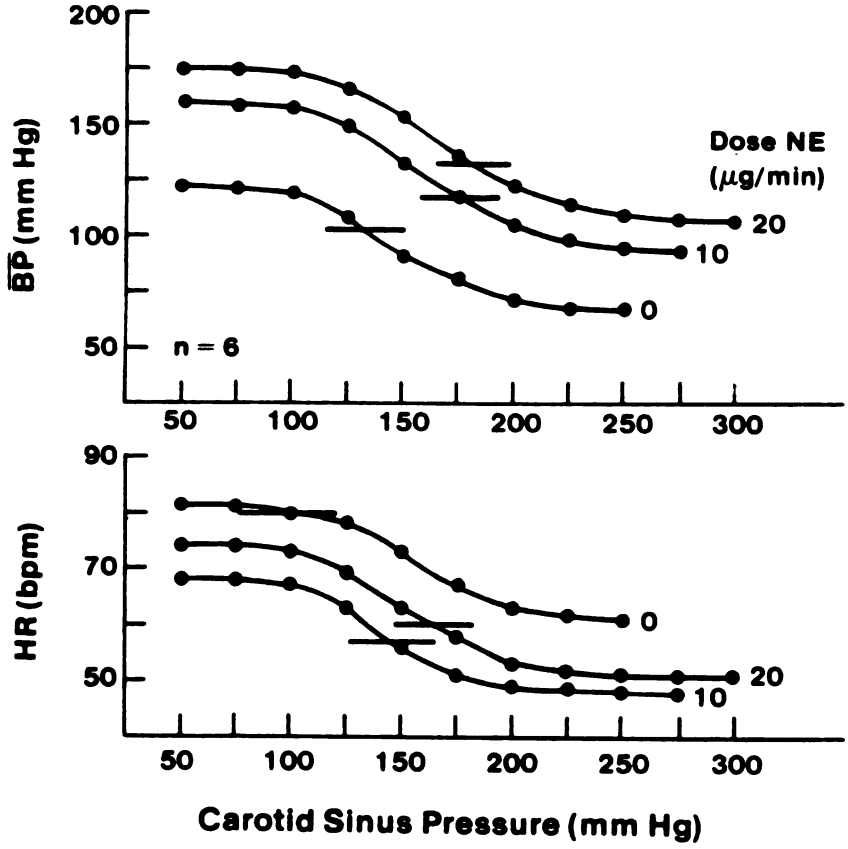

Figure 5. Intravenous infusion of norepinephrine in normotensive, aortic-intact dogs. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated.

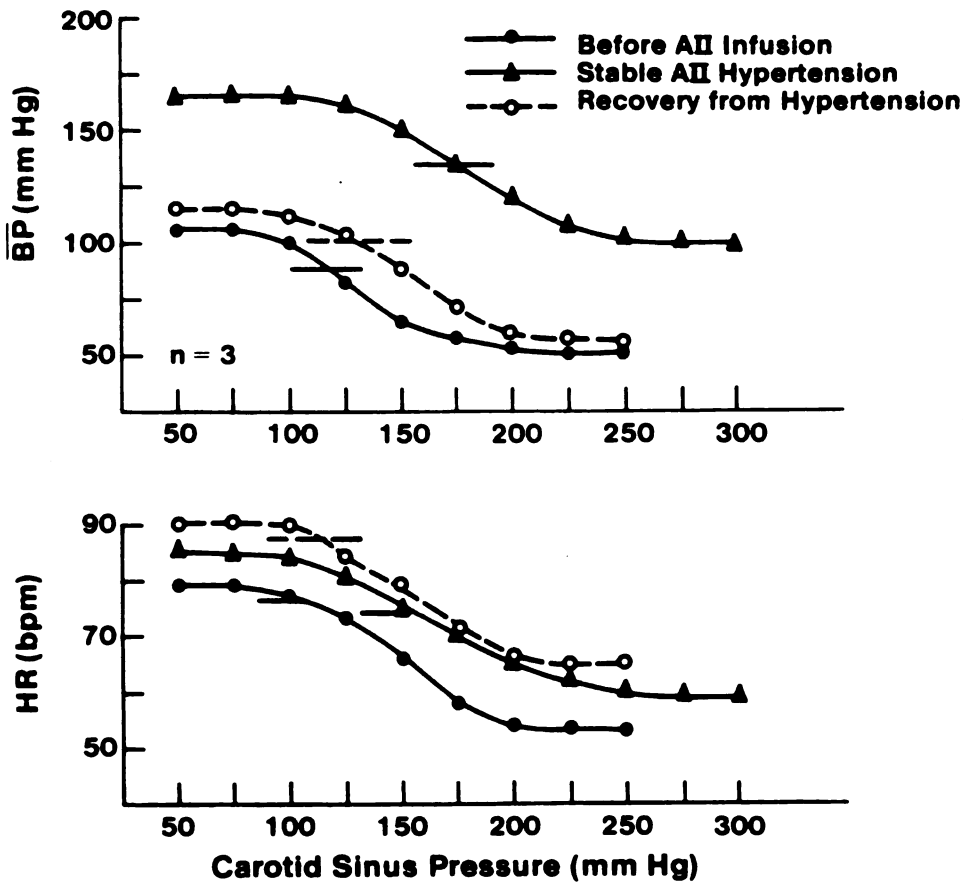

Figure 6. Reversibility of baroreflex changes in chronic salt-AII hypertension--aortic-intact dogs. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated.

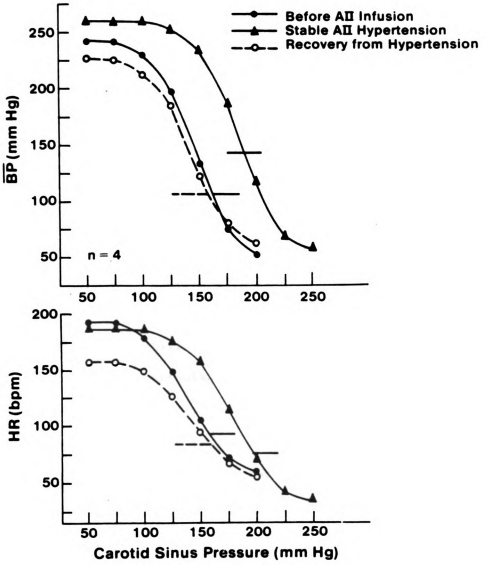

Figure 7. Reversibility of baroreflex changes in chronic salt-AII hypertension--aortic-denervated dogs. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated

DISCUSSION

The primary contribution of this study is that for the first time the overall stimulus-response characteristics of the baroreflex have been compared quantitatively during acute and chronic elevations of blood pressure brought about by angiotensin infusion. Previously, the timecourse and magnitude of angiotensin-induced hypertension has been described for various species (Koletsky et al., 1966; Dickinson and Lawrence, 1963; McCubbin et al., 1965; Ames et al., 1965). Furthermore, the time course and magnitude of the hypertension has been compared in intact and baroreceptor-denervated dogs (Cowley and DeClue, 1976). However, the characteristics of an intact and functioning baroreflex have not been directly assessed in salt-AII hypertension. Also, previous studies of the baroreflex in other types of experimental hypertension have largely been limited to an analysis of baroreflex control of heart rate. The overall ability of the baroreflex to control blood pressure has been difficult to ascertain in concious subjects due to the lack of a technique for precise manipulation of the stimulus to the baroreceptors. We utilized a surgical preparation which allowed subsequent, reversible, vascular isolation of the cartoid sinus regions in conscious dogs. Therefore, the stimulus to the baroreceptors in our study could be varied over a wide range in a precisely repeatable manner and the effects of carotid sinus pressure on both blood pressure and heart rate could be determined.

The results indicate that the carotid baroreflex is reset in pace with the rising arterial pressure during the development of chronic salt-AII hypertension. Also, the gain of the carotid baroreflex is not reduced in chronic salt-AII hypertension. Therefore, the baroreflex

retains its ability to regulate blood pressure on a moment-to-moment basis, but blood pressure is regulated at a progressively higher level as the salt-AII hypertension develops. These conclusions are based on an analysis of the open-loop stimulus-response curves for the effects of carotid sinus pressure on heart rate and blood pressure. Shifts in the stimulus-response curves are indicative of resetting on the baroreflex, whereas changes in the slope of the curves would indicate changes in baroreflex gain.

Interpreting the Stimulus-Response Curves

Acute AII infusion and chronic salt-AII hypertension all caused similar rightward shifts in the stimulus-response curves. Rapid resetting of the baroreceptors is the most likely reason for the rightward shift. Reset baroreceptors would respond over an elevated range of carotid sinus pressure, but the upper limit of blood pressure (reached when carotid sinus pressure is below threshold for activation of baroreceptors) and the lower limit of blood pressure (reached when carotid sinus pressure is above the level required for maximal activation of the baroreceptors) would be unchanged. Several investigators have shown that threshold for activation of baroreceptors becomes reset within minutes after the baroreceptors are exposed to acutely elevated or depressed levels of blood pressure (Krieger, 1970; Salgado and Krieger, 1978; Coleridge et al, 1981; Kunze, 1981). The degree of rapid resetting is dependent on the prevailing level of arterial pressure. Central mechanisms could also contribute to the

rightward shift of the stimulus-response curves, since threshold phenomena in the CNS could potentially elevate the threshold level for baroreflex effects above the threshold of the baroreceptors, themselves.

An upward shift of the baroreflex stimulus-response curve indicates the presence of a pressor influence that is independent of (or superimposed on) the baroreflex (Korner, 1975). For example, our acute infusions of AII or norepinephrine constituted pressor influences that were independent of the baroreflex in the sense that the baroreflex could not affect the rate of infusion on the pressor drugs. Our data show that such baroreflex-independent pressor influences do, indeed, shift the stimulus-response curves upward. Furthermore, our data show that chronic salt-AII hypertension also involves a pressor influence that is independent of baroreflex effects. Even maximal stimulation of the baroreceptors in the hypertensive dogs could not lower blood pressure to levels reached in normotensive dogs. For equivalent increases in control blood pressure, the upward shifts of the stimulus-response curves were not significantly different for acute norepinephrine, acute AII, and chronic salt-AII hypertension. Therefore, we conclude that the degree to which the baroreflex buffers potential increases in blood pressure is not different for acutely or chronically elevated blood pressure.

