Perspectives

Ion Transport Defects and Hypertension
Where Is the Link?

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A large body of literature on the cellular pathophysiology of essential hypertension is focused on a variety of membrane transport systems that control the intracellular ionic milieu and thus have the potential to regulate vascular smooth muscle contractile activity. Defects in one or more of these transport systems have been proposed to play an important role in the pathogenesis of hypertension. Aviv and Gardner,1 in this issue of Hypertension, attempt to explain the marked differences in the disease among blacks and whites in terms of the cellular handling of Na+ and Ca2+ ions in vascular smooth muscle cells and in renal epithelial cells. These are provocative ideas that require further examination. However, it is important to balance them with a critical examination of the relations that are currently believed to exist between cellular Na+, Ca2+, vascular smooth muscle contractile force, and hypertension.

Most of the recent thinking on the role of ion transport defects in hypertension flows from the hypothesis, broached by Haddy and Overbeck2 and by Blaustein,3 that essential hypertension is due to the production of circulating Na+ transport inhibitors acting on renal epithelial cells and vascular smooth muscle cells. This hypothesis drew much of its force from Dahl’s earlier observations that salt-sensitive hypertension in rats could be transferred by renal transplantation4 or by exchange of fluids in parabiotic experiments.5 This led to the idea that, in response to salt loading, the kidney produces a circulating substance that causes both natriuresis and vasoconstriction. Work carried out over a number of years by Overbeck, Pamnani, Clough, and Haddy (for reviews, see References 2 and 6) suggested that this circulating substance might be an inhibitor of the sodium-potassium adenosine triphosphatase (Na+,K+-ATPase) or Na+ pump. Such an inhibitor would cause natriuresis by reducing Na+ reabsorption by renal epithelial cells.

Na+ pump inhibitors would also be expected to affect vascular smooth muscle function. In these cells, the inhibitors would cause cell Na+ and volume to rise, and membrane potential to fall. Blaustein3 argued that increased intracellular Na+, acting on a plasma membrane Na+-Ca2+ exchange system, would then lead to increased intracellular Ca2+. Increased vascular smooth muscle cell Ca2+, by its well-known action on the contractile machinery, would in turn lead to contraction of vascular smooth muscle cells or increased responsiveness to vasoconstrictors. Increased vascular tone would raise blood pressure, contributing to the desired natriuresis. In normotensive individuals, a steady state would be achieved where Na+ intake would be matched by Na+ excretion at a plasma volume and blood pressure very close to normal.7 The “salt-sensitive” hypertensive individual, by failing to excrete the Na+ load at an adequate rate, would remain volume overloaded, would continuously produce the natriuretic/hypertensive substance, and would become chronically hypertensive on a high salt diet.

This hypothesis, while seductive in its simplicity and broad explanatory power, has never been adequately substantiated. Numerous studies by a variety of investigators have examined the Na+,K+-ATPase activity, as well as a number of putative circulating inhibitors (“digitalislike” factors) in normotensive and hypertensive individuals. Space prohibits a thorough review of this information, which has been extensively reviewed elsewhere.8-12 However, I believe that studies of both human and experimental hypertension have failed to show a consistent correlation between Na+,K+-ATPase activity and blood pressure. Although circulating inhibitors of the Na+ pump have been found (for examples, see References 10 and 13), it is still not clear what their precise chemical makeup is, what stimulates their production, or most importantly whether they actually cause hypertension. A recent provocative editorial by Kelly and Smith14 even questions the assumption that the digitalis binding site on the Na+,K+-ATPase is the receptor for a circulating factor; the possibility is raised that this site may play a role in intracellular trafficking of the...
enzyme. The only convincing natriuretic substance found thus far, atrial natriuretic factor, is not a potent inhibitor of Na⁺,K⁺-ATPase and, quite contrary to the hypothesis outlined above, is not a vasodilator.

