Peripheral Neurogenic Factors in Acute and Chronic Alterations of Arterial Pressure

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FOR MANY years it has been well appreciated that the control of systemic arterial blood pressure is exerted at central as well as peripheral neural sites. Much attention has been directed recently at the central component of arterial blood pressure regulation, and numerous reviews have been devoted to this subject (see Brody et al., 1980; Chalmers, 1975; Hilton and Spyer, 1980; Paikovits and Zaborszky, 1977). Less emphasis has been placed on peripheral neurogenic influences on vascular tone relating to blood pressure regulation. One of the difficulties encountered when evaluating relative importance of peripheral or central factors is the imprecise methodology for studying them independently. Implicating a change in peripheral neurogenic function due to some intervention is often confounded by central influences. An example of this is provided if a representative change in sympathetic neural function is examined. A decrease in norepinephrine content in cardiac tissue due to DOCA-salt treatment was originally attributed to a defect in the storage capacity of the nerve vesicles of peripheral adrenergic nerves (Krakoff et al., 1967). However, further experimentation revealed that the decreased content was due to increased turnover of norepinephrine brought about by an increased central sympathetic outflow (De Champlain et al., 1969; Haeusler et al., 1972; Van Ameringen et al., 1977; Giachetti et al., 1979). This central mechanism is the explanation currently given for the observation of depressed adrenergic storage in DOCA-salt hypertension, rather than that of peripheral nerve impairment (Giachetti et al., 1979). Methods to study drug actions on central neurogenic function also present some difficulties. A common means to delineate the effects of agonists or antagonists upon central vasomotor function is to infuse the agents into the ventricular system, either intracerebroventriculally or intracisternally. Because of the relatively small volumes into which such infusions are made, unphysiologically high concentrations of these agents are often reached, and therefore conclusions drawn from these experiments must be made cautiously. Access to the central vasomotor areas via the vertebral and carotid arteries is also utilized. However, drugs, even if given in low doses, recirculate into the systemic vascular beds and may exert direct effects. Control experiments must be included to establish a definite central effect. A useful means of monitoring the central sympathetic discharge is by recording preganglionic sympathetic nerve activity (Bronk et al., 1936). This technique is used routinely in acute experiments but is applied less often to conscious animals. More precise methods are needed to quantify the relative participation of central and peripheral factors on vascular neurogenic function under more physiological conditions, e.g., in awake animals.

Peripheral neural function is capable of being altered, independent of what occurs centrally, and may intensify or suppress the influence of the impulses received from the central vasomotor centers. Also, peripheral modulation of centrally induced changes may be the limiting and, possibly, the dominant, factor in the control of blood pressure. As an example, consider the interaction between central vasomotor activity and modulation of that activity at the adrenergic nerve terminal by \( \alpha_2 \)-adrenoceptor-mediated negative feedback. In this case, even though central sympathetic outflow may be augmented, the actual adrenergic transmitter release from the nerve terminals may not be increased proportionately, if greater negative feedback via prejunctional \( \alpha_2 \)-adrenoceptors were imposed. Such a mechanism may come into play to cancel out the effect of increased sympathetic outflow on the vas-
culature. However, this example is highly speculative and, to my knowledge, there is no experimental evidence supporting such a mechanism.

The peripheral sites responsible for blood pressure control are the sympathetic ganglionic synapses, the postganglionic sympathetic nerve terminals, and the vascular smooth muscle itself. The focus of this Brief Review is upon the adrenergic nerve terminals and peripheral events which occur when sympathetic function is altered in various hypertensive states.

Experimental Models of Hypertension

Animals with hypertension induced either acutely or chronically by various renal interventions, DOCA–salt treatment, or genetic inbreeding exhibit evidence of increased sympathetic vascular tone. However, it is also known that other mechanisms play a role in these various types of experimental hypertension. A brief consideration follows of some commonly employed models of experimental hypertension pertinent to this review. For the sake of the present discussion, I will consider only the sympathetic and renin-angiotensin system participations in these models of hypertension.