The norepinephrine experiments allowed us to determine whether or not the effects of acute AII and chronic salt-AII hypertension on the baroreflex are unique to AII. The results show that acute norepinephrine, acute AII, and chronic salt-AII hypertension all caused similar shifts of the blood pressure response curves. Melcher and Donald (1981) used a similar carotid sinus preparation and showed that

graded exercise had effects on the baroreflex similar to those we saw with norepinephrine infusion. During exercise, higher centers in the CNS apparantly reset the baroreflex by activating a pressor influence that the baroreflex cannot oppose. During exercise, as during salt-AII hypertension, the baroreflex maintains its ability to regulate blood pressure, but at an elevated level.

The maximal slope of a stimulus-response curve provides a measure of baroreflex gain (ie., the sensitivity with which the baroreflex responds to a given change in carotid sinus pressure). At no time during the development of chronic salt-AII hypertension was baroreflex gain significantly changed. Therefore, the rise in blood pressure cannot be attributed to an inhibition of the baroreflex. The baroreflex retains its normal ability to regulate blood pressure, but the reflex is reset so that blood pressure is regulated at a progressively higher level.

It is frequently asserted that baroreflex gain is reduced in essential hypertension and in experimental renal hypertension. This assertion is based on the observation that a pressor stimulus leads to less cardiac slowing in hypertensive than normotensive subjects (Bristow et al., 1969; Gribben et al., 1971; West and Korner, 1974; Korner et al., 1974; Takeshita et al., 1975; Thames et al., 1981). In addition, a subnormal cardiac acceleration has also been found in response to depressor stimuli (Bristow et al., 1969; Thames et al., 1981). However, arterial blood pressure, not heart rate, is the component of the baroreflex that is of primary importance in hypertension. It may be invalid to extrapolate from baroreflex control of heart rate to baroreflex control of blood pressure. For example, the heart rate component of the baroreflex is impaired in anesthetized, renal

hypertensive rabbits, but the ability of the baroreflex to control blood pressure is normal or enhanced (Angell-James and George, 1980; Guo et al., 1983). Technical difficulties have hampered the study of baroreflex control of blood pressure in conscious, normotensive and hypertensive subjects. Specifically, baroreflex gain has not previously been measured during the development of salt-AII hypertension. We have previously prepared the carotid sinuses of dogs for reversible isolation and have found that baroreflex gain is significantly reduced in conscious dogs with chronic renal hypertension. We anticipated that the gain of the baroreflex would be similarly impaired during chronic salt-AII hypertension. However, at no time during the development and maintenance of the hypertension was the slope of the stimulus-response relation significantly reduced.

Mechanisms of Baroreflex Changes

Three factors may account for the fact that baroreflex gain decreased in renal hypertension but not in salt-AII hypertension. First, the mechanisms of hypertension-induction in chronic renal hypertension and chronic salt-AII hypertension may be different. Second, the level of hypertension achieved by our renal hypertensive dogs (161 $\pm$ 10 mm Hg) was approximately 30 mm Hg higher than the steady state hypertensive levels obtained during chronic salt-AII hypertension. Third, stimulus-response relations were not determined until 6 weeks after the renal hypertension commenced, whereas with salt-AII hypertension, baroreflex characteristics were determined only up to 30 days. Therefore, the severity and duration of hypertension was greater in the renal hypertensive dogs, which may have contributed to the

attenuated baroreflex gain. Nevertheless, the data indicate that depressed baroreflex gain is not a universal accompaniment of experimental hypertension.

It is likely that the decrease in baroreflex gain during acute AII infusion at 600 and 1200 ng/min resulted from a central action of blood-borne AII. Vascularly administered AII can act centrally to impair baroreceptor-induced sympathoinhibition (Stein et al, 1984) and to inhibit vagally mediated bradycardia (Ismay et al, 1979). Acute, intravertebral infusions of AII reduce the depressor responses to stimulation of the carotid sinus nerves (Fukiyama, 1973; Goldstein et al., 1974; Marker et al., 1980). Blood-borne AII may have to reach levels beyond the physiological range in order to exert central effects (Abraham et al, 1975; Brown et al, 1976). However, infusions of 600-1200 ng/min probably elevated blood levels of AII beyond the physiological range. Trippodo et al (1976) found that infusion of one-fourth to one-half this dose of AII for 4 hours resulted in blood levels of AII that corresponded closely to the levels at the end of 3 days of sodium depletion. Although the 600 and 1200 ng/min doses of acutely infused AII probably elevated blood AII beyond the physiological range, blood levels of AII during chronic infusion (5 ng/kg/min) almost certainly remained within the physiological range. However, even elevated levels of AII within the physiological range may have a chronic central effect to increase sympathetic activity (Dickinson and Yu, 1967a and 1967b; Yu and Dickenson, 1971; Fukiyama et al., 1971; Sweet et al., 1971).

Cowley and DeClue (1976) compared the development of salt-AII hypertension in intact and aortic-denervated dogs. They found that

blood pressure rose more slowly in dogs with intact baroreflexes for the first 28 hours of continuous angiotensin infusion. Thereafter, the blood pressure levels were similar in intact and baroreceptor-denervated dogs. They attributed 35% of the eventual increase in blood pressure to resetting of the baroreflex. Their data imply that resetting of the baroreflex takes place over the first 28 hours of continuous angiotensin infusion. However, the process of adaptation to baroreceptor denervation may complicate the use of baroreceptor denervation as a method to infer the role of the baroreflex during the onset and maintenance of chronic hypertension. In rats, cats, and dogs, sino-aortic denervation results in marked, acute elevations of blood pressure. In the study by Cowley and DeClue, experiments were generally begun 3 weeks after baroreceptor denervation, by which time the dogs had largely adapted to the loss of their baroreceptors, as indicated by the fact that the 24 hour control blood pressure values were only 11 mmHg higher in the denervated dogs than the intact dogs. The mechanisms of adaptation have unknown influences on the subsequent development of salt-AII hypertension.

When aortic baroreceptors are left intact, they buffer reflex responses initiated by the carotid baroreceptors. Therefore, we studied the carotid baroreflexes in both intact and aortic-denervated dogs. To our knowledge, the development of salt-AII hypertension has not previously been studied in aortic-denervated dogs. Arterial pressure reached a hypertensive plateau in 1 day in aortic-denervated dogs verses 7-10 days in aortic-intact dogs, which indicates that aortic, but not carotid, baroreceptors oppose the development of the hypertensive state for a period of several days. Aortic baroreceptors may adapt more

slowly and less completely to chronically elevated blood pressure than do carotid sinus baroreceptors McRitchie et al, 1976). Jones and Thoren (1977) showed that aortic baroreceptors with c-fiber afferents do not reset completely in chronic hypertension. Aortic baroreceptor denervation causes a chronic increase in blood pressure in conscious dogs, whereas carotid sinus nerve section does not (Ito and Scher, 1978; Ito and Scher, 1979). These results imply that the aortic baroreceptors exert a chronic anti-hypertensive influence, whereas the carotid baroreceptors simply function to stabilize blood pressure on a moment-to-moment basis. Cowley and DeClue (1976) found that salt-AII hypertension developed more quickly in sino-aortic denervated dogs than in dogs with intact baroreceptors. Our results suggest that denervation of the aortic baroreceptors was the principal reason for the faster development of salt-AII hypertension in their sino-aortic denervated dogs.

In conclusion, the present results indicate that the carotid baroreflex resets in pace with the rise in blood pressure during the development of salt-AII hypertension. Baroreflex gain was not significantly reduced. Therefore, the baroreflex maintained its ability to regulate blood pressure on a moment-to-moment basis. Experimental evidence that has demonstrated that it takes 48 hours for 90% resetting of the baroreceptors (Krieger, 1986), as well as studies which infer that the baroreflex opposes the development of hypertension for at least 1 day (Cowley and DeClue, 1976), led us to expect that changes in baroreflex characteristics would be dependent on the duration of hypertension as well as on its magnitude. Therefore, we had expected greater changes in baroreflex characteristics, for a given increase in

arterial pressure, during the development of chronic, salt-AII hypertension than during acute elevations of blood pressure caused by infusions of AII or norepinephrine. However, the data clearly indicate that the changes in the baroreflex characteristics were very similar during acute elevations of blood pressure as during chronic salt-AII hypertension. Therefore, the carotid baroreflex does not appear to influence the development of elevated arterial pressure as observed within the boundries of our experimental design. By contrast, the aortic baroreceptor reflex does appear to retard the development of salt-AII hypertension.

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SYMPATHETIC AND PARASYMPATHETIC CONTRIBUTIONS TO THE CAROTID BAROREFLEX IN ANGIOTENSIN-INDUCED HYPERTESION

INTRODUCTION

In normotensive, conscious, resting dogs, sympathetic tone is minimal, so the baroreceptor reflex must rely on parasympathetic activation, rather than withdrawal of sympathetic tone, to decrease heart rate and blood pressure (Thames et al., 1981; Stephenson and Osborn, 1981). By contrast, several lines of evidence sympathetic tone is elevated and that sympathetic responses are exaggerated in various forms of experimental hypertension (Abboud et al., 1982). In particular, the slow rise in blood pressure during the continuous infusion of small amounts of angiotensin is mediated through the sympathetic nervous system (Yu and Dickinson, 1971). The level of hypertension reached during continuous infusion of angiotensin is dependent on sodium intake (Cowley and DeClue, 1976). If sympathetic tone contributes to the maintenance of elevated blood pressure in salt-AII hypertension, then sympathetic withdrawal could contribute significantly to reflex decreases in blood pressure. Therefore, our first hypothesis is that the sympathetic component of the baroreflex is enhanced in chronic salt-AII hypertension.