Variants of the Haddy/Blaustein hypothesis argue that abnormal cell Na⁺ in vascular smooth muscle cells might arise from decreased Na⁺ efflux via Na⁺,K⁺-ATPase but rather from increased Na⁺ uptake via Na⁺ entry pathways. A similar defect on the apical membrane of renal epithelial cells would enhance renal sodium reabsorption and thus reduce urinary Na⁺ excretion. Such increased Na⁺ entry into renal epithelial cells would not be expected as a response to volume overload, but rather might play a role in the development of volume overload.

Na⁺ entry pathways that could participate in enhanced Na⁺ uptake include the Na⁺-H⁺ exchanger, the Na⁺-K⁺(2Cl⁻) transporter, and the Na⁺ channel. Of these, the system that has received the most recent attention is the Na⁺-H⁺ exchanger.

**Na⁺-Li⁺ and Na⁺-H⁺ Exchange**

The possibility that Na⁺-H⁺ exchange might be involved in the development of hypertension was first brought forward after the discovery 10 years ago that red blood cells from hypertensive patients have increased erythrocyte Na⁺-Li⁺ exchange activity when compared with normal individuals. Although it is still not clear what role Na⁺-Li⁺ countertransport plays in cellular physiology, it seems at least plausible that this system represents a mode of operation of the ubiquitous Na⁺-H⁺ exchanger. Among its many functions, the Na⁺-H⁺ exchanger is the most important Na⁺ uptake pathway on the apical membrane of the proximal tubule epithelial cell, and therefore plays an essential role in Na⁺ transport by this nephron segment. It is still not known whether red blood cell Na⁺-Li⁺ exchange and proximal tubule Na⁺-H⁺ exchange are actually related transport systems, but it is known that Li⁺ is an excellent substrate for the Na⁺-H⁺ exchanger (i.e., operating in the Li⁺-H⁺ exchange mode) and that protons interact with the red blood cell Na⁺-Li⁺ exchanger. On the other hand, Na⁺-H⁺ exchange is amiloride sensitive, and erythrocyte Na⁺-Li⁺ exchange is resistant to this agent. Furthermore, amiloride-sensitive Na⁺-H⁺ exchange actually can be demonstrated in erythrocytes, but only when cell pH is lowered to 6.4. Taken together, the data seem to suggest that the renal Na⁺-H⁺ exchanger and the red blood cell Na⁺-Li⁺ countertransport system are not identical, but may represent different modes of operation of the same or related transport systems.

The idea that Na⁺-H⁺ exchange is involved in the pathogenesis of hypertension has been somewhat bolstered by several recent observations. First, cultured vascular smooth muscle cells from spontaneously hypertensive rats (SHR) had significantly higher Na⁺-H⁺ exchange activity than cells from normotensive Wistar-Kyoto (WKY) rats. Second, intact vessels from 5-week-old SHR rats were more alkaline than similar vessels from WKY rats, possibly due to increased Na⁺-H⁺ exchange in the former. The interpretation of these findings is made difficult by the likelihood of numerous genetic differences between SHR and WKY rats. Ideally one would like to study a hypertensive strain that arose from an inbred normotensive strain as the result of a mutation. Any phenotypic difference found in cells from such an animal would have a great likelihood of being related to hypertension. Even so, it would still be necessary to cross the hypertensive with the normotensive strain to prove that the cellular defect segregated with the hypertension. When there are a large number of genetic differences between the strains being compared, one can no sooner ascribe the hypertension to Na⁺-H⁺ exchange than to a difference in fur color or ear size. Interestingly, human studies actually do not suffer from this defect because the possibility of drawing a false conclusion from genetic differences is reduced by examining a large population of genetically distinct individuals.
muscle, but this has not been carefully examined. Lastly, osmotic agents, via cell shrinkage, dramatically activate the exchanger in many cell types, including vascular smooth muscle. The point of this brief summary is that increased Na\(^+-\)H\(^+\) exchange activity might be a primary defect in hypertension, or perhaps more likely, it might be a secondary phenomenon arising from altered intracellular Na\(^+\) or pH, increased angiotensin II, vasopressin, endothelin, glucocorticoids, or even shape changes in the cells under study. To date, there is no solid evidence that increased Na\(^+-\)H\(^+\) exchange is a primary defect in hypertension.

