Increased sympathetic activity appears to play an important role in the development or maintenance of elevated blood pressure in hypertensive patients and various animal models of hypertension. Alterations of adrenergic receptor number or responsiveness might contribute to this increased activity. We therefore reviewed the data on adrenergic receptor alterations in hypertension with special emphasis on several key cardiovascular tissues (i.e., heart, vascular smooth muscle, and kidney) and on lymphocytes and platelets as human tissues available for such studies. The data suggest that the number of $\alpha$-adrenergic receptors in hypertension is regulated by catecholamines, dietary salt intake, and genetic factors. Increases in renal $\alpha$-adrenergic receptor number may be etiologic in genetic forms of essential hypertension. $\beta$-Adrenergic receptor alterations in states of elevated blood pressure do not appear to be specific for genetic hypertension. Desensitization of $\beta$-adrenergic receptor function in hypertensive animals and patients contrasts with reports of decreased, unchanged, and increased $\beta$-adrenergic receptor number, suggesting that signal transduction of $\beta$-adrenergic (and possibly other) receptors that stimulate adenylyl cyclase is disturbed in hypertension. The mechanisms of such heterologous desensitization in states of elevated blood pressure remain to be elucidated. (Hypertension 1990;16:107-120)

M ultiple etiologic factors, such as renal disease, mineralocorticoids, glucocorticoids, or cyclosporine have been identified as secondary causes of hypertension. However, in the majority of patients a specific hypertensinogenic factor cannot be defined ("primary or essential hypertension"). Essential hypertension has a strong genetic component, and the increase in blood pressure in many of these patients depends at least in part on dietary sodium intake. The chain of events that leads from genetic predisposition and excess sodium intake to elevated blood pressure is not well defined.

Various animal models are available to study genetic hypertension such as spontaneously hypertensive rats of the Wistar-Kyoto (SHR), the Dahl salt-sensitive (DS), the Milano (MHS), and the Sabra strain (SBH). Such models confirm the existence of strong genetic components in the control of blood pressure. The physiological heterogeneity between the genetically hypertensive rat strains also suggests that genetic hypertension can be caused by one or more of a number of genetic alterations. It is likely that human essential hypertension is also a polygenic disorder. Therefore, identification of an alteration in one model of genetic hypertension may not necessarily explain the pathophysiology of all hypertensive animals or patients. Thoughtful use of genetically hypertensive animals in comparison with their respective control strains and with animal models of acquired hypertension, however, can help reveal alterations that are secondary to blood pressure elevation and can give hints to genetic alterations that can produce high blood pressure. This knowledge can then be applied to study hypertensive patients.

Studies in animal models of genetic hypertension as well as investigations in hypertensive patients have provided four lines of evidence that suggest an elevated sympathoadrenal activity might play an important role in the pathogenesis of genetically determined blood pressure elevations: 1) Sympathetic activity, as reflected by plasma catecholamine levels and neuronal catecholamine release, is elevated in many hypertensive patients and animal models of hypertension. 2) Renal denervation can prevent or delay the onset of hypertension. 3) Sympatholytic
agents (e.g., the nonselective $\beta$-adrenergic antagonist propranolol or the $\beta_2$-selective antagonist ICI 118,551) can prevent or delay the onset of hypertension.\textsuperscript{6,9} Prevention of catecholamine formation by treatment with a dopamine $\beta$-hydroxylase inhibitor can attenuate the development of hypertension and reduce blood pressure in hypertensive animals.\textsuperscript{10}

Considerable evidence suggests that altered postjunctional sensitivity to adrenergic stimulation contributes to the overall increase in sympathoadrenal activity in the hypertensive state. Functional studies on alterations of adrenergic responsiveness in hypertension have been reviewed previously.\textsuperscript{4,11-14} This article will focus on alterations of the post-synaptic targets of catecholamines, the adrenergic receptors, in key cardiovascular tissues (i.e., heart, vascular smooth muscle, and kidney) as well as in human lymphocytes and platelets. For the sake of brevity and to narrow the scope of this review, we will not discuss adrenergic receptors in the central nervous system although considerable data implicating changes in these receptors have been reported.\textsuperscript{15-24} In addition, we will not discuss the role of peripheral presynaptic adrenergic receptors, which have been reviewed recently elsewhere.\textsuperscript{5} It will become clear from the following that the large number of studies on adrenergic receptors in hypertension markedly contrasts the many unresolved questions in this field. In our presentation, we will identify some of the reasons for this dilemma and some of the unresolved questions as well as possible approaches for their resolution.

**$\alpha$-Adrenergic Receptors**

**Cardiac $\alpha$-Adrenergic Receptors**

Although the number of cardiac $\alpha$-adrenergic receptors in some species (including humans) is quite small, they appear to be important in rats. In rat hearts, $\alpha$-adrenergic receptors outnumber $\beta$-adrenergic receptors,\textsuperscript{25,26} mediate positive inotropic effects,\textsuperscript{27} and have been implicated in the development of cardiac hypertrophy.\textsuperscript{28} Therefore, it is possible that cardiac $\alpha$-adrenergic receptors play a role in the regulation of systolic blood pressure and cardiac hypertrophy in hypertension in rats.

Cardiac $\alpha_1$-adrenergic receptors have been studied in models of genetic (SHR and DS rats) and acquired hypertension (renal vascular and deoxycorticosterone acetate (DOCA)-salt hypertension and salt-induced hypertension in DS rats). In rat models of acquired hypertension cardiac $\alpha_1$-adrenergic receptor density is decreased\textsuperscript{25,28,29,30} or unchanged,\textsuperscript{25,31,32} Similarly, in a baboon model of renal hypertension cardiac $\alpha_1$-adrenergic receptor density is unchanged.\textsuperscript{33} In the SHR, genetic hypertension model, however, decreased\textsuperscript{25,26,28} and increased\textsuperscript{30,35} receptor numbers have been reported.