The mere existence of elevated sympathetic tone in salt-AII hypertension would not obligate an enhanced reliance by the baroreflex on sympathetic mechanisms, because some descending sympatho-excitatory pathways do not interact with baroreceptor afferents (Gebber et al.,

1973; Judy and Farrel, 1979). If these baroreflex-independent pathways were activated in salt-AII hypertension, then substantial sympathetic tone might persist despite maximal stimulation of baroreceptors. Furthermore, evidence from acute studies suggests that AII may act centrally to impair the ability of the baroreflex to inhibit sympathetic tone (Stein et al., 1984; Sweet and Brody, 1970). Therefore, additional studies are needed to determine whether or not the sympathetic component of the baroreflex is enhanced in chronic salt-AII hypertension.

The effect of chronic salt-AII hypertension on the parasympathetic component of the baroreflex remains unknown. However, acutely administered AII blunts the cardiac parasympathetic component of the baroreflex. Scroop and Lowe (1969) demonstrated a vagal inhibitory action of AII in greyhounds, and Ismay et al. (1979) found less reflex bradycardia following AII administration than following equipressor doses of phenylephrine. Lumbars et al. (1979) showed by direct recording that baroreceptor-evoked activity in cardiac vagal efferents is inhibited by AII in the dog. On the basis of these acute effects of angiotensin, we hypothesize that the parasympathetic component of the baroreceptor reflex is blunted in chronic salt-AII hypertension.

Technical limitations in previous studies have hampered the quantitative assessment of the baroreflex in conscious subjects. We have utilized a preparation that allows controled pressures to be applied to the temporarily isolated carotid sinus regions of conscious dogs (Stephenson and Donald, 1980). Complete stimulus-response relations were derived for the effects of carotid sinus pressure on heart rate and blood pressure in normotensive dogs and dogs with established salt-AII hypertension. The relative roles of sympathetic and parasympathetic mechanisms in mediating carotid baroreflex responses

were assessed by comparing baroreflex characteristics before and after the administration of various autonomic blocking drugs, singly and in combination.

The balance between sympathetic and parasympathetic mechanisms in the carotid baroreflex may be altered both by salt-AII hypertension and by denervation of the aortic arch baroreceptors. Specifically, sympathetic mechanisms may be more prominent in carotid baroreflex responses of aortic-denervated dogs than in dogs with intact aortic baroreceptors; because, when the carotid baroreceptors are unloaded in dogs with intact aortic baroreceptors, the reflexive increases in sympathetic activity and blood pressure are buffered by activation of the aortic baroreceptors (Walgenbach, 1981). Therefore, we have evaluated sympathetic and parasympathetic contributions to the carotid baroreflexes of normotensive and hypertensive dogs with and without intact aortic depressor nerves.

METHODS

Diet

Twelve healthy, mongrel dogs, weighing 20-35 kg were maintained on a high dietary sodium intake (6 mEq Na^+/kg/day) and fresh water *ad libitum*. This diet commenced at least two weeks prior to baroreflex experiments. The high sodium diet was prepared by adding sodium chloride tablets (Lilly) to low sodium dog food (Prescription Diet, k/d, Hills). The salted food was divided between morning and evening feedings.

Surgical Preparation

Anesthesia was induced with sodium thiamylal (Biotal, Bio-Ceutic) (20 mg/kg, iv) and maintained with halothane and nitrous oxide in oxygen. The carotid sinus regions of each dog were surgically prepared for subsequent, reversible isolation from the systemic circulation by the method previously reported (Stephenson and Donald, 1980). Briefly, both carotid arteries were approached through a midline incision in the neck. The thyroid, lingual, occipital, internal carotid, and ascending pharyngeal arteries were ligated, which left the common carotid and external carotid arteries as the only pathways for blood flow to and from the carotid sinuses. On these vessels were placed inflatable occlusion cuffs. When these cuffs were deflated, the carotid sinuses communicated freely with the systemic circulation; inflation of the cuffs isolated the carotid sinuses. To permit the imposition of known pressures on the isolated carotid sinuses, non-occlusive catheters (Tygon Microbore, 0.040" ID x 0.070" OD, Norton) were placed bilaterally into the carotid arteries near the carotid sinuses. The occluder tubes and catheters were exteriorized on the lateral aspects of the neck.

The aortic baroreceptors were denervated in 7 dogs. These 7 dogs were designated "aortic-denervated" as opposed to the 5 "aortic-intact" dogs. Identification of specific aortic depressor nerves within the vagosympathetic trunk was attempted by the method of Edis & Shepherd (1971). Positive identification of aortic nerves was made by recording whole nerve activity on a bipolar platinum electrode. Nerves with a characteristic, pulse-synchronous activity were sectioned. If identification of the aortic depressor nerves was uncertain, the entire left cervical vagosympathetic trunk was sectioned as was the right cervical sympathetic tract. We performed left vagosympathectomy in lieu

of selective section of the cervical aortic nerves in some dogs, because Walgenbach et al. (1981) had shown that aortic baroreflexes are predominantly mediated via afferents in the left vagosympathetic trunk, but parasympathetic control of heart rate is predominantly mediated via right vagal fibers.

In a second surgery 10 days later, each dog was equipped with an arterial catheter for measurement of blood pressure and a venous catheter for administration of drugs. For this purpose silicone rubber tubes (Silastic, 0.065" ID x 0.125" OD, Dow Corning) were inserted in the right femoral artery and vein and advanced into the abdominal aorta and vena cava. An additional catheter (Tygon Microbore, 0.046" ID x 0.070" OD, Norton) for chronic AII infusion, was inserted into the left external jugular vein and advanced toward the right atrium. The distal ends of the catheters were routed subcutaneously and exteriorized at the mid-scapular region. An analgesic (Nubain, Endo Pharmaceuticals) and antibiotics (Combiotic, Pfizer) were given following surgeries.

Derivation of Complete Stimulus-Response Relations

To obtain stimulus-response curves for the effects of carotid sinus pressure on arterial blood pressure and heart rate, the occluders on the common and external carotid arteries were inflated, which isolated the sinuses from the systemic circulation. The carotid catheters were attached to an external, pressurized reservoir that had been filled with Lactated Ringers, equilibrated with 95% O_2-5% CO_2, and brought to pH 7.4 by addition of $NaHCO_3$. The isolated sinuses were exposed to increments of static pressure (25 mm Hg steps) beginning at 50 and ending with 250 mm Hg or more. Each level of carotid sinus pressure was maintained long enough (40-120 sec) to ensure that a steady-state response of blood pressure and heart rate had developed. Strain gauges (Statham

Intruments, Model P23Db) were used to monitor left and right carotid sinus pressure and systemic arterial blood pressure. These pressures were displayed on an oscillograph (Grass Instruments, Model 7D). Mean blood pressure was derived by electronic damping (0.5 Hz half amplitude point). Heart rate was derived from the phasic blood pressure signal.

For each level of imposed carotid sinus pressure, the steady-state responses of mean blood pressure and heart rate were read from the oscillograph record and plotted as functions of carotid sinus pressure. Smooth curves were fitted to the points. The natural values of blood pressure and heart rate were determined before and after the derivation of each stimulus-response relation, when the carotid sinuses were not isolated. These readings were averaged and plotted as short horizontal lines (control values) intersecting the stimulus-response relationshps. The resulting graphs (Figures 8, 9, and 10) permit the following parameters to be specified: amount by which the carotid baroreflex can increase blood pressure (or heart rate) above control, amount by which the carotid baroreflex can decrease blood pressure (or heart rate) below control, carotid sinus pressure at threshold for a response, and carotid sinus pressure that leads to saturation of the reflex response. Upper limit is the blood pressure or heart rate in response to subthreshold carotid sinus pressure. Likewise, lower limit defines the response to maximum carotid sinus pressure. The difference between the upper and lower limits is the response range. The maximal slope of the blood pressure response curve is taken as a measure of the open loop baroreflex gain. In the case of heart rate responses, the slope of the curve provides a measure of the sensitivity of the cardiac component of the baroreflex.

The adequacy of aortic-denervation was tested with the dogs in a conscious, resting state. Several 100 ug boluses of phenylephrine HCl (Neo Synephrine, Winthrop) were injected intravenously. When the carotid sinuses were in continuity with the circulation, a 100 ug bolus of phenylephrine typically increased arterial blood pressure 25 mm Hg and decreased heart rate at least 40%. When the sinuses were isolated from the circulation and held at a fixed pressure, phenylphrine increased blood pressure more than 25 mmHg but did not evoke a significant bradycardia, therefore indicating that the degree of denervation was adequate.

Induction of Hypertension

Chronic hypertension was induced by continuous infusion of initially subpressor amounts of AII (MuCubbin et al., 1965; Cowley and DeClue, 1976). AII was diluted in 0.9% saline to a concentration of 1.0 ug/ul and infused intravenously at a rate of 5 ng/kg/min, using a calibrated ambulatory infusion pump (Cormed, Model ML-6-4). The pump and the exteriorized catheters were protected by a fitted canvas vest.

Blood pressure was significantly elevated within 4 hours after the start of AII infusion in both aortic-intact and aortic-denervated dogs. A stable, elevated plateau of pressure was evident within 7-10 days in the aortic-intact group and within 1 day in the aortic-denervated group. Experiments on the relative contributions of sympathetic and parasympathetic mechanisms to baroreflex responses were done prior to the start of AII infusion and again after 14-30 days of continuous AII infusion.

Autonomic Blockade

The relative contributions of sympathetic and parasympathetic mechanisms to the carotid baroreflex were determined by comparing

stimulus-response curves for the baroreflex before and after intravenous administration of various autonomic antagonists. For alpha adrenergic blockade the dogs were given prazosin HCL (Pfizer, Inc.) (0.3 mg/kg). The efficacy of alpha blockade was tested at least once in each dog. Before the administration of prazosin, a 100 ug bolus of phenylephrine HCL (Neo Synephrine, Winthrop) would increase mean arterial pressure approximately 25 mm Hg. Thirty to sixty minutes after the administration of prazosin, more than 1000 ug phenylphrine was required to evoke the same pressor response.

