Ann. Rev. Pharmacol. Toxicol. 1985. 25:621–41

ALTERATIONS IN THE RELEASE OF NOREPINEPHRINE AT THE VASCULAR NEUROEFFECTOR JUNCTION IN HYPERTENSION

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INTRODUCTION

The mechanism(s) for the development of elevated blood pressure in human essential hypertension has defied precise understanding despite numerous studies. This is probably because hypertension is a multifactorial disease involving many alterations in the nervous and endocrine systems as well as alterations in vascular smooth muscle function (1–3). In an effort to obtain more information on the pathophysiology of essential hypertension, investigators have developed a large number of experimental models. The hope is that knowledge obtained about the pathophysiological mechanisms of these various experimental hypertensive models will provide clues to understanding human hypertension. Experimental hypertension has been induced by a number of procedures, including acute and chronic renal interventions, endocrine manipulations such as deoxycorticosterone (DOCA)-salt treatment, genetic inbreeding (the spontaneously hypertensive rat, or SHR, and the Dahl–salt sensitive hypertensive rat), and neurogenic manipulations.

Although other mechanisms play a role, a tremendous body of information suggests an increase in sympathetic nerve activity in the development and possibly the maintenance of hypertension in several of these models as well as

0362-1642/85/415-0621$02.00

in essential hypertension itself. In this review, emphasis will be placed on models where increased sympathetic nerve activity has been implicated (SHR, renal hypertension, DOCA-salt, Dahl-salt, and others). The reader is referred to several of the many recent and comprehensive reviews that discuss the evidence for increased sympathetic nerve activity in various models of hypertension (4–10).

An increase in peripheral sympathetic nerve activity may be due to alterations in either the afferent or the efferent limb of the nervous system, as well as at one or more sites within the central nervous system. Numerous studies have implicated a centrally mediated increase in sympathetic nerve activity as being of primary importance in the development and/or maintenance of hypertension in such models as the SHR (11, 12–15, 16–24), which is thought by many to be an excellent model of essential hypertension (25). Despite this fact, peripheral nerve activity may be altered independently of what occurs centrally. Such changes could take place at the vascular neuroeffector junction with the participation of either the pre- or the postsynaptic system. Alterations at the presynaptic nerve terminals could either increase or decrease the influence of impulses arriving from the central vasomotor centers. Zimmerman (26) discusses the difficulties encountered when evaluating the relative importance of peripheral or central factors in the development and maintenance of hypertension and how interpretations are tempered by imprecise methodology.

The purpose of this review is to discuss the evidence for and against the idea that alterations or dysfunction of the sympathetic nervous system at the level of the presynaptic nerve terminal of the vascular neuroeffector complex in hypertensive animals results in changes in transmitter release.

ADRENERGIC NEUROTRANSMITTER DYNAMICS IN PRESYNAPTIC NERVE TERMINALS

The events that take place in presynaptic noradrenergic nerve varicosities have been thoroughly studied and have been themselves the subject of numerous reviews (7, 8, 27–29). Only a brief summary will be presented here.

The adrenergic neurotransmitter norepinephrine is synthesized by three enzymatically controlled steps after the uptake of tyrosine into the adrenergic varicosity. Tyrosine is subsequently converted to dihydroxyphenylalanine (dopa), dopamine, and finally norepinephrine by the enzymes tyrosine-3-monooxygenase, aromatic L-amino acid decarboxylase, and dopamine-3-monooxygenase respectively. The conversion of dopamine to norepinephrine takes place in the storage vesicles, where the transmitter is stored in a complex with protein, ATP, and various ions. Upon the arrival of an action potential and depolarization of the terminal varicosity, norepinephrine is released together

with other soluble contents, including dopamine ß-hydroxylase, ATP, and chromogranins, into the extracellular space. Norepinephrine migrates to the vascular effector cell, where it interacts with α_1 and/or α_2-adrenoceptors to cause vasoconstriction. In some cases it interacts with $ß_2$-adrenoceptors to cause vasodilation. Norepinephrine's action is terminated by a specific carrier-mediated uptake system (uptake 1) across the neuronal membrane. This is an active transport process requiring Na^+ as well as energy. Following the recapture of norepinephrine inside the adrenergic varicosity, the amine is further transported into the storage vesicles for reuse or is metabolized by monoamine oxidase located on the outer membrane of the mitochondria. A second way norepinephrine is inactivated is via the extraneuronal enzyme, catechol O-methyltransferase, following uptake into smooth muscle cells (uptake 2). The synthesis, storage, release, receptor activation, and inactivation of norepinephrine are obviously subject to various control mechanisms that must operate in concert for the smooth operation of the adrenergic neurons. Much information on the regulation of these processes is available.