Both Canessa et al\(^{17}\) and Woods et al\(^{30}\) found that hypertensive subjects and their normotensive relatives exhibited comparably increased red blood cell Na\(^+-\)Li\(^+\) countertransport, suggesting that increased activity may be a predisposing genetic factor, but that it does not itself cause increased blood pressure. Several groups have reported lower rates of red blood cell Na\(^+-\)Li\(^+\) countertransport in black individuals compared with whites; furthermore, they find no relation between transport and blood pressure in blacks.\(^{31,32}\) With regards to Na\(^+-\)H\(^+\) exchange, Livne et al\(^{27}\) found that treated hypertensive persons had significantly lower rates of platelet Na\(^+-\)H\(^+\) exchange than untreated hypertensive persons. These latter data suggest that differences in the phenotypic expression or activation of Na\(^+-\)H\(^+\) exchange may be associated with hypertension, but actually argue somewhat against a causal role for increased transport in the disease.

If increased Na\(^+-\)H\(^+\) exchange is indeed a primary defect in essential hypertension, the link between its operation and increased vasomotor tone has yet to be made. Increased Na\(^+-\)H\(^+\) exchange activity could have several effects on the vascular smooth muscle cell, including increased cell Na\(^+\), increased pH, and increased cell volume. According to the Blaustein hypothesis,\(^3\) increased cell Na\(^+\) would elevate cell Ca\(^{2+}\) by action of the Na\(^+-\)Ca\(^{2+}\) exchange system. Na\(^+-\)Ca\(^{2+}\) exchange has a well-established role in Ca\(^{2+}\) metabolism in nerve\(^{33}\) and cardiac muscle\(^{34}\) where it was originally described. Although Na\(^+-\)Ca\(^{2+}\) exchange activity has been found by a number of investigators both in intact vascular smooth muscle cells\(^{35}\) and in plasma membranes from these cells,\(^{36,37}\) its physiological role in vascular smooth muscle has been surprisingly difficult to ascertain.

Na\(^+-\)Ca\(^{2+}\) Exchange

Isolated plasma membrane vesicles have been the preparation of choice for the study of many membrane transport systems. Unfortunately, Na\(^+-\)Ca\(^{2+}\) exchange activity in smooth muscle membranes appears to be very low, at most 1% of that found in cardiac muscle membranes.\(^{36,37}\) This may be due to loss of activity or activating factors in the preparation. Alternatively, Na\(^+-\)Ca\(^{2+}\) exchange may not be abundant in smooth muscle. Evidence for Na\(^+-\)Ca\(^{2+}\) exchange has also been obtained with intact vascular smooth muscle strips and cultured cells, but such evidence is somewhat more difficult to interpret because of the greater complexity of intact systems. Determination of the physiological role of Na\(^+-\)Ca\(^{2+}\) exchange in intact systems has also been made more difficult by the lack of sufficiently specific inhibitors of the transport system. Certain amiloride analogues inhibit Na\(^+-\)Ca\(^{2+}\) exchange,\(^38\) but these agents suffer from a lack of adequate specificity.