More recently, the generation of inositol phosphates after cardiac $\alpha_1$-adrenergic receptor stimulation has been studied. Whereas Eid and de Champlain\textsuperscript{31} described enhanced inositol phosphate generation despite normal receptor number in DOCA-salt hypertension. Matsumori et al.\textsuperscript{35} report normal inositol phosphate generation and increased receptor number in hearts of SHR. The positive inotropic effect in response to $\alpha_1$-adrenergic stimulation in SHR heart has been reported to be increased in prehypertensive rats\textsuperscript{36} and reduced in established hypertension.\textsuperscript{26,37} Thus, the published data on cardiac $\alpha$-adrenergic receptor number and function in hypertension are inconclusive. Further information, especially with regard to their function and role in the development of hypertensive cardiac hypertrophy, would be desirable.

**Vascular $\alpha$-Adrenergic Receptors**

Increased peripheral resistance is the basic hemodynamic abnormality in most patients with essential hypertension. As $\alpha_1$- and $\alpha_2$-adrenergic receptors can mediate vasoconstriction in most vascular beds,\textsuperscript{38} hyperresponsiveness of vascular smooth muscle to $\alpha$-adrenergic receptor-mediated vasoconstriction has been proposed as a factor involved in maintenance of the elevated vascular resistance. However, no conclusive experimental evidence has been demonstrated in favor of this hypothesis. Few radioligand binding studies on vascular $\alpha$-adrenergic receptors in rat hypertension have been published,\textsuperscript{39-41} but they have not provided convincing evidence in favor or against alterations of receptor number or agonist affinity.

Functional studies on $\alpha$-adrenergic receptor-mediated vasoconstriction in patients with essential hypertension have also yielded contradictory results. Some studies have demonstrated greater vasoconstriction in response to $\alpha$-adrenergic agonists in hypertensive patients compared with normotensive subjects\textsuperscript{42-44} and enhanced vasodilatation in response to $\alpha$-adrenergic antagonists.\textsuperscript{45,46} More recent studies, however, could not detect a specific alteration of vascular $\alpha$-adrenergic receptor function in hypertensive patients\textsuperscript{46,47}; rather they have proposed that a general enhancement of vascular responsiveness may account for increased vasoconstriction, probably based on structural alterations of the vascular wall.\textsuperscript{4} Future investigations in this field should control for $\alpha$-adrenergic receptor-independent vasoconstriction (e.g., by use of angiotensin) and compare vasoconstriction in resistance vessels with that in conduit vessels.

**Renal $\alpha$-Adrenergic Receptors**

The majority of studies on $\alpha$-adrenergic receptors in hypertension have been performed in the kidney. Most investigators have described an increased density of renal $\alpha_1$-adrenergic receptors in SHR when compared with Wistar-Kyoto (WKY) rats.\textsuperscript{25,48-51} Although two studies did not detect significant changes,\textsuperscript{52,53} this alteration appears to be specific for SHR and has not been described in other models of genetic hypertension such as the MHS,\textsuperscript{24} the SBH,\textsuperscript{19} or the DS rat\textsuperscript{24} when compared with their respective control strains. The increase in renal $\alpha_1$-adrenergic
receptor in SHR precedes the elevation of blood pressure.48 Animal models of acquired hypertension have unchanged25,51 or decreased renal α2-adrenergic receptors.18,25

Similarly, many studies have demonstrated an elevated density of renal α2-adrenergic receptors in SHR.48–52,55–57 Such increases have also been found in two other models of genetic hypertension, the DS54,58 and the SBH rat.19,22 The renal α2-adrenergic receptor density in MHS rats is unchanged in young animals and decreases with developing hypertension.24 Animal models of acquired hypertension have unchanged18,51,55 or decreased renal α2-adrenergic receptors.57 Additionally, some investigators have found that the elevation of renal α2-adrenergic receptors precedes the development of high blood pressure in the SHR.48,55

The increased α-adrenergic receptor number in genetically hypertensive animals is quite surprising if one considers the high renal catecholamine content57–59 and the increased activity of renal nerves in these animals.7 As increases in renal α-adrenergic receptors do not occur in animal models of acquired hypertension, it appears that this increase in SHR is not a consequence of high blood pressure but rather specific for genetic hypertension. Studies with WKY×SHR hybrids may help to determine whether this alteration is a marker of genetic hypertension.

We have recently summarized evidence that an increase in renal α-adrenergic receptors might be a marker of genetic hypertension and involved in the pathophysiology of this disease.60 Based on these data, we have proposed a model in which a genetically increased density of renal α-adrenergic receptors leads to an overall enhancement in renal sodium reabsorption. According to our model, the resulting sodium retention and volume expansion activate various mechanisms that protect the sodium and volume homeostasis at the expense of an elevated blood pressure. This model views genetic hypertension as a regulatory mechanism that turns into a disease state on the basis of a genetic defect in α-adrenergic receptor regulation and that may be further exaggerated by an excessive dietary salt intake.

To assess the contribution of renal α-adrenergic receptors to the development or maintenance of elevated blood pressure, it will be necessary to learn more about the functional relevance of an increased number of renal α-adrenergic receptors and on the physiological role of renal α2-adrenergic receptors in normotensive animals and humans. However, until recently, virtually nothing was known about possible alterations of renal α2-adrenergic receptor function in genetic hypertension. Some data are beginning to emerge for the signal transduction of renal α2-adrenergic receptors,53,61 but at present these data are inconclusive (see below).