It is now well established that neural and hormonal substances can influence the quantitative release of norepinephrine per nerve impulse by an action on receptors located on the adrenergic varicosities and thereby influence the concentration of transmitter at the neuroeffector junction. Substances reported to decrease adrenergic neurotransmission include α_2-adrenoceptor agonists (including norepinephrine itself), purines such as ATP and adenosine, prostaglandins (PG) of the E series, acetylcholine (ACh) via muscarinic receptors, dopamine (DA), histamine, serotonin (5-HT), morphine, and opioid peptides. Substances facilitating adrenergic neurotransmission include ß-adrenergic agonists, ACh via nicotinic receptors, angiotensin (ANG), and possibly PG of the F series, and thromboxanes. In addition to influencing adrenergic neurotransmission, they may also contribute to the regulation of vascular tone by acting directly on vascular smooth muscle and/or influencing the activity of other vasoactive substances. Several extensive reviews have appeared that discuss this aspect of the control of adrenergic neuronal function in greater detail (30–37, 27, 38–41, 42). Modulation by these substances is thought to have important physiological functions and may play important pathophysiological roles as well.

EVIDENCE FOR INCREASED NORADRENERGIC TRANSMISSION IN THE BLOOD VESSELS OF HYPERTENSIVE ANIMALS

Numerous studies suggest that there is an increase in norepinephrine release from blood vessels in experimental hypertensive animals. It has been demon-

strated that sympathetic nerve stimulation results in an enhancement of vasoconstriction with or without a parallel increase in the response to exogenously administered norepinephrine. This has been demonstrated in young SHR (43, 44, 11), rabbits made hypertensive by partial constriction of the abdominal aorta above the kidneys (45), the Dahl–salt sensitive genetic model of hypertension (46), one clip–one kidney or two-kidney renal hypertension in the dog (47, 48), and one-clip–one kidney hypertension in the rat (49). Such a situation is consistent with the increased release of norepinephrine from adrenergic nerve terminals. Studies suggesting an increase in the reactivity of blood vessels to nerve stimulation remain inconclusive and controversial, since several investigators have failed to observe similar increases in some of those models of hypertension (50–52).

Although there are many problems with using plasma catecholamines as an index of sympathetic nerve activity or as a marker for neurotransmitter release (see below), researchers generally agree that there is an increase in plasma catecholamines and in dopamine ß-hydroxylase in young SHR (53–56) as well as in other models of hypertension (26, 48). The interpretation of these data is more complicated, since an increase in plasma catecholamines, especially norepinephrine, could represent increased release from nerve terminals, decreased uptake, or decreased clearance from the plasma. Plasma norepinephrine concentrations therefore represent the net overflow of the transmitter from adrenergic nerve endings and may or may not be proportional to the amount that reaches postsynaptic receptors, thereby resulting in physiological effects. In contrast to studies in young SHR, results obtained in adult SHR are quite controversial. The majority of studies have failed to observe differences in plasma catecholamines in adult SHR compared to normotensive controls (57–61), while a few studies have reported higher values in SHR (62). Of considerable interest is the report that the O-methylated metabolite normetanephrine is significantly higher in five– and six–month old SHR compared to Wistar-Kyoto (WKY) rats, a normotensive strain developed along with the SHR. Since normetanephrine is mainly an extraneuronal metabolite of norepinephrine, the possibility exists that its plasma concentration reflects the amount of neurotransmitter that reaches effector cells and is consistent with an enhanced sympathetic function in adult SHR (63).

Several studies have directly demonstrated an increase in nerve traffic in peripheral sympathetic nerves of SHR or DOCA-salt hypertensive rats compared to normotensive controls (64–66, 12–15). Stress also results in a greater increase in peripheral sympathetic nerve activity in SHR compared to normotensive controls (57–61, 67–69, 44–51). Peripheral sympathectomy has been shown to markedly attenuate hypertension in the SHR (70, 71) as well as in other hypertensive models (16).