Early studies with intact vascular smooth muscle systems clearly showed that replacement of medium Na\(^+\) with other cations significantly increased isotopic Ca\(^{2+}\) influx\(^{39,40}\) and caused contraction of vascular strips.\(^{39,40}\) These findings were interpreted to mean that the plasma membrane of vascular smooth muscle cells contains a Na\(^+-\)Ca\(^{2+}\) exchange system and that Na\(^+\) removal leads to rapid Na\(^+\) efflux and Ca\(^{2+}\) entry. However, removal of extracellular Na\(^+\) is a drastic maneuver with several potential nonspecific effects; these include alterations in surface charge, membrane potential, Ca\(^{2+}\) or other ion channel activity, and Na\(^+\) pump activity. Any of these side effects could give rise to altered contractile state or Ca\(^{2+}\) transport. The interpretation of such experiments is also clouded by the possibility of Na\(^+-\)Ca\(^{2+}\) exchange at extracellular Ca\(^{2+}\) binding sites.\(^41\) More recently, Smith et al\(^{42}\) have found that removal of extracellular Na\(^+\) reveals abundant Na\(^+-\)Ca\(^{2+}\) exchange activity in cultured aortic smooth muscle cells. However, such activity is latent unless cell Na\(^+\) is raised from the basal value of 7 mM to approximately 25 mM. In the platelet, a cell often used as a model for vascular smooth muscle, neither Na\(^+\) removal nor ouabain alters intracellular Ca\(^{2+}\).\(^{43,44}\) Thus, Na\(^+-\)Ca\(^{2+}\) exchange has been an elusive link\(^{45,46}\) in transport theories of hypertension. Further work in this area is essential before we can accept the idea that this transport system plays a central role in the pathogenesis of hypertension.

Na\(^+-\)H\(^+\) Exchange and Intracellular Ca\(^{2+}\): Is There a Link?

Even if we accept the hypothesis that Na\(^+-\)Ca\(^{2+}\) exchangers play an important role in vascular smooth muscle Ca\(^{2+}\) metabolism, it is not clear that physiological changes in intracellular Na\(^+\) are sufficient to alter cell Ca\(^{2+}\) significantly in vascular smooth muscle. Blaustein\(^3\) argued that Na\(^+-\)Ca\(^{2+}\) exchange would carry three Na\(^+\) ions and would therefore be highly sensitive to small changes in Na\(^+\) concentration. To test this hypothesis, Mitsuhashi, working in my laboratory, asked whether physiological alterations in Na\(^+-\)H\(^+\) exchange activity would alter intracellular Ca\(^{2+}\) in cultured vascular smooth muscle cells.\(^47\) She used three potent stimuli of Na\(^+-\)H\(^+\) exchange. The first was phorbol myristate acetate, which works via activation of protein kinase C and is also known to cause contraction of vascular smooth muscle.\(^48\) The second was osmotically induced cell shrinkage, and the third was cell acid-
ification by NH₄Cl prepulse. Surprisingly, all three stimuli activated Na⁺-H⁺ exchange as expected, but none of them had any measurable effect on intracellular Ca²⁺. Other investigators, working with different cell types, have shown that in some cases phorbol esters activate the Na⁺-H⁺ exchanger, but actually decrease cell Ca²⁺. If such potent stimuli of Na⁺-H⁺ exchange do not increase cell Ca²⁺, it is difficult to envisage how changes in Na⁺-H⁺ exchange such as those reported in fibroblasts from black individuals could be expected to increase cell Ca²⁺.