Human Platelet α2-Adrenergic Receptors

The study of human α-adrenergic receptors in hypertension is hampered by the lack of easily accessible cardiovascular tissues. Therefore, numerous investigators have used platelets as a model system to study α-adrenergic receptors in humans. Although platelet α2-adrenergic receptors have similar in vitro properties, as have solid human tissues such as myometrium and kidney,62 and platelet α2-adrenergic receptor density in vivo is correlated with that in myometrium,63 this model system has considerable limitations: First, adrenergic receptors of blood platelets are regulated by circulating catecholamines, whereas receptors of most tissues are regulated perhaps primarily by sympathetic nervous activity rather than blood-borne catecholamines. Second, platelets lack nuclei and therefore might not be capable of some processes that regulate receptor number or activity in other tissues. Third, tissues respond differentially to various stimuli, and it is unclear whether and for which tissues platelets might be representative. Fourth, the interindividual differences in platelet α2-adrenergic receptor density are considerable in normotensive populations,64 and therefore data obtained on small patient groups might be misleading. These limitations should be kept in mind in the analysis of published data on platelet α2-adrenergic receptors in hypertensive patients.

Three major studies have been published on platelet α2-adrenergic receptor density in essential hypertensive patients: Brodée et al65 compared 40 male patients and 40 male control participants and found a significant increase in α2-adrenergic receptor density; moreover, the aggregation of platelets in response to 10 μM epinephrine (acting via α2-adrenergic receptors) was enhanced in the hypertensive patients. In contrast, Motulsky et al66 did not detect different platelet α2-adrenergic receptor number in 20 male hypertensive patients and 17 control subjects. Finally, Jones et al67 found a lower number of platelet α2-adrenergic receptors in 19 hypertensive patients compared with 19 age- and sex-matched control subjects. Additionally, some studies with small patient numbers have been published that generally did not detect significant differences in platelet α2-adrenergic receptor density between normotensive and hypertensive subjects56–72; Kafka et al73 found an increased receptor number in 12 female hypertensive patients compared with 10 female normotensive subjects but could not reproduce that difference in a male population of a similar size. The statistical power of these small studies, however, is weak. Additionally, in one study on platelet α2-adrenergic receptors in SHR,74 the authors were unable to detect any specific α2-adrenergic binding in platelet membranes from WKY rats, but binding was detectable in SHR, suggesting an increase in receptor number from a very low level.

The reason for the divergent data on platelet α2-adrenergic receptors in established hypertension can most likely be attributed to heterogeneity in the populations studied. α2-Adrenergic receptors can be regulated by a number of factors such as genetic disposition, dietary sodium intake, and catechol-
amine exposure. Most published studies did not appropriately control for these factors and make it hard to interpret the resulting data.

Factors Regulating α-Adrenergic Receptors in Hypertension

The endogenous sympathetic tone is important for the regulation of adrenergic receptors. Although agonist-induced desensitization of α-adrenergic receptors is not always observed in noninnervated cells such as platelets or in cultured cells,75 considerable evidence suggests that α-adrenergic receptors in tissues such as those in rat kidney can undergo down-regulation by agonists and up-regulation by antagonists. For example, prolonged infusion with epinephrine or norepinephrine decreases renal α₁ (but not renal α₂)-adrenergic receptors,76 and treatment with the α₂-selective antagonist yohimbine can up-regulate renal α₂-adrenergic receptors.77 Whether agonist-mediated desensitization of α-adrenergic receptors is intact in states of elevated blood pressure is not completely clear. Antagonist-induced α₁-receptor up-regulation, which is believed to be the reversal of endogenous agonist-mediated down-regulation, has been demonstrated in kidneys of SHR and DOCA-salt hypertensive rats.50,77 Agonist-mediated down-regulation of platelet α₂-adrenergic receptors in hypertensive patients has been suggested in two studies that compared the effect of antihypertensive treatment on plasma catecholamines and platelet α₂-adrenergic receptors in hypertensive patients.55,78 In these studies, α₂-adrenergic receptor number was decreased by treatment with nifedipine (which increases plasma catecholamines) and increased by treatment with guanadrel or hydergine (which lower plasma catecholamines). On the other hand, two studies did not detect down-regulation of platelet α₂-adrenergic receptors after treatment of hypertensive patients with the exogenous, centrally acting α₂-adrenergic agonist guanabenz.66,69 Moreover, physiological increases in platelet catecholamines can desensitize platelet α₂-adrenergic receptors in normotensive subjects within 3 hours without an alteration of receptor number, but this mechanism appears to be defective in hypertensive patients.71 The latter data suggest that either α-adrenergic receptor regulation by agonists may be disturbed in hypertension or additional factors might participate in this regulation, which can overcome the effects of agonists. Two possible regulatory factors are genetic disposition and dietary sodium intake.

A genetic component of α-adrenergic receptor regulation has been demonstrated in animals and humans. As mentioned above, the density of renal α-adrenergic receptors is increased in the SHR and possibly also in some other models of genetic hypertension and such increases precede the development of high blood pressure, but they are not found in animal models of acquired hypertension. In humans, it has been found that platelet α₂-adrenergic receptor density correlates better among monozygotic than among dizygotic twins, in whom receptor number correlates better than among age-matched random pairs; heritability estimates calculated from these data yield high values for receptor number.80 In addition, three studies have compared platelet α₂-adrenergic receptor density in subjects with a positive and a negative family history of hypertension. Michel et al84 found a significantly higher receptor number in 34 normotensive children with one essential hypertensive parent compared with 37 normotensive children with normotensive parents; moreover, the variance of platelet α₂-adrenergic receptor number was significantly greater in the children with one hypertensive parent, as might be expected if receptor density is under genetic control. Preliminary data from two similar studies support these findings. Van Hoof et al81 studied children with two normotensive parents, one hypertensive parent, or two hypertensive parents and found the lowest receptor number in those with normotensive parents and the highest in those with two hypertensive parents. Fritschka et al82 studied a group of hypertensive and a group of normotensive adults. Within both groups, those subjects with a positive family history of hypertension had a greater platelet α₂-adrenergic receptor density than those with a negative family history. Genetic control may also exist for human α₂-adrenergic receptors: Skrabal et al83 have described that young normotensive subjects with a positive family history of hypertension have significantly greater blood pressure increases in response to the α₁-adrenergic agonist phenylephrine than those subjects with a negative family history. Thus, genetic factors participate in the control of α-adrenergic receptors, and genetically hypertensive patients and animals have greater platelet and renal α₂-adrenergic receptor numbers, respectively, than do normotensive controls.