Two-Kidney One-Clip Goldblatt Hypertension

Application of a Goldblatt clip to a single renal artery produces a lasting hypertension in the rat (Leenen et al., 1973; Gavras et al., 1975; Davis, 1977), and a rise in blood pressure of shorter duration in the dog, unless a very marked initial constriction is imposed (Zimmerman et al., 1969; Lupu et al., 1972) or a two-step technique is utilized (Masaki et al., 1977). The first phase of this form of Goldblatt hypertension is characterized by elevated plasma renin and angiotensin II levels (Leenen et al., 1973; Bianchi et al., 1970a; Caravaggi et al., 1976), and angiotensin II is believed to account for the increased blood pressure by causing vasoconstriction. The acute administration of angiotensin antagonists (Pals et al., 1971; Masaki et al., 1977), angiotensin-converting enzyme inhibitors (Krieger et al., 1971; Zimmerman et al., 1980a), and angiotensin II antibody (Bing and Poulsen, 1970) lowers blood pressure during this initial phase of the hypertension. There are indications, too, of sympathetic involvement in the early and later phases of two-kidney one-clip Goldblatt hypertension. Interaction(s) between angiotensin II and the sympathetic nervous system also exist (Zimmerman, 1978). As far as sympathetic involvement is concerned, much evidence is available, but for the sake of brevity I will cite only a few examples. Elevated sympathetic tone has been demonstrated in pithing experiments (Dock, 1940), through the use of agents which obtund adrenergic function (Zimmerman et al., 1980b; Gavras and Liang, 1980) and by measurements of peripheral as well as central adrenergic transmitter (Zimmerman et al., 1969; Wijnen et al., 1980). Although the suggestion has been made that sympathetically mediated vascular tone may come into play more during the later than earlier phase of two-kidney one-clip Goldblatt hypertension (McCubbin and Page, 1963), other work indicates immediate sympathetic participation (Gavras et al., 1980; Faber and Brody, 1982), as well as involvement several days to 2 weeks after constriction of the renal artery (Wijnen et al., 1980; Zimmerman et al., 1980b). It is known, however, that renin and angiotensin II levels are normal during the chronic phase of the hypertension (Bianchi et al., 1970), and agents that block the renin-angiotensin system are less effective in lowering blood pressure at this time (Brunner et al., 1971; Gavras et al., 1975; Masaki et al., 1977).

One-Kidney One-Clip Goldblatt Hypertension

There are similarities between one-kidney one-clip and two-kidney one-clip Goldblatt hypertension, in that plasma renin activity is initially increased and, later, is decreased in both of these types of hypertension. The initial increase in plasma renin activity seems to contribute to the blood pressure rise in the dog (Bianchi et al., 1970b), but perhaps not in the rat, and this form of renovascular hypertension can develop fully even in the presence of sustained converting enzyme inhibition with captopril (Watkins et al., 1978; Freeman et al., 1979). Augmented sympathetic tone also probably contributes to the pathogenesis of one-kidney one-clip Goldblatt hypertension (Haeusler et al., 1972; Dargie et al., 1975), but other influences on blood pressure are also evident (Davis, 1977; Bianchi et al., 1970b). As in two-kidney one-clip Goldblatt hypertension, much evidence points to sympathetic involvement in the one-kidney model, and the emphasis has been on the central sympathetic component (Haeusler et al., 1972; Dargie et al., 1975).

Other Forms of Experimental Renovascular Hypertension

A role of the renin-angiotensin system in Grollman (figure-of-eight ligature) and perinephric (cel-lophane wrap) hypertension is less definite (Campbell et al., 1973, 1980); however, renin release may occur (Lewis and Lee, 1971) due to renal cortical compression, and contribute to an elevated blood pressure. Failure to detect an increase in plasma renin activity in all cases probably relates to a lower renal secretion rate. Although other factors may contribute to or totally account for this type of hypertension, a sympathetic component has not been convincingly demonstrated (Angus et al., 1975; Overbeck et al., 1971). Aortic constriction above or between the renal arteries also results in hypertension in the rabbit and rat, respectively (Fuji et al., 1969; Carretero et al., 1971), and renin release is an accompanying phenomenon (Carretero et al., 1971; Laffan et al., 1977). There is also evidence for an adrenergic component in the rabbit with aortic constriction (Bevan et al., 1975).
Spontaneously Hypertensive Rat (SHR)