DIRECT EVIDENCE FOR THE INCREASED RELEASE OF NOREPINEPHRINE FROM THE BLOOD VESSELS OF HYPERTENSIVE ANIMALS

Although all of the studies mentioned above suggest an increase in peripheral sympathetic nerve activity in hypertensive animals over normotensive controls, they do not differentiate between the effect being mediated primarily by the increased activation of central vasomotor centers and that due to increased activity at the vascular neuroeffector junction. As already mentioned, several studies suggest that the increase in peripheral sympathetic activity in pre-, young, and established hypertensive animals is secondary to alterations in the central nervous system, with increased impulse traffic from central vasomotor systems over pre- and postganglionic sympathetic fibers (17–24).

On the other hand, several studies have directly demonstrated an increase in the release of norepinephrine from isolated blood vessels (72–76), isolated perfused organs (77–80), and isolated perfused vascular beds of SHR (81–83) compared to normotensive controls (Table 1). Such increases have been observed when both ^{3}H-norepinephrine and endogenous norepinephrine are used as markers for transmitter release (72–83). Moreover, a greater release from the blood vessels of hypertensive animals has been seen following various types of stimulation, including field stimulation, nerve stimulation, depolarization with high potassium, and the application of veratradine. It appears that the greatest release of norepinephrine occurs in pre- or young SHR animals, suggesting that the increased release of norepinephrine may participate in the development of hypertension. A greater release of norepinephrine has also been observed from the blood vessels of older SHR (28 weeks), although this has not been reported by all investigators (84). The fact that increased release of norepinephrine is seen in isolated blood vessels of hypertensive animals suggests that such alterations can take place at the level of the noradrenergic nerve terminal.

Although there have only been a few studies of other hypertensive models, results to date suggest that the enhanced release of norepinephrine from isolated blood vessels is not a property common to all types of hypertension. For instance, no difference in the field stimulation–induced release of ^{3}H-norepinephrine or endogenous norepinephrine was seen from the portal vein or caudal artery of either DOCA-salt or one-kidney, one-clip renal hypertensive rats (74, 85). The hyperresponsiveness of the mesentric vasculature to periarterial nerve stimulation in DOCA-salt hypertensive rats appears to be due to increased sensitivity of the vascular smooth muscle rather than to facilitation of transmitter release (86). Similarly, adrenergic neurotransmission is not altered in the mesenteric artery of rats with chronic neurogenic hypertension (87).

Table 1 Alterations in the release of norepinephrine from the vascular neuroeffector junction of experimental hypertensive animals

Type of hypertension (animal)	Age	Blood vessel	Observation	References
Genetic (SHR)	6 weeks	Perfused kidney	Periarterial nerve stimulation; ^{3}H release SHR>WKY	77
Genetic (SHR)	18 weeks	Perfused mesentery	Periarterial nerve stimulation; ^{3}H release SHR>WKY	81, 82
Genetic (SHR)	6, 10, 28 weeks	Isolated caudal artery	Potassium depolarization; endogenous norepinephrine SHR>WKY at all ages	72, 74
Genetic (SHR)	7–9 weeks	Isolated caudal artery	Field stimulation ^{3}H release; SHR>WKY	76
Genetic (SHR)	14–16 weeks	Perfused mesentery	Periarterial nerve stimulation; ^{3}H release SHR>WKY	83
Genetic (SHR)	6 months	Perfused kidney	Periarterial nerve stimulation; ^{3}H or endogenous norepinephrine release WKY>SHR	84
Genetic (SHR)	14–21 weeks	Perfused kidney	Periarterial nerve stimulation; ^{3}H release SHR>WKY	78, 79
Genetic (SHR)	6, 10, 28 weeks	Portal vein	Field stimulation; ^{3}H release SHR>WKY at 10 and 28 weeks	73–75
Genetic (SHR)	6, 10, 28 weeks	Caudal artery	Field stimulation; endogenous norepinephrine release SHR>WKY at all ages	74, 85
Renovascular (one clip-one kidney)		Caudal artery and portal vein	Similar increase in release of endogenous norepinephrine or ^{3}H-norepinephrine to field stimulation	85
DOCA-salt (rat)		Caudal artery and portal vein	Similar increase in release of endogenous norepinephrine or ^{3}H-norepinephrine to field stimulation	85
Neurogenic (baroreceptor deafferentation rat)		Mesenteric artery	Similar increase in release of ^{3}H-norepinephrine to field stimulation	87

Since there is evidence of increased sympathetic nerve activity in these hypertensive models as there is in young SHR, yet no evidence of enhanced release from isolated blood vessels, we suggest that in the former models increased sympathetic nerve traffic is primarily mediated by an increase in central nervous system activity, while in SHR, on the other hand, both a central and a peripheral mechanism may be operational.