Whether α-adrenergic receptors and their function in other tissues are similarly regulated by genetic factors remains to be elucidated.

Dietary sodium intake also exerts a role in the regulation of α-adrenergic receptors in essential hypertension. A high sodium diet increases renal α₂-adrenergic receptor density in normotensive rats,22,49,51,57 as well as in SHR,49,51,57 DS,49,57 and SBH rats.22 Significant elevations of renal α₂-adrenergic receptor density after a high sodium diet were observed by some,51 but not other,49 investigators. The mechanism of dietary sodium-induced up-regulation of renal α₂-adrenergic receptors is poorly understood. One possible explanation involves withdrawal of endogenous sympathetic tone as a high sodium diet decreases the renal norepinephrine content in normotensive as well as in hypertensive rats.57 Similarly, a high sodium diet decreased plasma catecholamines and increased platelet α₂-adrenergic receptors in normotensive Caucasian subjects.84 In hypertensive Japanese subjects, however, a high sodium diet reduced platelet α₂-adrenergic receptors72; in this study a separate analysis was performed of those patients who responded with increases in
blood pressure to increased sodium intake and those who did not. "Sodium-responders" on a high sodium diet had 35% lower plasma norepinephrine concentrations compared with the low sodium phase; non-responders, however, decreased their plasma norepinephrine by 60%. These data suggest that dietary sodium intake regulates \( \alpha \)-adrenergic receptors not only through alteration of endogenous catecholamines but also through other, yet unknown, pathways. In this context, it should be mentioned that sodium can also alter the properties of \( \alpha \)-adrenergic receptors in vitro and that this might be important for the effects of dietary sodium intake.\(^{85}\)

In a related context, treatment with the \( \alpha_1 \)-selective antagonist prazosin reportedly enhances sodium retention\(^{86}\) and up-regulates renal \( \alpha_2 \)-adrenergic receptors in normotensive and hypertensive rats.\(^{50,77,87}\) Treatment with the sodium-retaining mineralocorticoid DOCA, however, does not alter renal \( \alpha_2 \)-adrenergic receptor density;\(^{85}\) moreover, DOCA treatment can prevent the sodium-induced elevation of renal \( \alpha_2 \)-adrenergic receptors.\(^{18,49,51,55,77}\)

Thus, it can be concluded that endogenous catecholamines, genetic factors, and dietary sodium intake can participate in the regulation of \( \alpha \)-adrenergic receptors. The mechanisms of \( \alpha \)-adrenergic receptor regulation by genetic factors and by dietary sodium intake are not yet understood and require further investigation. Moreover, future studies of \( \alpha \)-adrenergic receptors in hypertension should monitor these variables.

### \( \alpha \)-Adrenergic Signal Transduction in Hypertension

\( \alpha \)-Adrenergic receptors can couple to multiple signal transduction pathways. The classical second messenger of \( \alpha_2 \)-adrenergic receptors is inhibition of adenyl cyclase via the inhibitory G protein \( G_i \).\(^{88}\) However, inhibition of adenyl cyclase cannot explain all physiological effects of \( \alpha_2 \)-adrenergic receptor stimulation.\(^{88}\) More recently, it has been described that \( \alpha_2 \)-adrenergic receptors can also couple to modulation of Ca\(^{2+} \) channels,\(^{38}\) mobilization of intracellular Ca\(^{2+} \),\(^{89}\) and activation of the Na\(^{+}-\)H\(^{+} \) antiporter.\(^{88}\) However, none of these signal transduction pathways have been assessed in hypertensive animals or patients.

\( \alpha_1 \)-Adrenergic receptors couple to activation of a phospholipase C; additional signal transduction pathways such as activation of Ca\(^{2+} \) channels and activation of a phospholipase A\(_2 \) have also been proposed.\(^{90}\) The \( \alpha_1 \)-stimulated activation of phospholipase C is the only \( \alpha \)-adrenergic second messenger pathway that has been studied in states of elevated blood pressure. Such studies have yielded quite contradictory results.\(^{16,51,53,61,91-95}\) Published results vary with respect to the tissues and animal models studied and the methods used to assess phospholipase C activation. Some data suggest that the basal activity of phospholipase C may be altered in hypertensive animals (for review see Reference 53). Therefore, it is not yet possible to draw definite conclusions regarding alterations of \( \alpha \)-adrenergic signal transduction in hypertension.