Much work has been done to delineate the possible contribution of the renin-angiotensin system and sympathetic nervous system in the pathogenesis of the blood pressure increase in the SHR. Generally speaking, there does not appear to be a clear-cut involvement of the renin-angiotensin system in SHR; however, suggestions of enhanced activity of this system, at least during certain stages of the development of SHR, have appeared (Sinaiko and Mirkin, 1981). In established SHR, however, the elevated blood pressure is not attributable to an activated renin-angiotensin system.

A more likely contributing factor to the elevated pressure in the SHR is an increase in sympathetic vascular tone. Many investigations have dealt with various sympathetic mechanisms which may influence blood pressure in this hypertensive model. Numerous studies stemming from those of Folkow et al. (1970) have provided evidence for increased vascular reactivity in pump-perfused vascular beds and, also, in isolated vessels of SHR, while others have implicated increased central sympathetic outflow (Okamoto et al., 1967; Judy et al., 1976; Judy and Farrell, 1979) to account for the increased blood pressure in SHR. Neurogenic vascular tone, however, was not found to be increased in 8-week-old or 3-month-old SHR, compared with WKY (Wistar-Kyoto), when a conscious instrumented rat preparation was studied (Touw et al., 1980). In fact, in this preparation, vascular reactivity was not increased in the renal, and hindquarter vascular beds, but only in the mesenteric bed. Furthermore, lumbar sympathetic nerve activity did not differ between SHR and Wistar control rats when monitored in these rats at 6–7 months of age (Laiz et al., 1974).

DOCA-salt Hypertension

In contrast to the models discussed above, DOCA-salt-induced hypertension results in a suppression rather than an activation of the renin-angiotensin system. One of the primary, but not only, factors involved in the pathogenesis of DOCA-salt hypertension, as was mentioned above, is increased sympathetic vascular tone (DeChamplain et al., 1977). Studies demonstrating enhanced peripheral and suppressed central catecholamine turnover (Van Ameringen et al., 1977) and reversal of both the hypertension and increased turnover by ganglionic blockade or 6-hydroxydopamine implicate a central role in this condition (DeChamplain et al., 1968). Peripheral adrenergic function appears also to be involved (Finch, 1971; Ekas and Lokhandwala, 1980), and this aspect will be further analyzed.

I will discuss below functional and structural neurogenic factors which are brought into play in experimental hypertension. Some of the changes found appear to depend upon when in the hypertensive process they are examined, and therefore it is critical to take this into consideration when comparing results between studies.

Functional Factors

Facilitation of Adrenergic Transmitter Release

Few substances are known to enhance the liberation of the adrenergic transmitter during nerve depolarization. The quaternary ammonium compound, tetraethylammonium, facilitates adrenergic transmitter release (Thoenen et al., 1967), and it has been suggested that PGF\textsubscript{2\alpha} also has this effect (Kadowitz et al., 1972). For some time it has been known that angiotensin II facilitates norepinephrine release (Zimmerman and Whitmore, 1967), and more recently it was discovered that activation of prejunctural \( \beta \)-adrenoceptors could also enhance the release of adrenergic transmitter (Adler-Grachinsky and Langer, 1975). A potential role has been proposed for circulating epinephrine as a facilitator of adrenergic transmitter release in hypertension (Langer, 1981; Kawasaki et al., 1982a).