For beta adrenergic blockade, D,L-propranolol HCL (Sigma) was given (1 mg/kg). Thirty to sixty minutes after the administration of propranolol, it took at least 10 ug isoproterenol HCL (Isuprel, Breon) to increase heart rate by the same amount as did 1 ug before beta blockade.

For muscarinic cholinergic blockade, atropine sulfate (Lilly) was given (0.1 mg/kg). Twenty minutes were allowed to pass before baroreflex data were taken, by which time the initial, excitatory cardiac effects of atropine had largely subsided (Donald et al., 1967). Prior to atropine administration, a step increase in carotid sinus pressure would elicit profound reflex bradycardia within 1-2 seconds (Stephenson and Donald, 1980). The short latency of this response identifies it as parasympathetic in orgin (Scher and Young, 1970). The efficacy of cholinergic blockade was demonstrated 10, 20 and 40 minutes after administration of atropine by repeating the step increase in carotid sinus pressure and noting the absence of sudden bradycardia.

Statistics

The effects of autonomic blockade were analyzed with Students t-test for paired comparisons. The paired t-test was also used to make comparisons between baroreflex characteristics in the hypertensive and normotensive states. The Wilcoxin Rank-Sum test was used to make comparisons between aortic-intact and aortic-denervated dogs. In all cases, significance was assigned at the .05 level.

RESULTS

The control mean arterial blood pressure in the normotensive, aortic-intact dogs, averaged over all experimental days, was 98 $\pm$ 3 mm Hg. Blood pressure in the aortic-denervated dogs was significantly higher, averaging 109 $\pm$ 2 mm Hg. At the plateau of salt-AII hypertension, blood pressure averaged 134 $\pm$ 1 mm Hg in the aortic-intact group and 140 $\pm$ 1 mm Hg in the aortic-denervated group. The magnitude of the hypertension, expressed as absolute or percent change in blood pressure, was not significantly different for the two groups.

Control heart rate was 84 $\pm$ 8 bpm in the aortic-intact group and 99 $\pm$ 5 bpm in the denervated group, but the difference was not significant. At the plateau of hypertension, heart rate was significantly reduced in both groups, averaging 68 $\pm$ 10 bpm for the aortic-intact dogs and 80 $\pm$ 10 bpm for the denervated dogs. The effect of hypertension on heart rate was not significantly different for the aortic-intact and aortic-denervated groups.

Alpha Adrenergic Blockade

Figure 8 and Tables 5, 6, 7, and 8 allow one to compare the characteristics of the carotid baroreflex of aortic-intact and aortic-denervated dogs, in a normotensive and hypertensive state, and

before and after alpha adrenergic blockade with prazosin. Prior to the administration of prazosin, the baroreflex of normotensive, aortic-intact dogs, could increase blood pressure 19 ± 4 mm Hg above, and decrease it 45 ± 6 mm Hg below, its control level of 102 ± 5 mm Hg. Prazosin did not significantly alter either the control blood pressure or the ability of the reflex to increase blood pressure above its control level. The lower limit of blood pressure was not affected by prazosin. The only significant change produced by prazosin in the aortic-intact dogs was reduction of the maximum gain of the baroreflex. After aortic-intact dogs had been made hypertensive, the administration of prazosin significantly lowered the whole stimulus-response curve. Prazosin decreased control blood 14 ± 4 mm Hg, and the lower limit of blood pressure was reduced similarly. The upper limit was decreased 33 ± 3 mm Hg; however, the ability of the reflex to increase blood pressure was not significantly altered by prazosin.

Prazosin did not alter the heart rate parameters in either the normotensive or hypertensive condition.

The effects of prazosin on carotid baroreflex control of arterial pressure were substantially greater in aortic-denervated dogs (Figure 8, right and Table 7). All baroreflex characteristics except the lower limit of arterial pressure were significantly altered by alpha adrenergic blockade in normotensive, aortic-denervated dogs. Prazosin particularly attenuated the ability of the carotid baroreflex to increase blood pressure above its control level. The total range of blood pressure responses was reduced 63% by prazosin. The effects of prazosin were qualitatively similar in the hypertensive state. When the

dogs were hypertensive (Figure 8 and Table 8), prazosin reduced the baroreflex response range 42%. As in the normotensive case, prazosin particularly reduced the upper limit of blood pressure.

The effects of prazosin on heart rate were similar in the normotensive and hypertensive states.

Beta Adrenergic Blockade

Figure 9 (left) and Table 5 show that propranolol had negligible effects on the baroreflex characteristics of aortic-intact, normotensive dogs. After the same dogs had become hypertensive, propranolol elevated the lower limit of blood pressure 11 $\pm$ 1 mm Hg and the range of blood pressure responses was reduced by 10%.

Propranolol reduced control heart rate 7 $\pm$ 2 bpm in the intact normotensive dogs, but had no other significant effects on the heart rate responses in normotension or hypertension.

Propranolol had much greater effects on the carotid baroreflex characteristics of the aortic-denervated dogs (Figure 2, right and Table 9). Propranolol did not alter control blood pressure but it reduced by 42% the ability of the carotid baroreflex to increase blood pressure above its control level. Similar effects of propranolol were evident after these same dogs were made hypertensive (Figure 9 and Table 8).

Control heart rate was not altered by propranolol, but the ability of the carotid baroreflex to increase heart rate above its control level was significantly reduced in both the normotensive and hypertensive states.

Parasympathetic Blockade

As shown in Figure 10 (left) and Table 5, parasympathetic blockade with atropine had profound effects on the baroreflexes of aortic-intact, normotensive and hypertensive dogs. In the normotensive state, atropine

did not significantly affect control blood pressure. However, atropine abolished the ability of the baroreflex to decrease blood pressure below control and reduced by 77% the amount by which the baroreflex could increase blood pressure above control. Reflex gain was reduced 89%. In the hypertensive dogs, atropine increased control blood pressure 30 ± 6 mm Hg. As in the normotensive state, atropine abolished the ability of the baroreflex to decrease blood pressure below control and substantially reduced the ability of the baroreflex to increase blood pressure above control. Reflex gain was reduced by 85%. Atropine increased the control heart rate and substantially reduced the range of heart rate responses in both normotensive and hypertensive states.

In the aortic-denervated dogs atropine did not alter control blood pressure but depressed by 63% the ability of the reflex to decrease blood pressure below its control level (Figure 10, right and Table 7). The apparent ability of atropine to attenuate increases in blood pressure above control was highly variable and insignificant. In the presence of salt-AII hypertension (Figure 10, right and Table 8), parasympathetic blockade caused control blood pressure to increase 18 ± 6 mm Hg. Atropine nearly abolished the ability of the baroreflex to decrease blood pressure below control.

The effects of atropine on the baroreflex responses of heart rate were qualitatively similar in normotension and hypertension.

Combinations of Blocking Drugs

Tables 5, 6, 7, and 8 illustrate the effects of: 1) sympathetic blockade with propranolol plus prazosin, 2) cardiac blockade with atropine plus propranolol, and 3) total autonomic blockade with atropine, propranolol, and prazosin. The effect of these drugs in combination were similar to the sum of their effects when given singly.

Table 5. Effect of autonomic blockade on carotid baroreflex characteristics of normotensive, aortic-intact dogs. Baroreflex parameters defined in the text. Values in table are mean ± S.E.M. * indicates significant effect of treatment. / indicates that effect of treatment is significantly different in hypertensive and normotensive groups. Prz = prazosin, Prp = propranolol, Atr = atropine.

Treatment		Blood Pressure Parameters				
	n	Control (mm Hg)	Upper Limit (mm Hg)	Lower Limit (mm Hg)	Range (mm Hg)	Gain (max) (dimensionless)
No Drug	5	102±5	121±8	58±2	64±9	.73±.06
Prazosin		92±1	104±4	57±2	46±5	.48±.05 *
No Drug	5	95±2	115±4	56±2	58±3	.67±.06
Propranolol		97±2	116±4	61±1	55±4	.62±.07
No Drug	5	106±3	128±6	64±4	64±9	.73±.05
Atropine		106±5	111±5	103±6 *	8±3 *	.08±.03 *
No Drug	5	99±6	116±10	54±1	67±7	.67±.06
Prz + Prp		89±2	99±3 *	51±4	48±6	.49±.07
No Drug	5	102±5	129±7	59±3	96±5	.80±.07
Prp + Atr		113±7	121±8	111±8 *	11±5 *	.11±.05 *
No Drug	5	95±2	114±3	54±2	61±3	.63±.03
Prz + Prp + Atr		96±5	102±5	97±6 *	5±2 *	.05±.02 *
		Heart Rate Parameters				
		(bpm)	(bpm)	(bpm)	(bpm)	(bpm/mm Hg)
No Drug	5	89±7	89±7	62±7	30±4	.28±.01
Prazosin		84±10	88±12	57±6	31±6	.36±.06
No Drug	5	79±9	80±8	55±5	24±3	.29±.05
Propranolol		72±8 *	76±6	55±7	20±2	.24±.03
No Drug	5	99±8	103±8	69±9	37±5	.38±.06
Atropine		159±13 *	162±13 *	151±11 *	10±3 *	.15±.05 *
No Drug	5	83±9	85±8	54±6	31±3	.32±.04
Prz + Prp		79±7	82±5	51±5	30±3	.37±.06
No Drug	5	93±9	100±9	62±7	38±4	.36±.05
Prp + Atr		140±8 *	143±9 *	134±7 *	10±3 *	.14±.05 *
No Drug	5	79±9	81±8	56±6	26±2	.33±.09
Prz + Prp + Atr		132±13 *	135±14 *	127±14 *	9±4 *	.10±.04 *

Table 6. Effect of autonomic blockade on carotid baroreflex characteristics of hypertensive, aortic-intact dogs. Baroreflex parameters defined in the text. Values in table are mean ± S.E.M. * indicates significant effect of treatment. / indicates that effect of treatment is significantly different in hypertensive and normotensive groups. Prz = prazosin, Prp = propranolol, Atr = atropine.