PRESYNAPTIC MODULATION OF NOREPINEPHRINE RELEASE FROM THE BLOOD VESSELS OF HYPERTENSIVE ANIMALS

As mentioned above, it is now well accepted that a variety of endogenous substances can modify the evoked release of norepinephrine from the adrenergic neuroeffector junction. An examination of whether there are alterations in the activity of these release modulatory substances in hypertension has recently been undertaken as a possible explanation for the increased release of norepinephrine from the blood vessels of hypertensive animals (Table 2). The general hypothesis on which these experiments are based is that a decrease in the activity of presynaptic inhibitory receptors results in an enhancement of adrenergic neurotransmission. On the other hand, a similar enhancement would be seen if there was an increase in the activity of presynaptic facilitatory receptors.

Angiotensin is one of the substances that has been shown to enhance the evoked release of norepinephrine from adrenergic nerve terminals (88, 89). Evidence for an increased activity of presynaptic angiotensin receptors in blood vessels of SHR has been obtained in several laboratories (73–75, 81, 90). Kawasaki and co-workers (90) observed that angiotensin enhances the pressor response of the mesenteric vascular bed to periarterial nerve stimulation to a greater extent in SHR than it does in WKY. In addition, the angiotensin response to periarterial nerve stimulation is potentiated in the presence of cocaine. These results suggest that the presynaptic facilitatory modulation of adrenergic vascular neurotransmission mediated by angiotensin receptors is enhanced in the perfused mesenteric vascular bed of SHR.

Similar results were obtained by Eikenburg and co-workers using a similar preparation (81). These investigators observed that sub-pressor concentrations of angiotensin potentiate the responses to nerve stimulation in SHR to a greater extent than they do in WKY. A direct demonstration that angiotensin causes a greater enhancement of the field stimulation–induced release of norepinephrine has been obtained in the isolated superfused portal vein. In these studies, angiotensin was observed to enhance the field stimulation–induced release of ^{3}H-norepinephrine from vessels obtained from SHR to a greater extent than those of normotensive controls (73–75). Enhancement of the facilitatory

Table 2 The role of presynaptic receptors on adrenergic neurotransmission in the blood vessels of hypertensive animals

Receptor type	Type of hypertension	Blood vessel or vascular bed	Observation	References
Angiotensin	Genetic (SHR)	Caudal artery	Greater enhancement by angiotensin of endogenous norepinephrine release to field stimulation in 10 and 28 weeks SHR>WKY	74, 85
Angiotensin	Genetic (SHR)	Portal vein	Greater enhancement by angiotensin of ^{3}H-norepinephrine release to field stimulation in 10- and 28-week SHR>WKY	73–75
Angiotensin	Genetic (SHR)	Perfused mesentery	Greater enhancement by angiotensin of pressor response to periarterial nerve stimulation in 18-week SHR>WKY	81
Angiotensin	Genetic (SHR)	Perfused mesentery	Potentiation by angiotensin of the pressor response to nerve stimulation in 15–16 week SHR>WKY	90
β-Adrenoceptor	Genetic (SHR)	Portal vein	Similar enhancement by β-agonist of ^{3}H-norepinephrine release to field stimulation in 10- and 28-week SHR and WKY	73, 85
β-Adrenoceptor	Genetic (SHR)	Perfused kidney	Similar enhancement by β-agonist of ^{3}H-norepinephrine release and reactivity to field stimulation in 14-week SHR and WKY	79
β-Adrenoceptor	Genetic (SHR)	Perfused mesentery	Greater enhancement by β-agonist of the response and ^{3}H-norepinephrine release to perivascular nerve stimulation in 14–16 week SHR>WKY	83
α_2 Adrenoceptor	Genetic (SHR)	Caudal artery	Decreased enhancement by yohimbine of endogenous norepinephrine release to field stimulation or high K^+ in 28-week SHR versus WKY. Similar response in 6- and 10-week SHR and WKY	72–74