My discussion will concentrate on the prejunctional adrenergic effect of angiotensin II, and its participation in renovascular hypertension and in the SHR. Because the circulating level of angiotensin II is elevated in the early phase of renovascular hypertension, it was logical to assume that augmented vascular responses and adrenergic transmitter release in hypertensive states were due to angiotensin II. Early investigations on intact renovascular hypertensive dogs and rats revealed, in general, increased vasoconstrictor responses to nerve stimulation in various pump-perfused vascular beds. Unfortunately, the experimental conditions and the results obtained varied between these studies, yet several important points do emerge which are useful to the forthcoming discussion of altered adrenergic neural function in experimental hypertension. In two of these early studies on Goldblatt hypertensive dogs, augmented adrenergic transmitter release was suggested, based on measurement of norepinephrine release into the venous effluent of the cutaneous bed, or by a relatively greater response to nerve stimulation compared to the response to injected norepinephrine in the hypertensive than in the normotensive animal (Zimmerman et al., 1969; Brody et al., 1970). However, in the hypertensive rat, responses to sympathetic nerve stimulation in the hindquarters were greater, compared with control rats, only at an early interval (2 weeks) after renal compression (one-kidney Grollman), and the responses to exogenously administered norepinephrine were more consistently increased (Baum and Shropshire, 1967a). Likewise, in the spleen of one-kidney one-wrap hypertensive dogs, increased vasoconstrictor responses were not associated with enhanced, but with inhibited, transmitter release (Moerman and DeSchaepdryver, 1969). This study was conducted 2–3 months after wrapping. Based
on these studies, it would seem that facilitated transmitter release mediated by angiotensin II may be involved in the hypertensive process, but probably only at an early stage, several weeks to a month into its development. Whether or not facilitated transmitter release participates in the hypertension may depend upon the concentration of angiotensin II in the plasma or tissue of the experimental animal at the time of the study.

Angiotensin-mediated support of vascular neural function during acute augmentation of renin release has also been explored. Vasconstrictor responses to sympathetic nerve stimulation in the perfused intact paw of the anesthetized dog were enhanced during suprarenal aortic constriction, and administration of saralasin inhibited the increase in these neurally elicited responses (Zimmerman and Kraft, 1979). This suggested a possible role of angiotensin II in the support of adrenergic responses during the acute activation of the renin-angiotensin system. In a study on conscious dogs, acute unilateral renal artery occlusion caused increases in resistance of the coronary, renal, hepatic, and splanchnic circulation, and the administration of saralasin decreased resistance in these beds after the occlusion (Gavras and Liang, 1980). Similar changes were observed after renal artery occlusion and saralasin in phentolamine-and propranolol-treated animals, suggesting a direct rather than neural involvement of angiotensin in the acute stage of renal ischemia. The results of the above two studies may be reconciled by greater sensitivity of conscious animals than anesthetized surgically traumatized dogs to the direct vasoconstrictor action of angiotensin. Results obtained in conscious instrumented animals may show that the direct vascular action rather than adrenergic involvement of angiotensin predominates. Higher concentrations of angiotensin II may be necessary to evoke adrenergic effects.

Other evidence for an influence of angiotensin II on vascular neural function was found in pithed normal and spontaneously hypertensive rats. Captopril attenuated pressor responses to spinal cord stimulation and intravenously injected norepinephrine in the normal rats, while an infusion of angiotensin, but not bradykinin, reversed the depression of the responses (Hatton and Clough, 1982). The results in the SHR were somewhat different in that the responses to nerve stimulation, but not norepinephrine, were decreased by captopril, suggesting a prejunctional rather than postjunctional effect of angiotensin in the SHR (Antonaccio and Kerwin, 1980). These studies in the pithed rat raise the question of whether an action of angiotensin on vascular neural function is actually demonstrable under normal basal conditions of renin release, or only when renin release is augmented, e.g., by the pithing procedure itself (Vollmer and Myers, 1983; E. Sybertz, personal communication).