### \( \beta \)-Adrenergic Receptors

#### Cardiac \( \beta \)-Adrenergic Receptors

The regulation of cardiac \( \beta \)-adrenergic receptors in hypertension has received more attention than that in any other tissue. Despite the large number of studies in animal models of genetic and acquired hypertension, the issue of whether \( \beta \)-adrenergic receptor number is altered in the hypertensive heart is controversial: decreased,\(^{18,29,94-103}\) unchanged,\(^{25,101-110,111,112,113}\) and increased receptor numbers\(^{103,111}\) have been reported. Four methodological reasons contribute to this controversy:

1. Studies on the SHR as a model for genetic hypertension suffer from the lack of a suitable normotensive reference strain. Although WKY rats are commonly used as a control, their usefulness is questionable. The inbreeding of WKY rats began several generations later than that of SHR, and WKY rats were delivered to commercial breeders in early generations before genetic homogeneity was achieved. Accordingly, commercially available WKY rats from different sources vary considerably in their physiology and are genetically heterogenous.\(^{112,113}\) This problem applies not only to studies of cardiac \( \beta \)-adrenergic receptors but to all investigations that compare SHR and WKY rats. This problem also highlights the general issue that any given difference between a genetically hypertensive animal and its "control" strain is not necessarily related to the presence of hypertension.

2. Because data on receptor number are derived from radioligand binding studies, the validity of these data relies on the respective binding protocols, especially the definition of nonspecific binding. Many of the early studies on cardiac \( \beta \)-adrenergic receptors used lipophilic ligands such as \([H]^1\)dihydroalprenolol and defined nonspecific binding with very high concentrations (>1 \( \mu \)M) of other lipophilic antagonists, such as propranolol. "Specific" binding as determined under these conditions does not reliably quantitate \( \beta \)-adrenergic receptors\(^{114}\) and may label serotonin recognition sites.\(^{115}\) Many of the studies demonstrating a decreased number of \( \beta \)-adrenergic receptors in the hypertensive heart used high concentrations of propranolol to define nonspecific binding, whereas recent studies (which defined specific binding more correctly) did not consistently detect differences in the number of \( \beta \)-adrenergic receptors between the hearts of hypertensive and normotensive animals.

3. Because the heart of hypertensive animals is hypertrophied,\(^3\) uncertainty exists with regard to the best control. For example, Jones et al\(^{94}\) detected decreased cardiac \( \beta \)-adrenergic receptors in rabbits with perinephritis-induced hypertension in comparison with age-matched rabbits (which have a much smaller heart) but not in comparison with rabbits matched according to heart weight. These data illus-
tate the problem of choice of the "best" denominator for the results of radioligand binding studies in broken cell preparations. Most investigators have used the amount of membrane protein as a marker of cell surface; other possibilities include the amount of DNA as a marker of cell number, tissue wet weight, or overall heart weight. Whether the membrane (sites/mm² of surface) or cell (sites/cell) density of receptors more closely determines responsiveness to hormonal stimulation is not yet known. A further problem is that receptors may be clustered or non-uniformly distributed on the cell surface. In addition, intracellular pools of receptor may contribute to estimates of receptor number but may not be functionally active. As cell size, but not cell number, increases in cardiac hypertrophy, a correct denominator for receptor number obtained in broken cell preparation is particularly important in this disease state. Whether protein content or marker enzymes such as adenyl cyclase, Na,K-ATPase, or S'-nucleotidase are the best marker of cell surface is not yet resolved.

Two studies attempted to control for cardiac hypertrophy in the investigation of β-adrenergic receptor number in hypertension. Upsher and Khairallah compared the regulation of β-adrenergic receptors in hearts of SHR, of renal hypertensive rats, and of rats that were chronically infused with epinephrine or angiotensin II. Although blood pressure increases and cardiac hypertrophy developed in all groups compared with their respective controls, cardiac β-adrenergic receptors were down-regulated in SHR, renal hypertensive rats, and those infused with epinephrine but not in those infused with angiotensin II. Vatner et al compared canine cardiac β-adrenergic receptor number in perinephritis-induced hypertension (a hypertensive model with low plasma catecholamines) with that after aortic banding (which induces a similar degree of cardiac hypertrophy); in both animal groups cardiac β-adrenergic receptor number increased compared with control. Although these two studies are not consistent with regard to β-adrenergic receptor regulation, the approach of using nonhypertensive controls with cardiac hypertrophy appears to be promising.

4) β₁- and β₂-adrenergic receptors coexist in the heart of most species, and differential regulation of the two β-adrenergic receptor subtypes might offset each other. Such regulation would be overlooked in studies that only determine total β-adrenergic receptors. In fact, it has been found that cardiac β₁-adrenergic receptors are decreased in SHR, whereas β₂-adrenergic receptors are unchanged or even increased. Moreover, additional blood pressure elevation in SHR by treatment with the immunosuppressant cyclosporine further decreased cardiac β₁-adrenergic but did not affect βₙ-adrenergic receptors. The interpretation of these data is hampered by the possibility that decreases of β₁-adrenergic and the increases of β₂-adrenergic receptors do not necessarily occur within the same cells or even within the same part of the heart. Quantitative autoradiographic studies may prove useful to test this possibility.

After a consideration of all these caveats, we conclude that the density of total cardiac β-adrenergic receptors is probably not altered to a great extent in most forms of hypertension, but severe forms of blood pressure elevation may be accompanied by a reduction of β-adrenergic receptors. A loss of cardiac β-adrenergic receptors can occur in genetic hypertensive rats, and in SHR bred by guest on June 12, 2017
http://hyper.ahajournals.org/ Downloaded from
1988), but one radioligand binding study did not detect such increases. Even if elevations of cardiac β₁-adrenergic receptors specific for SHR could be confirmed, their functional significance would still be unclear, as the overwhelming majority of rat cardiac β₁-adrenergic receptors are not found on cardiomyocytes but rather on endothelial cells and prejunctional nerve endings. Facilitated norepinephrine release via elevated prejunctional β₁-adrenergic receptors has been postulated by some investigators but could not be demonstrated by others (see Reference 6 for review).