α_2 Adrenoceptor	Genetic (SHR)	Portal vein	Decreased enhancement by yohimbine of ^{3}H-norepinephrine release to field stimulation of 28-week SHR versus WKY. Similar response in 6- and in 10-week SHR and WKY	74, 75
α_2 Adrenoceptor	One clip-one kidney; DOCA-salt	Caudal artery and portal vein	Similar enhancement by yohimbine of endogenous norepinephrine or ^{3}H-norepinephrine release to field stimulation in hypertensive or sham controls	74, 85
α_2 Adrenoceptor	Neurogenic baroreceptor	Mesenteric artery	Similar enhancement by phentolamine of ^{3}H-norepinephrine release to field stimulation	87
α_2 Adrenoceptor	Genetic (SHR)	Perfused mesentery	Similar enhancement by α-antagonist on response and ^{3}H-norepinephrine release to periarterial nerve stimulation in 18-week SHR and WKY	79, 101
α_2 Adrenoceptor	Genetic (SHR)	Perfused kidney	Increased inhibition by α-agonist on response and ^{3}H-norepinephrine release to periarterial	78
Purine (adenosine, ATP)	Genetic (SHR)	Perfused mesentery	Decreased inhibitory response and ^{3}H-norepinephrine release by adenosine to perivascular nerve stimulation in 5-week and 15–18 week SHR compared to WKY	107, 108
Purine (adenosine)	Renal artery	Perfused mesentery	Similar inhibitory response and ^{3}H-norepinephrine release by adenosine	80
Serotonir	Genetic (SHR)	Perfused mesentery	Decreased inhibitory response by serotonin to periarterial nerve stimulation in 15–18 week SHR compared to WKY	110

effect of angiotensin was apparent in SHR at 10 weeks of age, as it was in older animals (28 weeks of age).

Although the enhancement of norepinephrine release by angiotensin may be very important in contributing to elevated blood pressure in young SHR as well as in older animals, other mechanisms must be involved in the initial increase in transmitter release, since such an increase has been observed in animals at six weeks of age. Additional evidence for the involvement of angiotensin in hypertension development in SHR comes from studies showing that the responses to nerve stimulation, but not to norepinephrine, in SHR are decreased by captopril, a converting enzyme inhibitor. These studies further suggest a presynaptic rather than a postsynaptic effect for angiotensin in SHR (91).

In addition to angiotensin, it has been shown that activation of presynaptic ß-adrenoceptors also leads to an enhancement in the evoked release of norepinephrine from a variety of neuroeffector junctions (92–95). Whether or not there are alterations in the activity of presynaptic ß-adrenoceptors in the blood vessels of SHR or other hypertensive animals is currently unclear. Two studies have reported that the functional activity of presynaptic ß-adrenoceptors is similar in blood vessels of normotensive and hypertensive animals (75, 79). In the isolated portal vein, the effect of isoproterenol or terbutaline to enhance the field stimulation–induced release of ^{3}H-norepinephrine is similar in vessels obtained from SHR and from age-matched WKY (75). Another study reported that presynaptic ß-adrenoceptor function is similar in the isolated kidney of 14–week old SHR and WKY (79). In contrast to these two studies, it has been reported that ß-adrenoceptor agonists produce an enhancement of the response of the isolated mesenteric vascular bed from SHR compared to WKY (83). These investigators concluded that this enhancement is due to the facilitated release of neurotransmitter from adrenergic nerves mediated by presynaptic $ß_2$-adrenoceptors. The results of these studies cannot be directly compared because the studies were carried out in different preparations (i.e. an isolated blood vessel versus a perfused vascular bed). In addition, in the two studies reporting no enhancement of neurotransmission by ß-adrenoceptor agonist, transmission was evaluated by monitoring transmitter release (75, 79), while in the study reporting enhancement, changes in perfusion pressure to periarterial nerve stimulation were monitored (83). It is possible that alterations in presynaptic ß-adrenoceptor activity take place at the level of the small resistance vessels and arteries but not in larger vessels or in veins. Since the vasculature exhibits such heterogeneity, there is need for great caution when extrapolating data from one vascular preparation to another. In view of the lack of changes in prejunctional $ß_2$-adrenoceptor activity in at least two vascular preparations (portal vein and perfused kidney) in contrast to evidence for a change in the mesenteric bed, specific changes may take place at some neuroeffector junc-

tions but not others. Clearly, additional studies are necessary to unravel the pathophysiological significance of these observations.