Facilitation of adrenergic transmitter release has been demonstrated or suggested by several investigations of other forms of experimental hypertension. In the young (46-day-old) SHR, vasconstrictor responses and transmitter release in the perfused renal vascular bed were greater (approximately 2-fold at 6 Hz) than in normotensive controls (Collis et al., 1980). Also, in 7- to 9-week-old SHR, tail arteries transmural stimulation released approximately twice as much 3H-labeled adrenergic transmitter as in WKY control rats (Zsoter et al., 1982). Older (6-month-old) SHR exhibited a decrease in norepinephrine overflow in the perfused kidney preparation during nerve stimulation, compared with WKY controls (Vanhoucke et al., 1982), yet, in this and other studies, the vasconstrictor responses to stimulation were similar (Lais et al., 1974; Webb et al., 1981). The greater transmitter release seen early in the development of the SHR, and the impaired release found later on, are similar to the pattern seen in renovascular hypertension described above. Although the number of investigations showing such a pattern are few, and verification is needed, it is suggested that there is an early stage in the hypertensive process, which could be likened to the 'labile' stage of essential hypertension, in which adrenergic transmitter release is facilitated by some factor(s). In the chronic phase of hypertension (equivalent to several months in the SHR), transmitter release is normal or even subnormal, and some other factor(s), e.g., increased vascular smooth muscle sensitivity, compensates for impaired adrenergic transmitter release to maintain elevated vascular tone, and thus the hypertension.

There are, however, exceptions to this interpretation of the involvement of facilitated transmitter release in the SHR. A recent study demonstrated greater adrenergic transmitter release evoked by potassium-induced depolarization of isolated tail arteries not only from young SHR (6–10 weeks), but in the adult rats (28 weeks old) as well (Galloway and Westfall, 1982). The adults, in fact, exhibited a greater release (46%) expressed as a fraction of the total store, compared with the WKY, whereas the young SHR did not show an increase in fractional release. These workers attributed this enhanced adrenergic transmitter release in the SHR to a decreased influence of the a2-adrenoceptor negative feedback mechanism (Galloway and Westfall, 1982). However, in another study in which a similar increase in adrenergic transmitter release was demonstrated in the perfused kidney of 18-week-old SHR, a super- rather than subsensitivity of prejunc- tional a2-adrenoceptors was suggested (Ekas et al., 1983). Whereas some alteration in the adrenergic prejunctional receptors may contribute to facilitation of adrenergic transmitter release in the SHR, it is possible that angiotensin II may also be involved. Angiotensin II has been shown to be more effective in augmenting adrenergically mediated vasoco- strictor responses on isolated perfused mesenteric.
arteries of SHR than those of WKY (Kawasaki et al., 1982b). In addition, facilitation of norepinephrine release in portal veins of SHR by angiotensin II appears to be sodium dependent (Meldrum et al., 1983). This relationship between adrenergic facilitation and angiotensin II in the SHR is a particularly intriguing one, and the apparent salt requirement may have very important implications.

DOCA-salt hypertensive rats exhibit augmented responses to adrenergic nerve stimulation in the mesenteric vascular bed perfused with Krebs medium (Ekas and Lokhandwala, 1980; Collis, 1981), but not in the intact canine or blood-perfused rat hindquarters (Baum and Shropshire, 1967b; Hamed and Lokhandwala, 1982; Matsuguchi et al., 1982). A postjunctional rather than prejunctional mechanism explains the enhanced responses in rats, since adrenergic transmitter release was unchanged or even decreased, and vasoconstrictor responses to various agonists were increased in the hypertensives' vessels (Finch, 1971; Collis, 1981; Baum and Shropshire, 1967b; Matsuguchi et al., 1982). The discrepancy between enhanced sympathetic responsiveness in isolated preparations perfused with Krebs medium and depressed or unchanged responsiveness in vivo, is not readily apparent, but may relate to inherent differences in vascular reactivity found in artificial media and blood. A partial explanation may be that vasodilator prostaglandins are released when utilizing perfusion techniques in vivo (Falotico and Zimmerman, 1981), and prostaglandin F is capable of antagonizing adrenergic responses and transmitter release (Hedqvist et al., 1970).

As we have seen above, facilitation of adrenergic transmitter release represents a means of amplifying sympathetically mediated vasoconstriction in renovascular hypertension and in the SHR. There is also suggestive evidence of enhanced adrenergic transmitter release in Dahl salt-sensitive rats (Takeshita and Mark, 1978) and in dogs fed a low salt diet (Wong and Zimmerman, 1981). Thus, facilitation of adrenergic transmitter release may serve as a common mechanism for amplifying adrenergic responses in a number of pathophysiological states. Whether the same or different peripheral factors mediate facilitation of release has not been determined, but it is intriguing to consider a single cause. The most likely candidate in renovascular hypertension and the SHR is angiotensin II; however, in SHR, elimination of $\alpha_2$-adrenoceptor-mediated negative feedback has also been implicated (Galloway and Westfall, 1982).