In contrast to the controversial literature on cardiac β-adrenergic receptor number, it is quite clear that the physiological effects mediated by cardiac β-adrenergic receptors, such as inotropy and acceleration of heart rate, are desensitized in hypertension (see Reference 120 for review). Desensitization has been found in SHR, especially in later phases of development and maintenance of hypertension, and in animal models of acquired hypertension. These
data suggest that the desensitization of cardiac β-adrenergic receptors (similar to their down-regulation) is likely to occur secondary to the development of blood pressure elevation. Similar studies on the responsiveness of human cardiac β-adrenergic receptors (mainly assessed as chronotropic responses to isoproterenol) have yielded less clear results.120 One possible explanation for this difference from studies in rats is that the inotropic and chronotropic responses in rat heart are almost exclusively mediated via β1-adrenergic receptors,121 whereas the chronotropic response to isoproterenol in humans is a mixed β1-adrenergic and β2-adrenergic receptor-mediated effect.122 If, as in rats, human cardiac β2-adrenergic receptors fail to down-regulate in hypertension, reduction of cardiac β1-adrenergic receptors could be expected to yield less desensitization in humans than in rats. Moreover, the attenuated chronotropic response to isoproterenol in hypertensive humans might be related to altered baroreceptor function, as it is abrogated after atropine pretreatment.123

The prominent desensitization of cardiac β-adrenergic receptor function relative to the controversial findings on receptor number points to the possibility that the signal transduction by these receptors is impaired in hypertension. Many investigators have found a reduced cyclic adenosine monophosphate (AMP) formation after β-adrenergic stimulation in the hearts of animals with genetic or acquired hypertension.96,98–100,105,106,108,124–126 although some have described unaltered cyclic AMP formation.98,110 Decreased β-adrenergic-stimulated cyclic AMP formation could be caused by diminution of receptor number, receptor/G protein coupling, G protein function or number, and by alterations of the catalytic unit of adenylyl cyclase. Cyclic AMP formation in response to other hormones such as dopamine, histamine, glucagon, or secretin is also reduced in hypertensive hearts.100,124 Because it is unlikely that attenuation could be explained by alterations in many types of receptors (although little is known regarding those other receptors in hypertensive hearts), these data suggest a postreceptor defect in coupling to stimulation of adenylyl cyclase; moreover, cyclic AMP formation after β-adrenergic stimulation is also reduced in SHR hearts, although these receptors do not down-regulate in hypertension.25,34,107,108 On the other hand, β-adrenergic receptor–stimulated cyclic AMP formation can be decreased in settings where receptor-independent stimulation (e.g., by guanosine triphosphate [GTP] or NaF) is unchanged.96,99,100,105,125 In some cases, however, in particular in adult SHR with established hypertension, adenylyl cyclase stimulation by NaF or GTP (acting by way of direct G protein activation) is also reduced.125,126 Taken together, the data suggest that hormone-stimulated adenylyl cyclase activity is mitigated early in the development of hypertension possibly because of impaired receptor/G protein interaction; receptor-independent stimulation of adenylyl cyclase can be attenuated in later phases of the disease, but it is not clear whether this is due to alterations of G proteins or of the catalytic unit of the enzyme. Some recent data suggest that the function of the stimulatory G protein G_s may be reduced in hypertension,102,127 but more information is necessary to confirm this suggestion.

In summary, the impaired function of cardiac β-adrenergic receptors in hypertension can be attributed partly to down-regulated β1-adrenergic receptors and partly to altered signal transduction of stimulatory receptors coupled to adenylyl cyclase. It should be added that even later events in the pathway of β-adrenergic receptor action, such as activation of cyclic AMP–dependent protein kinase, can also be impaired in hypertension.128

Vascular β-Adrenergic Receptors

One hypothesis regarding blood pressure elevation involves impaired β-adrenergic receptor–mediated vasorelaxation in the face of increased vasoconstriction via α-adrenergic and other receptors. Reduced vascular β-adrenergic responsiveness has been demonstrated in vitro and in vivo in rat models of genetic and acquired hypertension (see Reference 120 for review). Similar to the desensitization of cardiac β-adrenergic receptors, alterations of the receptors themselves, their signal transduction, or later events could be involved in the impaired vasorelaxation after β-adrenergic stimulation; limited evidence for all three possibilities has been presented.

In spite of the relevance of vascular β-adrenergic receptors and possible desensitization thereof, relatively few investigations have been published that examine this process. This might be related to the methodological problems of radioligand binding studies in vascular preparations. Reduced numbers of vascular β-adrenergic receptors were reported in some early studies.39,129–131 Because most vascular β-adrenergic receptors are of the β2-subtype and β2-adrenergic receptors in other tissues are not decreased in hypertension, these findings are somewhat surprising. However, none of the above studies has provided detailed pharmacological characterization of the β-adrenergic receptor involved. A reinvestigation of a possible down-regulation of vascular β-adrenergic receptor with more appropriate methodology and with reference to possible differences between resistance and conductance vessels appears to be necessary.

A reduction of the stimulatory G protein G_s in femoral arteries of SHR was found by Asano et al.127 Structural changes of the vasculature might further participate in the impaired vasorelaxation.4

Renal β-Adrenergic Receptors

Various investigators have studied renal β-adrenergic receptors in animal models of genetic and acquired hypertension. Although some investigators have found unaltered numbers of renal β-adrenergic receptors,18,110 in the majority of studies elevations of
renal β-adrenergic receptors were reported in rat models of genetic and acquired hypertension. Such increases were not always found in prehypertensive SHR. Moreover, in one study a positive correlation was found between renal β-adrenergic receptors and systolic blood pressure in seven groups of hypertensive animals and their respective controls. These data suggest that the increased number of renal β-adrenergic receptors accompanies blood pressure elevation, and thus a specific role of these receptors in the development of genetic hypertension seems unlikely.