In their review, Aviv and Gardner also raise the possibility of the converse relation between Na⁺-H⁺ exchange and intracellular Ca²⁺. Several investigators report that increased intracellular Ca²⁺ activates the Na⁺-H⁺ exchanger in fibroblasts and vascular smooth muscle cells. This point has been most controversial, as other investigators using similar systems report that increased Ca²⁺ does not activate Na⁺-H⁺ exchange primarily. The reason for these discrepancies is not yet clear. In analyzing this controversy, it is of course important to distinguish a causal relation between increased cell Ca²⁺ and increased Na⁺-H⁺ exchange from a simple association. There is abundant evidence for the latter. Hormone-mediated cleavage of phosphatidylinositol leads to the production of IP₃ and diacylglycerol. The former releases intracellular Ca²⁺, and the latter activates the Na⁺-H⁺ exchanger via protein kinase C. Thus, activation of phospholipase C leads to an associated increase in both Ca²⁺ and Na⁺-H⁺ exchange, but these two events are not causally related. Mitsunaga and Ives found that when the Ca²⁺ increase induced by thrombin was blocked by intracellular Ca²⁺ buffers, that Na⁺-H⁺ exchange activity was not blunted—in fact it was actually slightly enhanced. Furthermore, several groups have shown that Ca²⁺ ionophores do not primarily activate Na⁺-H⁺ exchange. Mitsuhashi did find that alterations in cell Ca²⁺ modulate the response of the Na⁺-H⁺ exchanger to particular stimuli, but the physiological relevance of this observation is not yet clear. In proximal tubule epithelial cells, much less evidence is available on the role of Ca²⁺ in activation of the Na⁺-H⁺ exchanger, but what evidence there is suggests that increased cell Ca²⁺ actually reduces Na⁺-H⁺ exchange activity.

Other Roles for Na⁺-H⁺ Exchange

Is it possible that a defect in Na⁺-H⁺ exchange could mediate changes in the contractile state of the vascular smooth muscle cell without the intermediate action of cell Ca²⁺? This is an important question that warrants further investigation. It is possible that Na⁺-H⁺ exchange–mediated changes in cell pH, cell volume, cell Na⁺, or membrane potential (arising from the effect of increased cell Na⁺ on the electrogenic Na⁺,K⁺-ATPase) could profoundly affect the contractile machinery independently of changes in Ca²⁺. There is a large literature on the effects of pH, on smooth muscle tone (for review, see Reference 56). Intracellular alkalinization causes vasoconstriction in brain vasculature, ductus arteriosus, and other vessels. Such pH₂⁻-induced changes in vascular tone may be mediated by effects of H⁺ on myosin ATPase activity or on the Ca²⁺ affinity for Ca⁺⁺ binding proteins. However, the mechanism of the pH effect on smooth muscle tone is still not well understood, and there are important exceptions to the principle that alkalinity causes vasoconstriction. Finally, it is also not clear under what conditions the Na⁺-H⁺ exchanger actually raises cell pH. Several investigators find that activation of Na⁺-H⁺ exchange in cultured cells causes cell pH to rise in bicarbonate-free medium, but that the increase becomes vanishingly small in bicarbonate-containing medium. Aalkjaer and Cragoe recently found that norepinephrine, which activates the Na⁺-H⁺ exchanger in cultured cells, failed to raise cell pH in intact arterial segments. Some of these findings may be explained by the recent discovery of Ganz et al that vasopressin (and presumably other agonists) activate two bicarbonate transporting systems simultaneously with Na⁺-H⁺ exchange in cultured mesangial cells. Thus, increased cell pH may not always be the ultimate outcome of increased Na⁺-H⁺ exchange activity.

Aviv and Gardner and others have argued that increased Na⁺-H⁺ exchange might also affect growth of vascular smooth muscle cells. Hypertension is usually associated with increased thickness of the vascular media and hypertrophy of vascular smooth muscle cells. However, the direction of causality between these two phenomenon has not been established. Vascular hypertrophy may be a primary defect leading to hypertension by causing a general increase in vascular resistance. Alternatively, hypertrophy may be the result of hypertension, arising from trauma-induced damage to the endothelium with subsequent release of growth factors from platelets and endothelial cells. Although numerous growth factors activate the Na⁺-H⁺ exchanger, there is little evidence to suggest that primary activation of Na⁺-H⁺ exchange, independent of growth factor action, causes cell growth. Rather, recent evidence suggests that increased Na⁺-H⁺ exchange is a housekeeping function that enables the cell to better defend against alterations in cell pH, which arise from the metabolic activity associated with cell division. Fibroblasts, which totally lack Na⁺-H⁺ exchange activity, actually grow normally as long as the pH of the medium is maintained above 7.2. Without knowing more about the precise relations between Na⁺-H⁺ exchange activity, growth factor production, and cell proliferation, we cannot assume that increased Na⁺-H⁺ exchange activity will lead to proliferation and increased vascular tone.