If we make the assumption that the overflow of norepinephrine into the perfusate or surrounding medium during nerve stimulation estimates adrenergic transmitter release from the nerve terminals, we can approximate the degree of enhanced release by the measurement of norepinephrine in these media. In various studies in which an increase in overflow of norepinephrine was found during adrenergic nerve stimulation in the presence of infusion of angiotensin or in renovascular hypertension, the increase ranged between 46 and 100% (Zimmerman and Whitmore, 1967; Zimmerman and Gisslen, 1968; Zimmerman et al., 1969; Collis et al., 1980; Zsoter et al., 1982; Galloway and Westfall, 1982). Thus, peripheral factors appear capable of amplifying adrenergic responses at the most by 2-fold, assuming the vasoconstrictor response is approximately proportional to transmitter release (Zimmerman and Gisslen, 1968).

Interestingly, the degree of central augmentation of sympathetic nerve activity in the SHR exceeds the degree of enhancement of peripheral adrenergic transmitter release seen in hypertensives when the nerves are stimulated directly. Thus, pre- and postganglionic sympathetic nerve activity were much higher in the SHR than in the Wistar or WKY controls at all ages, and the level of blood pressure correlated with sympathetic nerve activity (Okamoto et al., 1967; Judy et al., 1976, 1979). Resting renal nerve (postganglionic) activity was 140% higher (in $\mu$V) in early 15-week SHR and increased to more than 200% in the 40-week SHR, compared with the WKY (Judy et al., 1979). A more recent study demonstrated basal renal nerve activity, which was 200% higher in conscious SHR than in WKY, and the nerve activity was increased in both groups by 225–250% during mental stress (Lundin and Thoren, 1982). Thus, it would appear that adrenergically mediated vasoconstriction could be greatly amplified by this degree of central sympathetic outflow, if vasoconstriction increased proportionately to nerve activity. However, the concept of increased sympathetic nerve activity accounting for increased vascular tone in hypertension is brought into question by other results (Touw et al., 1980; Francisco et al., 1981). It has been suggested, and this remains a distinct possibility, that increased central sympathetic outflow doesn't necessarily bring about greater vasoconstriction in the SHR (Touw et al., 1980). If, in fact, adrenergic transmitter release is depressed due to impairment of the release process in SHR (Vanhoutte et al., 1982), increased nerve activity need not be equated with increased vascular tone. It is even possible that increased sympathetic nerve activity may represent a compensatory mechanism for depressed release from the nerve terminals. The relationship between sympathetic nerve activity and the actual quantity of transmitter release in hypertension has not been studied.

One of the difficulties often cited when results obtained in the SHR are compared with those in control rats is differences between strains of rats which may not relate to the hypertension. Genetic differences between the SHR and the WKY, the usual control rat, or other strains employed as controls, may confound the results. It is possible that the consistently greater sympathetic outflow in the SHR, compared with WKY, is a function of an
abnormally low sympathetic activity in the WKY rather than high sympathetic activity in the SHR. This raises the further question of whether or not the elevated blood pressure in the SHR is related to the magnitude of the central sympathetic outflow.

Inhibition of Transmitter Release

Many prejunctional receptors exist which, when activated, result in inhibition of adrenergic transmitter release (Westfall, 1977). α2-Adrenergic, dopaminergic, opioid, purinergic, peptidergic receptors, and receptors activated upon by prostaglandins, all seem to be involved. Activation of these various receptors may suppress adrenergic transmitter release by a common mechanism acting beyond the receptor site, e.g., by phosphorylation of some critical protein. The most often studied inhibitory prejunctonal receptor is the α2-adrenoceptor, but the exact process by which inhibition is exerted has not been defined. An impairment of α2-receptor-mediated feedback in the adult SHR was cited above (Galloway and Westfall, 1982). Such an inability of the nerve terminals to modulate release is of great interest and deserves additional investigation because of the potential role of this mechanism in hypertension. Although prostaglandins and adenosine are substances which participate in hypertension in a somewhat indefinite way, they are known to inhibit adrenergic transmitter release. There is evidence of a reduced modulating effect of exogenous adenosine and ATP in SHR (Kamikawa et al., 1980), but whether endogenous purines are playing a role in this respect is not known.