The increase of renal β-adrenergic receptors in hypertension is surprising because, in vivo studies with norepinephrine-secreting pheochromocytoma or chronic norepinephrine, epinephrine, or isoproterenol infusions, these receptors down-regulate. Similar effects would be expected in kidneys of hypertensive animals that have an increased catecholamine content. Thus, an as yet unknown factor may exist that can overcome the down-regulation induced by catecholamines and can even up-regulate renal β-adrenergic receptors.

Little is known about the function of the increased renal β-adrenergic receptors. Adenylyl cyclase stimulation by β-adrenergic agonists in glomerular preparations has been reported to be unchanged or decreased. β-Adrenergic receptors in the juxtaglomerular apparatus mediate renin secretion, but similar elevations of renal β-adrenergic receptors are found in high and low renin models of hypertension. Moreover, the majority of renal β-adrenergic receptors are located in distal tubules, and the physiological role of these β-adrenergic receptors is not yet understood. Because renal α1-adrenergic and α2-adrenergic receptors can act via generation of inositol phosphates and inhibition of adenylyl cyclase, respectively (see Reference 60 for review) and because renal β-adrenergic receptor can inhibit α-adrenergic generation of inositol phosphates and can stimulate adenylyl cyclase, it is tempting to speculate that the up-regulation of renal β-adrenergic receptors is a physiological mechanism to counteract the increased renal α-adrenergic tone. No experimental data, however, are available to support or disprove this speculation.

Human Lymphocyte β2-Adrenergic Receptors

Biochemical data on human β-adrenergic receptors have been obtained in circulating mononuclear leukocytes, predominantly lymphocytes. Human leukocytes contain a homogeneous population of β2-adrenergic receptors that couple to stimulation of adenylyl cyclase. The in vitro properties of lymphocyte β2-adrenergic receptors are quite similar to those of β2-adrenergic receptors in the human heart or saphenous vein. Under certain conditions lymphocyte β2-adrenergic receptor density can be correlated with that in solid tissues such as human heart, lung, or myometrium. Such a correlation is not always found when lymphocyte β2-adrenergic and total β-adrenergic or β1-adrenergic receptors are compared.

Circulating lymphocytes are composed of various subsets that vary with regard to the number and responsiveness of their β2-adrenergic receptors. Therefore, an alteration in the subset composition of circulating lymphocytes might easily mimic or conceal changes in receptor expression. Lymphocyte subset redistribution occurs in settings of altered immunological function and also in response to β-adrenergic agonists or disease states with heightened sympathetic activity, such as congestive heart failure. Thus, redistribution of lymphocyte subsets might also occur in hypertension, a disease state with increased sympathetic drive. This possibility has not yet been carefully examined.

Most investigators have described higher numbers of β-adrenergic receptors in lymphocytes from essential hypertensive patients than in cells from normotensive control subjects; this was found whether receptor number was assessed in intact cells or in cell membranes. One study with poorly defined methods and another study in a small population of borderline hypertensive patients failed to detect significant differences between hypertensive and normotensive subjects.

Three types of data suggest that the increase in lymphocyte β-adrenergic receptors is not specifically associated with genetic hypertension but rather occurs with blood pressure elevation: 1) Treatment of essential hypertensive patients with drugs that, at therapeutic concentrations, do not directly interfere with β-adrenergic receptors reduces the number of lymphocyte β2-adrenergic receptors. Such data have been obtained after treatment with the calcium entry blocker nifedipine, the β1-selective antagonist atenolol, diuretics of the hydrochlorothiazide type, or the pre-synaptic dopamine receptor agonist hydergine. 2) Patients with elevated blood pressure due to stenosis of a renal artery also have an increased number of lymphocyte β2-adrenergic receptors relative to the number observed after angiotensin-converting enzyme inhibitors. 3) Normotensive children of parents with essential hypertension have similar numbers of lymphocyte β2-adrenergic receptors as do age- and sex-matched children of normotensive parents. Thus, the higher number of β2-adrenergic receptors in lymphocytes of essential hypertensive patients appears to accompany alterations of blood pressure rather than to be a marker of genetic hypertension. However, it is unclear whether the higher number of lymphocyte β2-adrenergic receptors is caused by receptor up-regulation or by β-adrenergic receptor-independent effects such as redistribution of circulating lymphocyte subsets.

Although most investigators agree that the number of lymphocyte β2-adrenergic receptors is elevated in patients with established hypertension, controversial data exist on the functional state of these receptors. Brodde et al have constructed concentration-
response curves for the enhancement of cyclic AMP accumulation by isoproterenol in lymphocytes from 40 hypertensive patients and 40 normotensive subjects; cyclic AMP accumulation in the hypertensive subjects was approximately twice that of the normotensive subjects at each isoproterenol concentration. A carefully controlled study in a smaller number of borderline hypertensive patients assessed adenyl cyclase activity in a lymphocyte membrane preparation. On a high sodium diet hypertensive patients had a significantly lower isoproterenol-stimulated adenyl cyclase activity than did normotensive subjects, but on a low sodium diet the groups were no longer different. Unfortunately, other reports on β-adrenergic stimulation of cyclic AMP generation in lymphocytes of hypertensive patients have not been published. Therefore, it is premature to decide whether the increased number of lymphocyte β-adrenergic receptors is accompanied by an enhanced cyclic AMP generation. The defect in β-adrenergic signal transduction in other tissues such as heart and blood vessels (see above), however, would suggest that desensitization of β-adrenergic receptors may be a general phenomenon in hypertensive patients.