Even in the absence of alterations in presynaptic ß-adrenoceptor activity (i.e. increased activity), these receptors may still be implicated in hypertension. Several investigators have proposed that circulating epinephrine facilitates the release of norepinephrine by stimulating presynaptic ß-adrenoceptors. This is supported by several lines of evidence. First, presynaptic $ß_2$-adrenoceptors have been demonstrated in human omental blood vessels (94). Second, an increase in circulating epinephrine (96, 97) has been observed in some types of hypertension. Third, the implantation of rats with a slow-release preparation of epinephrine can raise blood pressure. Moreover, it has been shown that following such implants there is an increase in the epinephrine content of tissue such as the atria (98, 99), suggesting the uptake of epinephrine into sympathetic nerve terminals. Sympathetic nerve stimulation of the atria could then lead to the release of epinephrine as a co-transmitter, which could then activate presynaptic ß-adrenoceptors, leading to the enhanced release of norepinephrine. Finally, bilateral demedullectomy has been shown to attenuate the pressor response to sympathetic nerve stimulation (100).

Several studies have been carried out to examine whether or not there are changes in presynaptic inhibitory receptor function in blood vessels of hypertensive animals. The selective prejunctional α_2-adrenoceptor antagonist yohimbine has been used to evaluate whether or not changes in the presynaptic α_2-adrenoceptors could help explain the increased field stimulation–induced release of norepinephrine from the isolated portal vein or caudal artery of SHR (72–75). Yohimbine was seen to produce the same degree of enhancement in the evoked release of ^{3}H-norepinephrine and endogenous norepinephrine from SHR (at six and ten weeks of age), one clip-one kidney renal hypertensive rats or DOCA-salt hypertensive rats compared to their respective sham controls. However, the effect of yohimbine to enhance the overflow of norepinephrine was greatly attenuated when examined in 28–week old SHR. The attenuation of the yohimbine effect was observed regardless of the way transmitter release was produced (field stimulation, potassium depolarization) and in both the caudal artery and the portal vein. These results are consistent with a decreased functional activity of presynaptic α_2-adrenoceptors in mature SHR.

The results obtained in the portal vein and caudal artery of six- and ten–week old SHR are consistent with the studies carried out in the mesenteric vascular bed in young SHR (81, 101), which suggests that presynaptic α_2–adrenoceptor mediated inhibition is similar in SHR and age-matched WKY at these ages. These investigators did not examine presynaptic α_2-adrenoceptor function in older animals, so it is not known whether the results obtained in the caudal artery and portal vein in 28–week old SHR represent only an age-related change or a difference in the response of different blood vessels.

In contrast to the results showing no difference in inhibitory presynaptic α_2-adrenoceptor function in the cadual artery, portal vein, or perfused mesenteric bed of young SHR (72–75, 81, 101) and a decreased α_2-adrenoceptor function in the caudal artery and portal vein of mature SHR (28–week old) (72–75), there is evidence for an increased α_2-adrenoceptor function in the perfused kidney of 14–week old SHR (79). It is not known whether this increased α_2-adrenoceptor activity in the kidney changes with age or whether it represents a tissue difference. Interestingly, there appears to be an increase in the binding of α_2-adrenoceptor ligands in the kidney membranes obtained from SHR compared to WKY (102–4). These results are consistent with an increase in α_2-adrenoceptors in the kidney. It is likely, however, that the vast majority of these receptors are located postsynaptically rather than presynaptically.

Adrenergic neurotransmission has been shown to be decreased by purine compounds such as adenosine and ATP (105, 106) presumably acting on purinergic receptors located on adrenergic nerve terminals. It has been observed that both ATP and adenosine inhibit the neurogenic vasoconstriction of the perfused mesenteric vascular bed to perivascular nerve stimulation in a dose-dependent manner in WKY (107). The effect of adenosine was approximately eight times greater than that of ATP. In the same preparation, isolated from 17- to 21–week old SHR, the inhibitory effects of both adenosine and ATP were significantly smaller than in WKY. In another series of experiments, adenosine was observed to decrease the efflux of ^{3}H-norepinephrine due to sympathetic nerve stimulation of the same preparation (108). The inhibition was smaller in both prehypertensive (five weeks old) and hypertensive (15–18 weeks) SHR compared with age-matched WKY. A decrease in the adenosine effect was not seen in Wistar rats rendered hypertensive by left renal artery occlusion. These results suggest that presynaptic inhibition of vascular adrenergic neurotransmission by purine compounds is reduced in SHR and that this diminished response to purines is genetically inherent to SHR. Studies carried out in the perfused kidney are at variance with the observations in the mesenteric bed (80). In the latter studies, it was observed that adenosine is equally effective in causing an inhibition of the stimulation-induced release of norepinephrine in both WKY and SHR.