Altered Adrenergic Uptake and Storage

Blockade of catecholamine uptake by cocaine and the consequent enhancement of vasoconstrictor responses to adrenergic stimulation are well known. Interference with adrenergic uptake is a potential mechanism of increasing sympathetic vascular tone, and could lead to an elevation of systemic blood pressure. It has also been suggested that augmented vasoconstrictor responses to sympathetic stimulation by angiotensin II could be explained by depression of the uptake process (Palaic and Khairallah, 1967). Confirmation of this action of angiotensin has, however, been lacking (Schumann, et al., 1970; Liao and Zimmerman, 1972). Results obtained in certain human essential hypertensives suggest depressed adrenergic uptake (Citlow, 1969; Esler et al., 1981 and evidence of inhibition of adrenergic uptake in experimental hypertension has also been found. In three models of hypertension—adrenal regeneration, one-kidney Grollman, and 10% salt feeding—uptake of labeled norepinephrine in rat heart and aorta was depressed (LeLorier et al., 1976). A depressed storage capacity of adrenergic vesicles was originally proposed to explain the reduced norepinephrine content in various organs in DOCA-salt hypertension (Krakoff et al., 1967). However, it is uncertain whether a defect in uptake actually exists (Giachetti, 1979), and as explained above it is more likely that increased adrenergic turnover which is centrally mediated is responsible for the decreased organ content of norepinephrine (DeChamplain et al., 1969; Giachetti, 1979).

Recent observations made in SHR indicate that adrenergic uptake may actually be increased in this form of hypertension (Rho et al., 1980; Whall et al., 1980). Uptake blockade by cocaine caused a greater shift in the frequency-response and norepinephrine dose-response curves in the SHR than WKY or Wistar controls (Mulvany et al., 1980; Webb and Vanhoutte, 1981). Also, a greater residual quantity of 3H was found in the SHR after incubation of tail arteries with 3H-norepinephrine after 120 minutes of superfusion (Zsoter et al., 1981). As indicated above, enhanced release of adrenergic transmitter also occurs in SHR, at least during a certain stage of the hypertensive process, and there is also a greater concentration of norepinephrine present in arterial tissue of SHR (Galloway and Westfall, 1982). The possibility exists that greater density of adrenergic innervation in the SHR partially accounts for these observations.

Structural Factors

Small arteries and arterioles mainly responsible for the resistance changes governing blood flow and pressure regulation are richly endowed with sympathetic adrenergic nerve terminals. This vascular adrenergic innervation has been described in detail using electron microscopic and histofluorometric techniques (Ehinger et al., 1967; Burnstock et al., 1970). Besides the adrenergic innervation, it has also been suggested that certain blood vessels possess a histaminergic, peptidergic, sympathetic cholinergic, and also sympathetic noncholinergic innervation. The few structural neural changes observed in hypertension have involved the adrenergic nerves.

Nerve Density

Medial thickening due to smooth muscle hypertrophy, hyperplasia, and accumulation of elastin and collagen are well-known characteristics of hypertensives' blood vessels. The autonomic innervation may undergo changes in density by becoming more concentrated or diffuse in relation to the vascular smooth muscle. The relative growth of the muscle and nerve as stimulated by elevated pressure would determine the direction of the change. Quantitative determinations of histological changes in nerve density have not often been made—however, an increase in nerve density was found in one study of experimental hypertension. In the rabbit made hypertensive by suprarenal aortic constriction, evidence was found for an increase in the adrenergic innervation (Bevan et al., 1975). Three observations led to this suggestion: (1) Norepinephrine content in the carotid arteries was increased but the concentra-
tion per g of tissue remained the same. (2) The contractile response in ear arteries to transmural stimulation increased in parallel to their wall thickness. (3) Uptake of \(^{3}H\)-norepinephrine was correlated with wall thickness. Thus, it appears that there was an increase in the adrenergic innervation in association with the hypertrophy and hyperplasia of vascular smooth muscle due to hypertension. As discussed in the previous section, the alterations in the adrenergic uptake process in the SHR might be due in part to a denser adrenergic innervation.