Mechanism of Contraction of Vascular Smooth Muscle

Most hypotheses linking abnormalities in ion transport to hypertension consider intracellular Ca²⁺ as...
the final common mediator of vascular tone. It is surprising that this assumption receives relatively little debate, because the control of vascular smooth muscle tone appears to be more complex than this. Assumptions about the primacy of Ca\(^{2+}\) regulation in vascular smooth muscle derive from well-established information obtained from skeletal and cardiac muscle. In these systems, the myosin ATPase is regulated by the troponin-tropomyosin system. Ca\(^{2+}\) binds to troponin C, causing a conformational change that is transmitted to the remainder of the troponin complex and to tropomyosin. These conformational changes allow actin to interact with myosin and to activate the myosin ATPase. Myosin ATPase activity induces movement of the myosin head along the actin strand. Thus, contractile force and cell Ca\(^{2+}\) appear to be well correlated in skeletal and cardiac muscle.\(^6\)

Smooth muscle myosin ATPase is not regulated in this way. In smooth muscle, regulation of contractile activity occurs on the myosin filament itself. One of the components of the myosin head, the myosin light chain, can be reversibly phosphorylated. Myosin light chain kinase, an exquisitely Ca\(^{2+}\)-sensitive enzyme, is one of several enzymes that phosphorylate the myosin light chain. After membrane depolarization or hormonal activation, smooth muscle cell Ca\(^{2+}\) rises, the myosin light chain becomes phosphorylated, and contractile force develops.\(^7\) In tracheal smooth muscle, there is a very close relation between the level of intracellular Ca\(^{2+}\) and myosin light chain phosphate content; moreover, this relation is invariant for several hormonal agonists and a Ca\(^{2+}\) ionophore.\(^8\) In response to a variety of agonists, light chain phosphate content also correlates well with initial shortening velocity of vascular smooth muscle strips.\(^9\) Thus, it seems likely that contraction is initiated by a rise in cell Ca\(^{2+}\), which leads to activation of the myosin light chain kinase, an increase in light chain phosphate content, and the development of tension.

Unfortunately, this straightforward model of smooth muscle contraction cannot explain all aspects of the smooth muscle contractile response. For example, in swine arterial smooth muscle, the relation between intracellular Ca\(^{2+}\) and light chain phosphate content was clearly dissociated when histamine and membrane depolarization were the agonists.\(^9\) More importantly, the relation between intracellular Ca\(^{2+}\) and contractile force is not unique. In rat aortic smooth muscle, norepinephrine caused contraction at considerably lower Ca\(^{2+}\) than did ionomycin, a Ca\(^{2+}\) ionophore.\(^9\) In fact, contraction in response to low concentrations of norepinephrine was found in the absence of demonstrable rises in cell Ca\(^{2+}\).\(^9\) Activation of protein kinase C by phorbol esters also causes contraction of vascular smooth muscle\(^4\) without raising cell Ca\(^{2+}\) measurably. Even more surprising is the finding that carbachol (a contractile agonist) and isoproterenol (a smooth muscle relaxant) both raised Ca\(^{2+}\) equally in tracheal smooth muscle strips.\(^4\) In ferret portal vein, a similar observation was made: isoproterenol caused small increases in Ca\(^{2+}\) during relaxation of vascular strips.\(^5\)