Serotonin has also been shown to modulate norepinephrine release in blood vessels and other adrenergic neuroeffector junctions (109), producing both inhibition and enhancement of adrenergic transmission most likely by acting on different receptors. In the perfused mesenteric vascular bed, serotonin has been shown to augment the nerve stimulation–induced pressor response (110). In the WKY such potentiation to nerve stimulation was less than to exogenously administered norepinephrine, which is most likely due to inhibition of the nerve stimulation–induced release of norepinephrine from adrenergic nerve terminals. In SHR, unlike WKY, there was little difference between the potentiating

effects of serotonin on nerve stimulation and norepinephrine-induced vasoconstriction. These results suggest that presynaptic inhibitory modulation by serotonin is diminished in the mesenteric vasculature from SHR.

ALTERATIONS IN THE SYNTHESIS STORAGE AND UPTAKE OF NOREPINEPHRINE IN PRESYNAPTIC NERVE TERMINALS IN HYPERTENSION

In addition to alterations in the release of norepinephrine and its modulation by presynaptic receptors, a large body of evidence shows changes in the synthesis, storage, and uptake of norepinephrine in adrenergic nerve varicosities in hypertensive animals and man. A discussion of this aspect of the adrenergic nerve terminal is beyond the scope of this review, and the reader is referred to several recent reviews that discuss this aspect of the pathophysiology of hypertension (7, 8, 26, 27). Because of the connection among the uptake, release, and presynaptic modulation of transmitter release, a brief summary of alterations in the uptake of norepinephrine is provided.

The principal mechanism for removing or inactivating norepinephrine from the neuroeffector junction following its release from adrenergic nerve terminals is the specific neuronal uptake process. Alterations in the uptake process can have profound biological responses, with an increase in uptake resulting in a decrease in the physiological response of the effector cell. Decreases in uptake result in an enhancement of the biological response. Several studies have examined the uptake of catecholamines in hypertensive animals, but many are controversial because of conflicting results. Most investigators report a decrease in the uptake of norepinephrine into myocardial tissue of a variety of hypertensive animals, including several strains of SHR (111–14), DOCA-salt hypertensives (115, 116), animals made hypertensive with 10% NaCl (117), adrenal regeneration hypertensives (117), and animals made hypertensive with a figure eight knot around the kidney (117). Decreased norepinephrine uptake has also been reported for the kidney of 14–week old SHR (118), the spleen of SHR (119), and the mesenteric arteries of perinephretic hypertensive dogs (120). A decreased uptake of norepinephrine into the vasculature of human essential hypertensive patients has also been reported (121).

On the other hand, a number of studies have provided evidence that there is an increase in the uptake of norepinephrine into the arteries of hypertensive animals. An increased uptake of norepinephrine has been indirectly implicated because there is a greater shift to the left of the response to sympathetic nerve stimulation or the administration of norepinephrine in SHR compared to WKY following cocaine treatment or sympathetic denervation (122). In addition, several reports indicate an increased accumulation (possibly due to increased uptake) of norepinephrine in the mesenteric and caudal artery of the SHR as

well as in the ear artery of rabbits made hypertensive by placing a ligature on the abdominal aorta proximal to the kidney (45, 123–26). In the latter study, it is of interest that an increase in norepinephrine uptake and levels was seen in vessels where the blood pressure was elevated, but not in arteries below the ligature, where the pressure was normal, or in the heart or veins. A lack of increased uptake of norepinephrine into veins has been consistently seen (75).