The concentration of storage vesicles in the adrenergic nerve terminals has not been studied in detail in hypertension, and only a few reports are available. By utilizing electron microscopy, a small decrease in the percentage of dense core vesicles (from 50 to 57%) was noted in pancreatic arteries of Goldblatt hypertensive rats, 6-7 weeks after clamping, compared with normotensive sibling controls (Graham et al., 1970), but the total number of adrenergic vesicles per unit area of axon was unchanged. The suggestion has also been made that a greater concentration of vesicles is present in the adrenergic terminals in the renal artery of Goldblatt hypertensive sheep (Burnstock et al., 1970).

**Nerve Defects**

Data accumulated over the years indicate that vascular adrenergic neural function is subnormal in experimental renovascular hypertension. This seems paradoxical based on what was presented in previous sections of this review. However, as already suggested, there are different phases in the hypertensive process in which sympathetic responses may be enhanced and in which responses are unchanged or even suppressed. Evidence of suppressed sympathetic neural function is often indirect, and somewhat inconsistent. There are studies indicating that tissue levels of norepinephrine are decreased, particularly renal levels. This has been seen in long-standing Goldblatt hypertension, and also in hypertension only 2–3 weeks in duration (Faredin et al., 1961; Wegmann et al., 1962; Lefer and Ayers, 1969). Partial depletion of the adrenergic transmitter may account for the depressed responses to sympathetic nerve stimulation seen in the one- and two-kidney Goldblatt hypertensive rat kidney, 1 week to over a month after renal wrapping (Fink and Brody, 1980; Barajas et al., 1976). Hyporesponsiveness to sympathetic nerve stimulation in renovascular hypertension is not limited to the renal vascular bed. Canine tibial arteries removed from Goldblatt hypertensive dogs at varying intervals after renal artery constriction also showed depressed responses to transmural adrenergic stimulation (Zimmerman et al., 1982). Since responses to norepinephrine were unchanged in the hypertensives' arteries, a pre- rather than postjunctional defect was suggested. The factor(s) which accounts for impaired sympathetic responsiveness in this form of hypertension is unknown; however, actual nerve damage resulting from an elevated blood pressure is a possibility. Evidence along this line has been presented based on electron microscopic examination of mesenteric arteries in Goldblatt hypertensive dogs (Azevedo et al., 1981). Degeneration of nerve terminals and a marked reduction (40–65%) in norepinephrine content of these blood vessels was found at 7–14 and 20 weeks after surgery. An alternative to nerve degeneration is that the outermost layers of vascular smooth muscle in close apposition to the adrenergic nerve plexus is selectively damaged by elevated blood pressure (Keatinge, 1976). This might explain how responses to exogenous amine which involve the inner smooth muscle remain unaffected, while responses to nerve activation are reduced.

**Conclusions**

I have considered various peripheral factors: transmitter release, uptake and modulation, and nerve defects which are involved in the enhanced and suppressed vascular adrenergic function which occurs in hypertensive states. It appears that, depending on the stage of the hypertension, peripheral adrenergic function may be potentiated or inhibited, with inhibition usually occurring later in the condition. It is uncertain whether intrinsic changes in the nerve terminals occur during the hypertensive process or whether the adrenergic function is being modulated by various circulating substances at these times. Longitudinal studies designed to discover the causes of these alterations in adrenergic processes are necessary to establish a better understanding of their implications. There is a strong need for more studies of alterations in vascular reactivity and sympathetic nerve activity under well-controlled conditions in conscious instrumented hypertensive animals. Ideally, these studies should be conducted over both the acute and chronic stages of the hypertensive process in these experimental models.

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