Blood Pressure Parameters

	n	Control (mm Hg)	Upper Limit (mm Hg)	Lower Limit (mm Hg)	Range (mm Hg)	Gain (dimensionles
No Drug	5	133±2	170±10	95±6	74±11	.63±.10
Prazosin		119±4 *	137±7 *✓	82±6 *✓	54±4	.58±.13
No Drug	5	137±2	182±7	105±6	77±10	.71±.11
Propranolol		144±3	184±8	116±6 *	69±12 *	.53±.10
No Drug	4	128±3	170±12	82±3	87±10	.86±.10
Atropine		158±7 *✓	170±5	160±7 *✓	10±4 *	.13±.08 *
No Drug	5	137±2	176±6	97±6	79±10	.70±.10
Prz + Prp		121±6	138±8 *✓	87±10	50±7 *	.43±.06 *
No Drug	5	131±3	174±9	93±8	81±13	.71±.14
Prp + Atr		171±5 *✓	183±5	171±4 *✓	12±5 *	.10±.06 *
No Drug	5	136±2	178±9	105±7	73±9	.62±.10
Prz + Prp + Atr		145±5	154±3 *	144±5 *	10±4 *	.06±.02 *

Heart Rate Parameters

		(bpm)	(bpm)	(bpm)	(bpm)	(bpm/mm Hg)
No Drug	5	66±11	78±9	56±11	22±4	.20±.03
Prazosin		75±11	84±11	55±10	29±6	.30±.04
No Drug	5	67±9	89±7	55±9	34±2	.32±.04
Propranolol		68±9	89±12	60±10	29±11	.26±.09
No Drug	4	56±8	75±4	44±5	33±3	.30±.01
Atropine		168±10 *	179±12 *✓	164±8 *	14±4 *✓	.15±.07
No Drug	5	65±11	79±9	56±11	23±4	.22±.03
Prz + Prp		70±9	75±7	54±10	21±4	.18±.04
No Drug	5	64±10	82±7	52±9	30±3	.26±.03
Prp + Atr		148±6 *	157±7 *	143±5 *	14±5 ✓	.13±.05
No Drug	5	74±12	93±7	59±9	35±3	.30±.04
Prz + Prp + Atr		146±5 *	150±7 *	137±6 *	13±4 *	.11±.03 *

Table 7. Effect of autonomic blockade on carotid baroreflex characteristics of normotensive, aortic-denervated dogs. Baroreflex parameters defined in the text. Values in table are mean ± S.E.M. * indicates significant effect of treatment. / indicates that effect of treatment is significantly different in hypertensive and normotensive groups. Prz = prazosin, Prp = propranolol, Atr = atropine.

Treatment	n	Control (mm Hg)	Upper Limit (mm Hg)	Lower Limit (mm Hg)	Range (mm Hg)	Gain (max) (dimensionless)
			Blood Pressure Parameters			
No Drug	7	111±4	219±14	47±2	172±15	3.45±.48
Prazosin		90±4 *	106±3 *	42±2	64±3 *	.99±.14 *
No Drug	7	108±3	215±12	49±3	167±10	2.89±.30
Propranolol		109±2	171±10 *	53±3	119±10 *	2.23±.32
No Drug	6	112±3	227±13	52±2	175±12	2.96±.45
Atropine		116±3	196±9	94±3 *	102±11 *	2.18±.41
No Drug	7	111±4	219±13	45±3	174±14	3.42±.59
Prz + Prp		89±4 *	107±5 *	47±5	59±7 *	.96±.22 *
No Drug	7	108±3	213±15	48±3	165±14	2.74±.47
Prp + Atr		116±4	163±6 *	94±4 *	69±7 *	1.40±.30 *
No Drug	7	111±3	220±9	51±3	168±11	3.19±.29
Prz + Prp + Atr		98±7	105±7 *	90±9 *	15±4 *	.16±.05 *
			Heart Rate Parameters			
		(bpm)	(bpm)	(bpm)	(bpm)	(bpm/mm Hg)
No Drug	7	100±6	159±10	54±6	105±14	1.71±.27
Prazosin		101±6	111±5 *	45±7	66±5 *	.98±.18
No Drug	7	98±5	162±10	55±7	107±10	1.44±.19
Propranolol		88±3 *	110±6 *	52±7	58±6 *	1.09±.24
No Drug	6	105±6	169±11	49±3	120±9	1.75±.26
Atropine		165±10 *	194±14 *	134±7 *	60±10 *	.92±.12 *
No Drug	7	100±6	160±10	51±7	109±13	1.69±.28
Prz + Prp		84±4 *	92±3 *	50±5	42±8 *	.67±.17 *
No Drug	7	101±7	156±13	50±6	106±9	1.49±.29
Prp + Atr		131±4 *	139±6 *	120±3 *	19±4 *	.20±.05 *
No Drug	7	100±6	173±9	59±10	114±11	1.76±.11
Prz + Prp + Atr		126±6 *	131±8 *	118±7 *	14±2 *	.14±.04 *

Table 8. Effects of autonomic blockade on carotid baroreflex characteristics of hypertensive, aortic-denervated dogs. Baroreflex parameters defined in the text. Values in table are mean ± S.E.M. * indicates significant effect of treatment. / indicates that effect of treatment is significantly different in hypertensive and normotensive groups. Prz = prazosin, Prp = propranolol, Atr = atropine.

	n	Control (mm Hg)	Upper Limit (mm Hg)	Lower Limit (mm Hg)	Range (mm Hg)	Gain (max) (dimensionle
Blood Pressure Parameters						
No Drug	5	140±5	249±14	60±3	189±17	2.80±.41
Prazosin		113±13 *	157±24 *	46±3 *	109±22 *	1.89±.46
No Drug	5	140±4	251±11	59±3	193±12	2.63±.43
Propranolol		141±3	223±11 *	55±1	168±10 *	2.37±.30
No Drug	6	141±4	261±6	58±2	205±6	3.10±.34
Atropine		159±5 *	247±10	154±7 *✓	93±13 *	1.25±.18 *
No Drug	5	138±6	246±17	58±3	188±17	2.76±.44
Prz + Prp		109±14 *	151±24 *	47±3 *	104±22 *	1.81±.42 *
No Drug	7	140±4	254±9	59±2	197±10	2.89±.36
Prp + Atr		149±4	209±10 *	144±7 *✓	64±9 *	.83±.12 *
No Drug	5	138±6	245±17	57±2	188±16	2.57±.47
Prz + Prp + Atr		134±16	152±19 *	132±17 *	20±3 *	.38±.16 *
Heart Rate Parameters						
		(bpm)	(bpm)	(bpm)	(bpm)	(bpm/mm Hg)
No Drug	5	87±13	190±11	48±15	143±15	2.20±.24
Prazosin		90±15	129±16 *	40±6	89±16 *	1.14±.20 *
No Drug	5	89±12	197±12	44±12	155±7	1.98±.27
Propranolol		84±7	141±7 *	35±5	140±12 *	1.38±.17
No Drug	6	71±3	191±6	33±3	159±7	2.58±.13
Atropine		173±9 *✓	224±7 *	146±5 *✓	79±5 *	1.18±.13 *
No Drug	5	88±14	188±11	48±15	140±17	1.93±.40
Prz + Prp		75±5	98±7 *	33±5	68±8 *	.91±.14 *
No Drug	7	80±9	196±7	41±9	157±6	2.37±.24
Prp + Atr		153±7 *	163±5 *	138±7 *	25±3 *	.28±.03 *✓
No Drug	5	89±12	184±11	45±13	139±20	1.86±.38
Prz + Prp + Atr		142±4 *✓	150±3 *	130±4 *✓	21±3 *	.22±.03 *

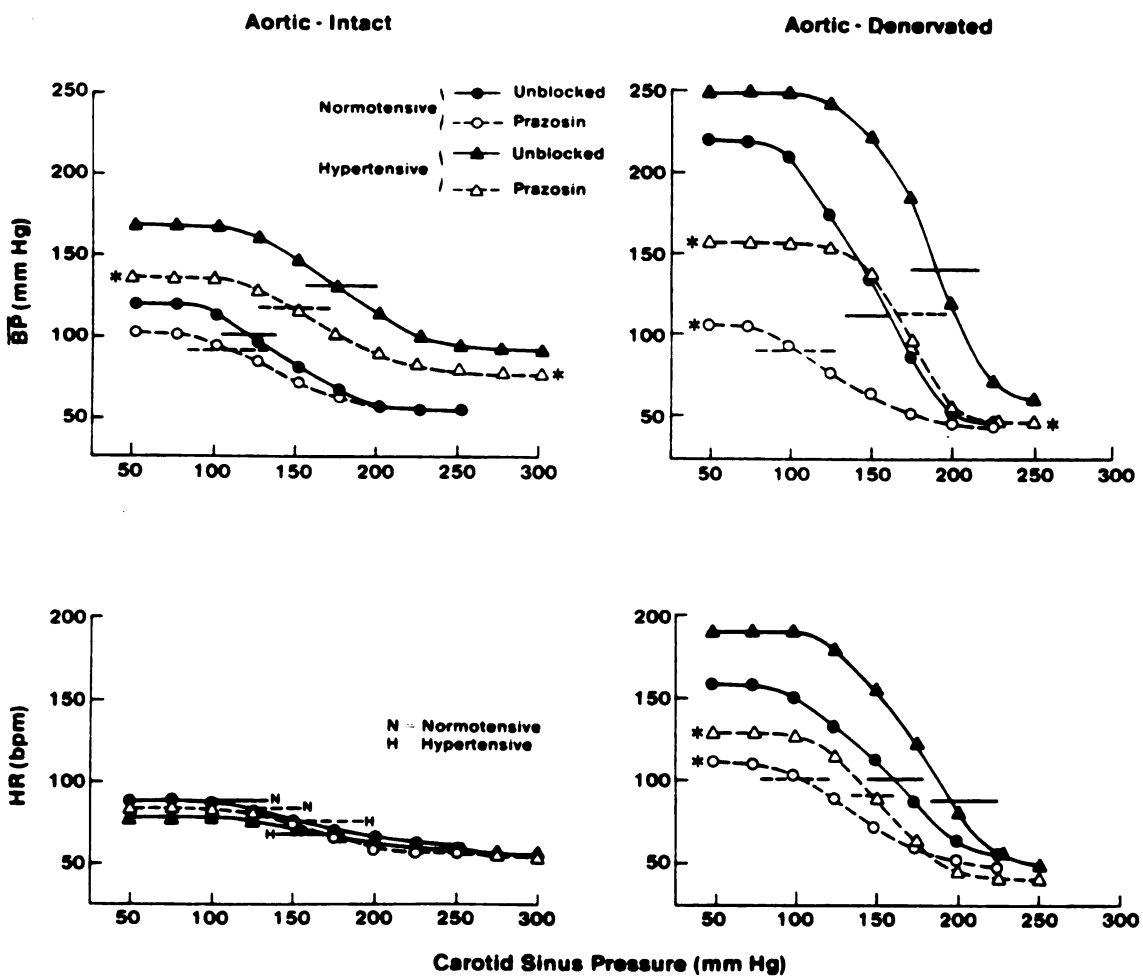

Figure 8. Carotid baroreflex characteristics before and after alpha adrenergic blockade with prazosin. Data from conscious dogs with intact aortic baroreceptors (left) and denervated aortic baroreceptors (right). The effects of prazosin were compared before (normotensive) and after (hypertensive) 11-30 days of continuous AII infusion. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated. Asterisks indicate significant effects of prazosin on the left or right endpoints of the curves.