INCREASED CATECHOLAMINE RELEASE IN ESSENTIAL HYPERTENSION IN MAN

A simple and accurate way of evaluating increased sympathetic and sympathoadrenal activity in humans is currently not available. The most common approach has been to measure plasma catecholamines. The introduction of sensitive, specific techniques for measuring plasma catecholamines (127, 128) has produced an explosion in studies attempting to relate alterations in plasma catecholamines with disease states such as hypertension (129). Increases in catecholamines do occur in many situations where there is an increase in sympathetic nerve activity. However, great caution must be used when attempting to relate plasma catecholamines to increased sympathetic nerve activity or to a specific disease such as hypertension. Such caution has been the subject of numerous reviews and editorials (e.g. 10, 130–38). Most authorities have identified at least three major problems with the use of plasma catecholamines as an index of neurogenic function. First, the assays themselves are difficult and tedious and the concentrations of catecholamines very low in most situations. Second, a large number of environmental factors contribute to the wide variation in plasma catecholamines. These include age, stress, drugs, and electrolytes, to name but a few. Third, the catecholamines found in the peripheral circulation are only a small part of the amount released from the postganglionic sympathetic nerve varicosities and the adrenal medulla. The amount of catecholamine, especially norepinephrine, that enters the circulation depends not only on the level of sympathetic nerve activity (nerve impulse frequency), but on the amount of catecholamine release per nerve impulse (subject to local regulation by release modulatory autocoids and endocoids), the extent of reuptake into nerve varicosities, the proportion metabolized in the tissues before reaching the circulation, the uptake into non-neural tissue, the binding to postjunctional receptors, the site of sampling, the rate of blood flow through the tissue, and other factors.

Recent techniques have approached the problem kinetically, utilizing the intravenous administration of high specific activity–labeled norepinephrine to reach steady-state plasma concentrations and to determine plasma norepinephrine concentration and specific activity under steady-state conditions (136, 139, 140). Such techniques allow a more accurate measurement of the

rate of entry of norepinephrine into the plasma as well as the clearance of norepinephrine from the plasma. Such approaches should have some advantages over the classical techniques.

As mentioned above, as long as the various factors are kept in mind or controlled for, measurement of plasma catecholamines has provided an index of sympathetic nerve activity for comparison within individuals or among large groups. Although this approach is still extremely controversial, comparing all of the more than 90 studies appears to indicate higher catecholamine levels in hypertensives. Multiple papers and reviews have summarized the results of these many studies (130, 141–149). About 40% report a statistically significant increase in plasma catecholamines over normotensive controls. The most consistent and dramatic differences were seen among young hypertensive patients. It seems that in subpopulations of patients increased catecholamine levels are positively correlated with the disease. The occurrence of elevated norepinephrine in the young, established hypertensive patient is consistent with a pathophysiological role for increased sympathetic neural activity in this subgroup. Whether or not enhanced sympathetic nerve activity is primarily mediated by the central nervous system or the peripheral nervous system in essential hypertension remains to be established. Likewise, whether the enhanced release of catecholamines is involved in the development or maintenance of this hypertension or both is unknown.

CONCLUSION

Available evidence suggests that there is an increase in sympathetic nerve activity in the development and maintenance of many forms of experimental hypertension in animals and in human essential hypertension. In many cases, other mechanisms may also be present. Increased sympathetic nerve activity is due in part to increased activity in central vasomotor centers. In addition, alterations at the level of the adrenergic nerve terminals may also be present. There is an increase in the stimulation-induced release of norepinephrine from isolated blood vessels, isolated perfused organs, and isolated perfused vascular beds of the spontaneously hypertensive rat, considered by many a good model of essential hypertension. These effects appear to take place in addition to increased central nervous system activity. The increased release of norepinephrine may contribute to the development and/or maintenance of hypertension. Some evidence suggests that there are alterations in presynaptic receptors at the vascular neuroeffector junction. The activity of angiotensin receptors and of ß-adrenoceptors may increase and the activity of adenosine receptors may decrease. Alterations in these presynaptic receptors could contribute to the increased release of norepinephrine that has been observed. In chronic hypertensive SHR, a decrease in presynaptic α_2-adrenoceptors may

take place. Because of the potential importance of these mechanisms, additional studies are clearly needed to further define the pathophysiological importance of these systems.

ACKNOWLEDGMENTS

The authors' research has been supported by grants from the Department of Health and Human Services, National Institutes of Health, NS 16215, HL 26319 and the Alcohol, Drug Abuse, and Mental Health Agency, DA-02668.

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