The role of Ca\(^{2+}\) in determining vascular tone is even less clear when considering the tonically contracted vascular smooth muscle cell. After initial development of contractile force, the cell contractile machinery enters the so-called "latch" state, in which tension is maintained despite a greatly diminished rate of cross-bridge formation and adenosine triphosphate use.\(^6,7\) Because hypertension is probably due to tonic increases in smooth muscle tone and not to transient increases, this latch state is of great importance in understanding hypertension. Yet, remarkably little is known about how this state of contraction is maintained. What is known is that during maintained contraction, cell Ca\(^{2+}\) and myosin light chain phosphorylation levels actually fall to basal or near basal levels.\(^6,7\) Very recent evidence in molluscan smooth muscle shows that the "catch" state, analogous to the latch state in mammalian smooth muscle, is maintained with cell Ca\(^{2+}\) at its basal level.\(^7\) Moreover, relaxation of the catch state involves no change in cell Ca\(^{2+}\). Thus, latch states appear to be maintained by increasing the sensitivity of the contractile machinery to Ca\(^{2+}\) or alternatively, by a Ca\(^{2+}\)-independent mechanism. Much more needs to be learned about the maintenance of these smooth muscle latch states before we can understand the maintenance of vascular tone.

In summary, Ca\(^{2+}\) is probably not the sole actor in the contraction of vascular smooth muscle cells. At the very least, some agents, like norepinephrine, appear to increase cell Ca\(^{2+}\) and to also increase the sensitivity of the contractile machinery to Ca\(^{2+}\). One doesn’t have to stretch the data far to believe that Ca\(^{2+}\)-independent modes of contraction may also exist. Thus, models of hypertension are not forced to include increased cell Ca\(^{2+}\) as the basis for the defect. Rather, in some individuals, hypertension may be due to an altered sensitivity of the vascular contractile machinery to Ca\(^{2+}\) or even to Ca\(^{2+}\)-independent processes.

**Future Directions**

Where should we now turn in the quest for a pathophysiological basis for essential hypertension? Despite the weaknesses outlined above, the "ion transport" theories of hypertension remain among the most plausible theories for the pathogenesis of the disease. However, the key to making these theories work is to gain a fuller understanding of all the factors that regulate the maintenance of tone in the vascular smooth muscle cell. Once these are understood, it may become possible to understand the role of altered intracellular Na\(^{+}\), Ca\(^{2+}\), or pH in vascular cells from hypertensive individuals. If, as it now seems, some of the regulators of vascular tone are protein kinases or other enzymes,
rather than ions, then a derangement in one of these may explain hypertension in an individual with normal intracellular ions.

Finally, entirely new possibilities must be explored. Space limitations preclude a discussion of all potential avenues for future research, but one area seems to deserve particular attention. The local control of vascular tone and the details of the endothelial cell–vascular smooth muscle cell paracrine system have only started to be fully appreciated. For example, the renin-angiotensin system appears to exist in a local form within the vasculature, which may operate independently of the renal system. Newly discovered, locally acting vasoactive substances may play a crucial role in the development of hypertension. These substances may not have been appreciated in the past because of their failure to circulate significantly. An excellent example of this is the endothelium-derived relaxing factor, discovered by Furchgott and Zawadski in 1980. This agent, whose chemical identity is probably nitric oxide, is released from endothelial cells in response to a variety of hormonal and physical factors. Because the half-life of nitric oxide is so short (several seconds), it probably acts to relax only the subjacent vascular smooth muscle cells before becoming rapidly inactivated in the circulation.

A potent endothelium-derived vasoconstrictor, endothelin, has also recently been discovered. This 21-amino acid peptide, a close relative of the asp venom toxin, sarafotoxin 6B, is released from cultured mammalian endothelial cells by thrombin, increased intracellular Ca²⁺, and possibly by physical forces acting on the cell surface. Like endothelium-derived relaxing factor, endothelin does not appear to circulate significantly, but rather may act directly on the subjacent vascular smooth muscle cell to cause contraction.

If the recent past is any guide, it seems almost certain that additional locally produced or circulating vasoactive substances will be found. Any or all of these may turn out to be important in the pathogenesis of essential hypertension. Only by keeping our minds open and focusing on important unexplained phenomena, such as the difference in the incidence of essential hypertension in blacks and whites, will the riddle be solved.

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