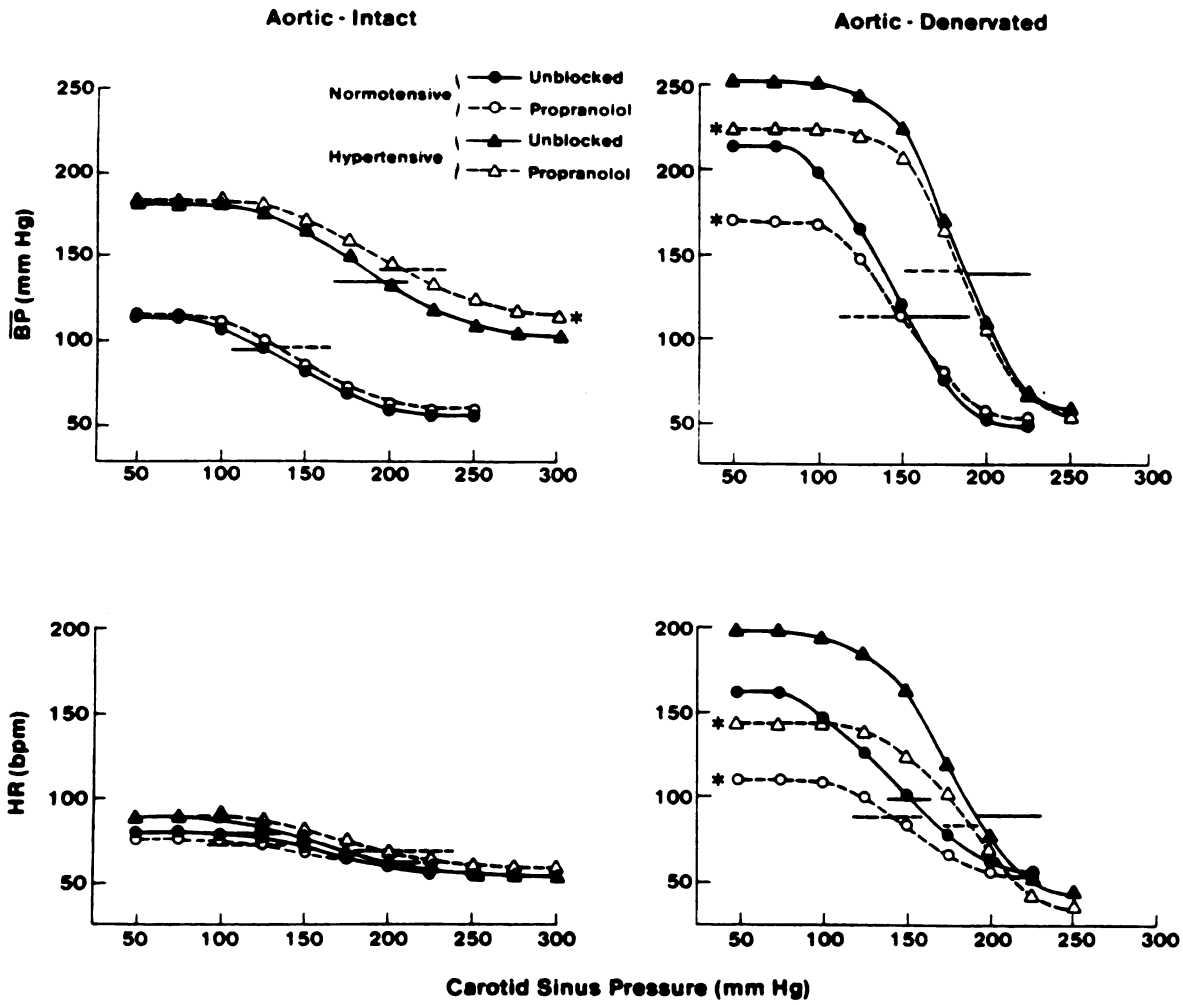

Figure 9. Carotid baroreflex characteristics before and after beta adrenergic blockade with propranolol. Data from conscious dogs with intact aortic baroreceptors (left) and denervated aortic baroreceptors (right). The effects of propranolol were compared before (normotensive) and after (hypertensive) 11-30 days of continuous AII infusion. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isoloated. Asterisks indicate significant effects of propranolol on the left or right endpoints of the curves.

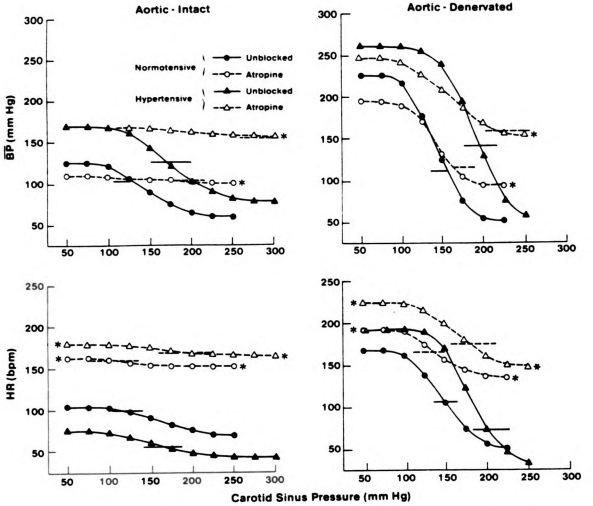

Figure 10. Carotid baroreflex characteristics before and after parasympathetic blockade with atropine. Data form conscious dogs with intact aortic baroreceptors (left) and denervated aortic baroreceptors (right). The effects of atropine were compared before (normotensive) and after (hypertensive) 11-30 days of continuous AII infusion. The short horizontal lines denote the control levels of blood pressure and heart rate when the carotid sinuses were not isolated. Asterisks indicate significant effects of atropine of the left and right endpoints of the curves.

DISCUSSION

The present study provides new information in that: 1) the relative contributions of the sympathetic and parasympathetic nervous systems to baroreflex changes in blood pressure and heart rate were determined in the same conscious animals before and after the establishment of chronic salt-AII hypertension, and 2) these experiments were performed both with and without the buffering influence of the aortic depressor afferents.

The experimental results demonstrate that the contributions of the sympathetic and parasympathetic nervous systems to baroreflex responses are very similar in normotension and in salt-AII hypertension. Specifically, parasympathetic activation is the predominant mechanism by which the baroreflex decreases blood pressure and heart rate in both normotensive and hypertensive states, and in both aortic-intact and aortic-denervated dogs. Second, in aortic-intact normotensive and hypertensive dogs, reflex increases in blood pressure appear to be brought about by a mixture of alpha adrenergic activation and parasympathetic withdrawal. Beta adrenergic mechanisms play a negligible role in baroreflex responses of aortic-intact normotensive and hypertensive dogs. In aortic-denervated normotensive and hypertensive dogs, alpha and beta adrenergic mechanisms both contribute to reflex-induced increases in blood pressure and heart rate. The only qualitative difference observed between normotensive and hypertensive states in regard to sympathetic-parasympathetic balance was that hypertension was associated with a degree of alpha adrenergic activity that was inaccessible to inhibition by the baroreflex.

Parasympathetic Mechanisms: It is generally agreed that reflex bradycardia in conscious dogs is primarily parasympathetic in origin (Scher and Young, 1970; Thames et al., 1981; Vatner et al., 1971; Vatner

et al., 1970). Our results confirm this view and additionally demonstrate that parasympathetic activation is the primary means by which the carotid baroreflex decreases both heart rate and blood pressure in normotensive and hypertensive states, and in both aortic-intact and aortic-denervated dogs. Cholinergic-muscarinic blockade with atropine eliminated the ability of the baroreflex to decrease blood pressure below control in both normotensive and hypertensive aortic-intact dogs (Figure 10 and Tables 5 and 6). In aortic-denervated dogs, atropine attenuated by 94% the ability of the carotid baroreflex to decrease blood pressure below control. The effects of cholinergic muscarinic blockade were not as dramatic in the normotensive aortic-denervated dogs, where atropine limited the ability of the carotid baroreflex to decrease blood pressure below control by 63%. However, alpha and beta adrenergic blockade, singly or in combination, failed to attenuate the ability of the carotid baroreflex to decrease blood pressure below control (Figures 8 and 9, Tables 7 and 8). Furthermore, blockade with atropine and propranolol elicited the same 63% limitation as atropine alone, suggesting that our cholinergic muscarinic blockade may have been incomplete. Therefore, we conclude that, parasympathetic responsiveness to baroreflex stimulation is preserved in chronic salt-AII hypertension.