Factors Regulating β-Adrenergic Receptors in Hypertension

Based on the above considerations, it would appear that the regulation of β-adrenergic receptors in hypertension results from different mechanisms than those operative on α-adrenergic receptors. Most importantly, β-adrenergic receptor alterations appear to be similar in animal models of genetic and of acquired hypertension, whereas the regulation of α-adrenergic receptors in hypertension appears to have a strong genetic component. Moreover, β-adrenergic receptors in normotensive patients with a genetic disposition for the development of elevated blood pressure are similar compared with those in normotensive subjects without family history of hypertension. Thus, alterations of β-adrenergic receptors are quite unlikely to play a primary role in the development of genetic hypertension but rather might be related to the development or maintenance of elevated blood pressure.

Three factors have been identified that regulate β-adrenergic responsiveness in the hypertensive state. First, hypertension is a state of heightened sympathetic activity. Thus, increased postsynaptic norepinephrine concentrations might desensitize β-adrenergic receptors. The ability of β-adrenergic receptors from hypertensive animals to undergo functional desensitization in response to agonists in vitro has been demonstrated. This view is also compatible with the selective loss of β-adrenergic receptors in the hearts of hypertensive animals because norepinephrine is a β₁-selective agonist. Heterologous desensitization after prolonged β-adrenergic stimulation might explain the loss of function of other hormones acting via stimulation of adenyl cyclase. However, some features of β-adrenergic receptor alteration cannot easily be explained by desensitization via enhanced catecholamine concentrations.

Second, similar to the regulation of α-adrenergic receptors, dietary salt intake may affect β-adrenergic responsiveness. In contrast to the large number of studies on the effects of salt intake on α-adrenergic receptors, few such data are available regarding β-adrenergic receptor function. Response to increased dietary salt intake is apparently different in normotensive and hypertensive subjects. Whereas dietary salt has little effect on the β-adrenergic receptors of normotensive subjects, it decreases response of these receptors in hypertensive subjects. This desensitization is not accompanied by a major alteration of receptor number but rather by a reduction of cyclic AMP formation. Moreover, increased dietary salt intake reduces the plasma levels of catecholamines. Thus, in hypertensive subjects β-adrenergic receptor desensitization occurs in spite of reduced sympathetic drive. The molecular mechanisms of this desensitization remain to be defined.

Third, alterations of β-adrenergic receptors in hypertension might directly be related to the height of blood pressure. This has been indicated by studies in three tissues; rat heart and kidney and human lymphocytes. In rat heart, some studies have demonstrated that effective antihypertensive treatment restores the desensitized β-adrenergic function. Most investigators have found an increased number of both β-adrenergic receptors in rat kidney and β-adrenergic receptors in human lymphocytes. Effective antihypertensive treatment lowers lymphocyte β-adrenergic receptor density. Moreover, the Ca²⁺ entry blocker nifedipine, which elevates plasma catecholamines, and the presynaptic dopamine receptor agonist hydergine, which decreases plasma catecholamines, lowered blood pressure and the number of lymphocyte β-adrenergic receptors of essential hypertensive patients to a similar extent. These data provide further evidence that the alteration of β-adrenergic receptors in hypertension cannot solely be explained on the basis of heightened sympathetic activity.

Perspectives

From the above data it is clear that hypertension is a disease state in which sympathetic activity, adrenergic responsiveness, and in some cases adrenergic receptors are altered. These alterations appear to be quite complex and many open questions remain to be answered. The following open questions seem to be especially important for future studies.

Although α-adrenergic receptor regulation in hypertension appears to have a genetic component, it will be necessary to establish this relation in a more direct way. For this purpose, determination of α-adrenergic receptors in cross-breeding experiments between genetically hypertensive animals and their
The large number of studies on α-adrenergic receptor number in hypertensive animals and patients is in pronounced contrast to the limited knowledge on the function and signal transduction of these receptors. Most importantly, very little is known about the functional relevance of increases in renal α1-adrenergic receptors in animal models of genetic hypertension and the effect of dietary sodium and altered sympathetic activity on renal α1-adrenergic receptor function. State-of-the-art studies might use specific biochemical probes for the signal transducing G proteins and effector molecules and physiological techniques for the studies of renal function using microdissected preparations enriched in particular regions of the kidney.

β-Adrenergic receptors are not specifically altered in genetic compared with acquired hypertension (see above). Nevertheless it is possible that impaired function of vascular β-adrenergic receptors contributes to the development or maintenance of the hypertensive state. It is important to note that desensitization of β-adrenergic receptor function in hypertension appears to involve alterations of signal transduction that may be more important than the alterations of receptor number. However, studies on β-adrenergic signal transduction in hypertension are just emerging. Specifically, it will be important to assess the molecular mechanism of the regulation of β-adrenergic receptor function by dietary salt intake and factors other than catecholamines. Studies on the function of renal β-adrenergic receptors in normotensive and hypertensive animals and patients might elucidate the perplexing finding of increased renal β-adrenergic receptor number in animals with elevated blood pressure. Such studies might further enhance understanding of the molecular basis for the antihypertensive action of β-adrenergic antagonists.

Finally, studies on the regulation of number and function of adrenergic receptors in hypertension might also provide insight about the nature of this disease state. They might shed light on the question of whether blood pressure elevation is a disease by itself or whether it is part of a homeostatic response to an underlying as yet ill-defined disorder related to sodium homeostasis. Because various forms of antihypertensive therapy effectively lower blood pressure but do not reduce overall mortality equally well, such pathophysiological knowledge about the nature of hypertension may aid in the development of new therapeutic strategies for the large number of patients with high blood pressure.

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Michel et al  Peripheral Adrenergic Receptors  117


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M C Michel, O E Brodde and P A Insel

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