The ability of the baroreflex to decrease heart rate and blood pressure has not previously been studied in chronic salt-AII hypertension. However, experiments on anesthetized dogs (Scroop and Lowe, 1969; Lumbers et al., 1979) and conscious sheep (Ismay et al., 1979) had previously indicated that acutely administered AII attenuates the parasympathetically mediated bradycardia in response to acute elevations in arterial pressure. Also, reflexive bradycardia in

response to baroreceptor stimulation is known to be impaired in experimental renal hypertension and in human essential hypertension (Bristow et al., 1969; Gribben et al., 1971; West and Korner, 1974; Korner et al., 1974; Takeshita et al., 1975; Thames et al., 1981). Therefore, it was plausible to expect that parasympathetic compensatory responses would be impaired in chronic salt-AII hypertension. However, our results demonstrate not only that parasympathetic responsiveness is preserved in chronic salt-AII hypertension, but that elevated parasympathetic tone may actually limit the degree of hypertension. Specifically, we found that atropine administration did not significantly alter control blood pressure in aortic-intact, normotensive dogs but significantly elevated control blood pressure in the hypertensive state. For the aortic-denervated dogs, the effect of atropine on control blood pressure was not significantly different for the normotensive and hypertensive states. Since intact aortic baroreceptors function primarily in an anti-hypertensive role (Pelletier et al., 1972), it is likely that they oppose chronic hypertension, to some extent, by stimulating parasympathetic activity. The absence of this parasympathetic restraint in aortic-denervated dogs could account for the observation that parasympathetic tone significantly limits the degree of hypertension only in aortic-intact dogs.

Sympathetic Mechanisms: Whereas reflex bradycardia in conscious dogs is generally acknowledged to be parasympathetic in origin, there is disagreement as to whether reflex tachycardia results from withdrawal of parasympathetic tone (Kirchheim and Gross, 1971; Thames et al., 1981) or from simultaneous parasympathetic withdrawal and sympathetic activation (Scher and Young, 1970; Vatner et al., 1974). Kirchheim and Gross (1971) showed that the magnitude of the pressor response to bilateral

carotid occlusion in concious dogs with intact aortic baroreceptors was unaffected by administration of propranolol and phentolamine. Likewise, our results with aortic-intact dogs show that the tachycardia and increase in blood pressure in response to unloading of baroreceptors are not strongly dependent on sympathetic activation. The administration of propranolol did not reduce the amount by which the baroreflex could increase heart rate or blood pressure above their usual normotensive or hypertensive control levels. Curiously, in the hypertensive state, propranolol elevated the lower limit of the blood pressure response curve. The reason for this unexpected response is not known to us. We conclude that cardiac sympathetic tone is minimal in normotensive and hypertensive aortic-intact dogs and that increases in cardiac sympathetic activity do not contribute importantly to reflexive increases in heart rate or blood pressure.

The administration of prazosin, by itself, or in combination with propranolol, shifted the whole baroreflex stimulus-response curve downward in hypertensive, aortic-intact dogs. However, neither treatment significantly reduced the ability of the baroreflex to increase blood pressure above control. We conclude that reflex increases in blood pressure in aortic-intact normotensive and hypertensive dogs are most likely to be brought about by a mixture of parasympathetic withdrawal and vascular sympathetic activation.

The pressor response to reduced carotid sinus pressure was much larger in aortic-denervated dogs, because the increase in blood pressure was not buffered by the aortic baroreflex (Walgenbach and Donald, 1983). We found that baroreflex-mediated increases in heart rate and blood pressure are more clearly dependent on adrenergic mechanisms in aortic-denervated than in aortic-intact dogs (Figure 8). In the

aortic-denervated dogs, beta adrenergic blockade significantly limited the ability of the carotid baroreflex to increase heart rate above control. Alpha and beta adrenergic blockade, separately or together, significantly reduced the amount by which the baroreflex could increase blood pressure above control. Therefore, we conclude that cardiac and vascular sympathetic mechanisms both make substantial contributions to reflex increases in blood pressure in aortic-denervated, normotensive and hypertensive dogs. However, our data do not support the hypothesis that the sympathetic component of the baroreflex is enhanced in chronic salt-AII hypertension.

In hypertensive, aortic-intact and aortic-denervated dogs, prazosin shifted the whole blood pressure response curve downward, so that both ends of the response curve were significantly depressed. The downward shift following prazosin is indicative of a degree of alpha adrenergic tone which is independent of the baroreflex (Korner, 1975). That is, a significant level of alpha tone existed, regardless of the level of carotid sinus pressure. Even maximal stimulation of the cartoid baroreceptors could not completely inhibit alpha adrenergic activity. Electrophysiological studies have shown that some descending sympatho-excitatory pathways are not susceptable to inhibition by the baroreceptors (Gebber et al., 1973; Judy and Farrel, 1979). Salt-AII hypertension may act centrally to enhance or unmask the activity of these fibers. Baroreflex-inaccessible sympathetic tone was not found in dogs with chronic renal hypertension (one-kidney, one-wrapped) (Stephenson and Tagett, 1983). Thus, sympathetic activity in baroreflex-inaccessible pathways does not occur in all forms of experimental hypertension.

In aortic-intact dogs, the combination of prazosin plus maximal stimulation of the cartoid baroreceptors did not reduce blood pressure as low in the hypertensive state as in the same dogs before the induction of hypertension. Therefore, salt-AII hypertension in aortic-intact dogs involves both a degree of baroreflex-inaccessible alpha tone and also another, non-adrenergic, pressor influence that is independent of the carotid baroreceptor reflex. The nature of this additional pressor influence is not known to us. The additional pressor influence was not evident in the aortic-denervated dogs, as indicated by the observation that the combination of prazosin plus maximal stimulation of the carotid baroreceptors lowered blood pressure in the aortic-denervated dogs to equivalent levels in the normotensive and hypertensive states.

It has previously been shown that the control level of blood pressure is significantly elevated in aortic-denervated dogs (Ito and Scher, 1979), which we also observed. Our data also indicate that control blood pressure is more dependent on alpha adrenergic mechanisms in aortic-denervated than aortic-intact dogs. Specifically, prazosin caused approximately twice the reduction in control blood pressure in the normotensive aortic-denervated dogs as in aortic-intact dogs (Figure 8). The effects of prazosin in the hypertensive groups were similar. Fink et al. (1980) also demonstrated a neurogenic elevation of blood pressure in rats following selective aortic baroreceptor deafferentation, which could be reversed by alpha adrenergic blockade with phentolamine.

Curiously, prazosin reduced the ability of the baroreflex to increase heart rate in the normotensive, aortic-denervated dogs. Prazosin had similar effects on the heart rate response of these dogs

after they became hypertensive. An alpha-1 blocking agent might not be expected to influence reflex heart rate responses. However recent studies have indicated that various alpha-1 adrenergic antagonists, prazosin included, act centrally to depress reflex increases in cardiac sympathetic activity (McCall and Humphrey, 1981). Such an effect could account for our result. Nevertheless, our data indicate that alpha adrenergic mechanisms contribute significantly to reflex increases in blood pressure in aortic-denervated dogs, independently of any interaction with heart rate responses. The depression of heart rate responses produced by prazosin was very similar to the 85% decrease in the ability of the baroreflex to increase heart rate brought about by cardiac blockade with propranolol plus atropine (the lack of complete blockade probably resulting from incomplete cholinergic muscarinic blockade). Nevertheless, after cardiac blockade, the carotid baroreflex could still increase blood pressure 45 mmHg above control, indicating that vascular sympathetic mechanisms play a major role in reflex-induced increases in blood pressure above control.

We conclude that, in conscious, resting dogs, the overall contributions of the sympathetic and parasympathetic nervous system to the baroreflex are the same in normotension and salt-AII hypertension. Specifically, alpha and beta adrenergic activation contribute to baroreflex mediated increases in blood pressure in the absence of aortic baroreceptor buffering influences. Furthermore, parasympathetic activation is necessary and entirely sufficient to account for the ability of the baroreflex to decrease blood pressure below control. Lastly, there exists a pressor influence which is inaccessible to

baroreflex inhibition in salt-AII hypertension. This pressor influence consists, to a degree, of alpha adrenergic activity which is independent of baroreflex modulation.

DISCUSSION

A formal discussion of the data has already been presented. Therefore, the last division of this dissertation will contain a broader and more chronological description of the studies that I was involved with during my graduate program.

Sympathetic/Parasympathetic Balance in Baroreflex of Normotensive Dogs

Initially, we studied the relative importance of sympathetic and parasympathetic mechanisms in mediating the baroreceptor reflex. Previously, some investigators had asserted that the control of heart rate by the baroreflex in anesthetized dogs involves reciprocal changes in sympathetic and parasympathetic tone (Thames and Kontos, 1970). Other investigators had found that the baroreflex elicits tachycardia primarily through sympathetic activation and bradycardia through parasympasthetic activation (Glick and Braunwald, 1965). Still others had concluded that reflex bradycardia results primarily from sympathetic inhibition (Berkowitz et al., 1969). Variations in anesthetics and surgical stress may have contributed to the discrepancies among these studies (Scher and Young, 1970; Vatner et al., 1971). Nevertheless, inconsistancies are also apparent among studies of baroreflex properties in conscious dogs. It is generally agreed that reflex bradycardia in conscious dogs is primarily parasympathetic in origin (Scher and Young, 1970; Thames et al., 1981; Vatner et al., 1970; Vatner et al., 1971).

However, there is disagreement as to whether reflex tachycardia results from withdrawal of parasympathetic tone (Kirchheim and Gross, 1971; Thames et al., 1981) or from simultaneous parasympathetic withdrawal and sympathetic activation (Scher and Young, 1970; Vatner et al., 1974). In addition there is disagreement regarding the role of vascular sympathetic mechanisms in baroreflex responses of conscious dogs. Kirchheim and Gross (1971) studied the hemodynamic respones to bilateral carotid occlusion and concluded that increases in total peripheral resistance occurred secondarily to parasympathetically mediated increases in cardiac output. Other investigators have attributed the entire carotid occlusion response to an increase in total peripheral resistance (Corcondilas et al., 1964). There is also a lack of concensus regarding sympathetic-parasympathetic balance in the baroreflex responses of human subjects (Mancia et al., 1977; Pickering et al., 1972; Robinson et al., 1966; Wallin and Eckberg, 1982).

We prepared dogs surgically for subsequent, reversible isolation of the carotid sinuses. We derived complete stimulus-response relations for the effects of carotid sinus pressure on blood pressure and heart rate in conscious, quietly resting dogs before and after administration of various autonomic antagonist drugs. The data from these experiments support two major conclusions. First, the ability of the baroreflex to decrease blood pressure below its prevailing level is entirely dependent on parasympathetic mechanisms. Second, vascular, but not cardiac, sympathetic mechanisms contribute to reflex increases in blood pressure. However, the aortic baroreceptors were intact in this study, and their buffering action limited the ability of the baroreflex to increase blood pressure above control. In resting dogs with their aortic baroreceptors

denervated, the upper limit of blood pressure approaches 200 mm Hg (Walgenbach and Donald, 1983). It is very likely that sympathetic activation plays a major role in generating such high levels of pressure. Thus, the results of our study were expressed as applying specifically to the conscious, quiescent, normotensive dog with intact aortic baroreceptor afferent nerves.

Baroreflex Characteristics in Renal Hypertension

We next turned our attention to the changes in the baroreflex that accompany the hypertensive state. As already stated in the Literature Review section, several elements of the baroreflex arc become abnormal in hypertension. The baroreceptors, themselves, adapt or reset to the elevated levels of prevailing pressure (McCubbin et al., 1956; Krieger, 1970). In addition, the sensitivity with which baroreceptors respond to changes in blood pressure may be reduced (Angell-James, 1973; Sleight et al., 1977; Koushanpour and Kenfield, 1981). Some forms of hypertension involve an increased vascular responsiveness to adrenergic stimuli, which could potentially offset a decreased sensitivity of the baroreceptors (Collis and Vanhoutte, 1977; Lais and Brody, 1978). Hypertension is also accompanied by complex changes within central and peripheral autonomic pathways (Fink and Brody, 1980; Webb et al., 1983; Fink and Bryan, 1982; Judy and Farrell, 1979).

Studies on baroreflex control of heart rate have led to the prevailing view that the baroreflex in hypertensive human beings both is reset to a higher level and has a diminished gain. This view is primarily based on the findings that (a) heart rate in hypertension is

near normal despite an elevated blood pressure (indicative of "resetting") and (b) artificial elevations of blood pressure cause less cardiac slowing in hypertension than normotensive subjects (thus diminished "gain") (Bristow et al., 1969; Gribbin et al., 1971; West and Korner, 1974; Korner et al., 1974; Takeshita et al., 1975; Thames et al., 1981). However, heart rate is only one of the determinants of blood pressure. Therefore, it may be invalid to assume that baroreflex regulation of blood pressure is impaired in hypertension simply because the ability of the baroreflex to control heart rate is impaired.

Moment to moment fluctuations in blood pressure are generally no greater in hypertensive than normotensive individuals, which implies that the ability of the baroreflex to stabilize blood pressure is not diminished in hypertension (Julius and Schork, 1971). Studies in which blood pressure rather than heart rate has been the primary dependent variable have indicated that the baroreflex gain is not diminished in hypertension (Rocchini and Barger, 1979; Mancia et al., 1978; Mancia et al., 1982). The basic question of how hypertension affects the ability of the baroreflex to regulate blood pressure has remained unanswered due to limitations in experimental techniques for study of the baroreflex in conscious subjects. Many of these experimental difficulties can be overcome in anesthetized animals. However, the use of anesthetics greatly complicates interpretation of experimental results, since both anesthesia and hypertension alter autonomic mechanisms of interest (Korner, 1975; Stephenson and Donald, 1980).

We therefore compared the stimulus-response relations for the effects of carotid sinus pressure on blood pressure and heart rate in conscious, normotensive dogs and dogs with 1-kidney, 1-wrapped Page

hypertension. In addition, the sensitivity of the cardiac component of the baroreflex was assessed by measuring the changes in heart interval resulting from acute elevations and depressions of blood pressure with phenylephrine and nitroglycerine respectively.

The data from our study corroborate the observations of others by showing smaller changes in heart interval in response to infusions of phenylephrine and nitroglycerine in renal hypertension than in normotension. However, when vasoactive drugs are used to measure baroreflex gain, blood pressure cannot be manipulated over a sufficient range to define the entire, sigmoidal relation between blood pressure and heart interval (or heart rate). When only a limited portion of the stimulus-response curve is available, the distinction between "resetting" and "altered gain" becomes ambiguous. We overcame this ambiguity by varying pressure in the isolated carotid sinuses of the same normotensive and hypertensive dogs and plotting complete stimulus-response curves for the effects of carotid sinus pressure on heart rate. We found that the heart rate responses occur over a broadened and elevated range of carotid sinus pressure, and that the sensitivity is unambiguously reduced in renal hypertension.

The data demonstrated that the stimulus-response relation for the effect of carotid sinus pressure on blood pressure is shifted upward, to the right, and has a diminished slope. The baroreflex in hypertensive dogs can increase and decrease blood pressure relative to the prevailing pressure level by amounts that are not significantly different than in the normotensive dogs. That is, the baroreflex retains its ability to buffer both acute increases and decreases in blood pressure. However, a broadened and elevated range of carotid sinus pressure is required to

drive the baroreflex of hypertensive dogs to its full response capability. Therefore, the overall effectiveness (gain) with which the baroreflex regulates blood pressure is diminished.

We concluded that the baroreflex is reset and has a diminished gain in dogs with chronic renal hypertension. Our results therefore confirmed the contentions of previous authors, which had been based on the study of a limited portion of the response range of the heart rate component of the baroreflex. In spite of the limitations of these previous studies, it appears that they led to an accurate prediction regarding the overall ability of the baroreflex to regulate blood pressure in chronic renal hypertension.

Our study elucidated one particular baroreflex aberation that the earlier methods could not predict. We were able to demonstrate that chronic renal hypertension involves a pressor effect that cannot be overcome even by maximal stimulation of the carotid baroreceptors. Such a baroreflex-independent pressor effect can be mimicked by the acute administration of norepinephrine in normotensive dogs. However, norepinephrine does not cause a resetting of the baroreflex toward an elevated range of carotid sinus pressure nor is reflex gain reduced. These latter changes are prominent in chronic renal hypertension, and they must be dependent on either the chronicity or the particular mechanism of renal hypertension.

Sympathetic/Parasympatheric Balance in the Baroreflex of Renal Hypertensive Dogs

The relative contributions of sympathetic and parasympathetic mechanisms to baroreceptor reflex responses may be different in normotension and hypertension. Several lines of evidence indicate that sympathetic tone is elevated and that sympathetic responses are exaggerated in various forms of hypertension (Abboud, 1982; Tarazi and Dustan, 1973; Bellini et al., 1979; Brody et al., 1980). The existence of elevated sympathetic tone in renal hypertension would not, by itself, assure enhanced baroreflex control of sympathetic responses, because some descending sympatho-excitatory pathways are not susceptible to inhibition by baroreceptors (Gebber et al., 1973; Judy and Farrell, 1979). If the activity in these baroreflex-independent pathways were enhanced in renal hypertension, then substantial sympathetic tone might persist despite maximal stimulation of baroreceptors. However, recent studies have indicated that the ability of the baroreflex to modulate vascular sympathetic responses is normal or enhanced in renal hypertensive rabbits (Abboud, 1982; Angell-James and George, 1980). By contrast, it seems clear that parasympathetically mediated responses of heart rate to baroreceptor stimulation are blunted in renal hypertension (Thames et al., 1981; Hollenberg et al., 1981; Aylward et al., 1983). The effects of renal hypertension on sympathetically mediated control of heart rate and cardiac contractility are less clear (Thames et al., 1981; Aylward et al., 1983). More data was needed to settle these issues. We hypothesized that: (a) control of blood pressure by the baroreflex would be relatively more dependent on sympathetic mechanisms in the renal hypertensive state than in the normotensive state, and (b)

sympathetic activity in renal hypertensive subjects would be completey inhibited by stimulation of the baroreceptors.

We were able to conclude that, in conscious, resting dogs with established 1-kidney, 1-wrapped Page hypertension, alpha adrenergic mechanisms help support blood pressure and contribute to reflex increases in blood pressure. However, baroreceptor activation can completely inhibit alpha adrenergic effects, so renal hypertension is not accompanied by a baroreflex-independent increase in alpha sympathetic tone. Cardiac sympathetic tone provides negligible support to blood pressure and does not participate in reflex changes in blood pressure. Parasympathetic mechanisms, directed at the heart, are predominant in reflex control of blood pressure. Specifically, parasympathetic activation is necessary and entirely sufficient to account for the ability of the baroreflex to decrease blood pressure below control. Overall, we found that the roles of sympathetic and parasympathetic mechanisms in mediating baroreflex responses were very similar in normtensive dogs and renal hypertensive dogs.

Baroreflex Characteristics in Salt-AII Hypertension

Technical limitations in our study on renal hypertension had prevented us from determining the exact time course of each change in overall baroreflex function. Also, additional studies were required to determine whether or not other models of hypertension are associated with similar changes in the baroreflex. Furthermore, our study had not addressed the possible influences of intact aortic baroreceptors on the changes in carotid baroreflex properties that were evident during renal hypertension.

Our studies on salt-AII hypertension have made it clear that decreased baroreflex gain is not a universal accompaniment of chronic experimental hypertension. However, renal and salt-AII hypertension do share the following features: 1) The baroreflex is reset to operate over a broadened and elevated range of carotid sinus presssure and 2) the pressor influences are independent of the baroreflex; that is, the baroreflex continues to regulate blood pressure,but at an elevated level.

Our experiments with the acute administration of AII, demonstrated that resetting of the baroreflex can occur very quickly. The great similarity between the effects of acute and chronic angiotensin infusion on the baroreflex provides credibility to the hypothesis that the changes which occur in the baroreflex with elevated arterial pressure are pressure-dependent not time-dependent.

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