What Makes the Pressure Go Up?

A Hypothesis

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SUMMARY Two observations we have made on pigs support the hypothesis that there is primary involvement of the central nervous system in the pathophysiology of DOCA-salt hypertension: 1) pressure appears to be a variable regulated by a center that is reset, since elevation in mean arterial pressure is a consistent phenomenon that is caused by an increase in either cardiac output or total peripheral resistance; and 2) elevation of pressure and its reversal on a low salt diet is paralleled by the development and reversal of polydypsia, suggesting that there is a similar resetting of an osmoreceptor. The nervous system is further implicated by two additional types of evidence: 1) specific hypothalamic lesions interfere with the development of experimental hypertension; 2) local denervation prevents a membrane abnormality that characterizes the vascular smooth muscle cell of the spontaneously hypertensive rat. Evidence from several sources indicates that vascular smooth muscle cell membrane in experimental hypertension has greater than normal excitability, which may be associated with abnormal membrane calcium binding. Abnormal permeability and calcium binding have also been observed in the cell membrane of erythrocytes and adipocytes of hypertensive rats.

These observations permit a hypothesis that a primary fault in the pathophysiology of hypertension is a defect in calcium binding of the plasma membrane of the cells of a pressure-regulating center in the hypothalamus. This causes an altered sodium permeability, which resets the center. The reset center has access to several efferent pathways capable of elevating pressure. One of these efferent pathways is a neurogenic control capable of altering the plasma membrane of vascular smooth muscle in such a way that its sensitivity is increased. (Hypertension 3 (suppl II): II-160-II-165, 1981)

KEY WORDS • neurovascular control • membrane permeability • cardiovascular center

It is my objective to make a case for a specific hypothesis that deals with the cause of the altered vascular reactivity that leads to the increase in total peripheral resistance of hypertension.

In considering the cause of the increase in the arterial pressure of hypertension, it is helpful to separate the events of this pathophysiology into the three components presented in figure 1. The importance of the vascular change is indicated by the fact that it is almost always the final common pathway responsible for the pressure elevation. In considering the causes of the vascular change, it is useful to differentiate the initiating factors or prime movers from the sequence of events that leads from this starting point to the vascular change. In essential hypertension or in spontaneous hypertension in the rat (SHR), the process is initiated by a specific, though not yet defined, genetic trait. In some cases this initiation requires the superimposition of specific environmental influences such as stress or excess sodium intake to get the hypertensive process started. Secondary hypertension has more evident initiating factors such as renal ischemia or mineralocorticoid excess. As indicated in figure 1, these “initiating factors” activate any one or more of a sequence of events that leads to the vascular change. Today it is the characterization of this secondary sequence that constitutes the most important subject in research dealing with the pathogenesis of hypertension.

I will introduce the thesis of this review by citing evidence for the involvement of the nervous system in mineralocorticoid hypertension, based on observed hemodynamic changes. I will then characterize the vascular changes in hypertension, and present additional evidence implicating the nervous system in these vascular changes.
Review

DOCA Hypertension and the Nervous System

Several lines of evidence invite the hypothesis that DOCA, in the presence of an adequate sodium intake, produces hypertension by altering a central sensing system that has a cardiovascular regulatory function. I will cite five such lines of evidence. First, following the administration of DOCA, young pigs develop hypertension in which the pattern of rise in blood pressure is always the same (fig. 2) regardless of whether it is caused by an increase in cardiac output or by an increase in total peripheral resistance (fig. 3). It is as if pressure, per se, were the regulated variable that was sensed. DOCA plus sodium seems to cause a shift in the setpoint of the regulatory system to a higher pressure level.

Second, the increase in arterial pressure is paralleled by an increase in water intake, and both tend to reverse when the sodium intake is reduced (fig. 4). Blood pressure appears to be regulated by a system similar to the osmoreceptor that regulates thirst.

Third, deoxycorticosterone acting directly on isolated vascular smooth muscle in the muscle bath does not produce an increase in vascular reactivity. Since it does produce an increase in reactivity in situ, the mechanism must be indirect and is compatible with a neurogenic influence.

Fourth, DOCA administered to an anephric animal causes a pressure elevation constituting further evidence of an extrarenal action of DOCA.

Fifth, an increase in mean arterial pressure does not occur in response to the standard DOCA-salt intervention when rats have been pretreated with 6-OH
Vascular Changes in Hypertension

The observation that the elevated arterial pressure of hypertension is usually due to an increase in total peripheral resistance establishes that it is caused by a vascular change. This change could be in either the

dopamine in their lateral cerebral ventricles. This observation is particularly relevant since the expected changes in vascular responsiveness following DOCA salt administration failed to develop in spite of the fact that sodium intake and, presumably, plasma DOCA levels were elevated.

**Figure 3.** Individual hemodynamics of six DOCA-treated pigs. Percent change in mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR) are shown individually for each pig. Pigs A, B, and C were selected as examples of animals in which the increase in MAP is caused predominantly by a rise in CO. In Pigs D, E, and F, the hypertension is caused primarily by elevations in TPR. In most of the 38 pigs (fig. 2), the elevated MAP was caused by increases in both CO and TPR (By permission, Miller et al.

**Figure 4.** Changes in blood pressure and water intake in response to DOCA treatment and to a subsequent low-sodium diet. The increases in both variables are reversed in parallel when the sodium intake is reduced from 200 to 20 mEq per day.
passive structural components of the vessel or in the contractile activity of the vascular smooth muscle. Folkow\(^7\) has championed the role of the structural change and it is now universally recognized\(^8,9\) that the vessel wall is thicker in hypertension and that this increased thickness encroaches on the lumen even when the vascular smooth muscle is completely relaxed.

The evidence for increased vascular smooth muscle sensitivity is extensive and has been reviewed recently by Webb and Bohr.\(^6\) This evidence supporting the functional changes is not as strong as that supporting structural changes. Nevertheless, observations suggest that the vascular smooth muscle sensitivity change may be more directly related to the early cause of the elevated total peripheral resistance than is the structural change, since chronologically the former either precedes or develops concomitantly with the increase in arterial pressure.

At a cellular level the increase in sensitivity of vascular smooth muscle appears to be associated with an increase in plasma membrane permeability to sodium and potassium\(^10,11\) and possibly also to calcium.\(^8\) Over the past decade, considerable evidence has appeared indicating that the membrane abnormality found in vascular smooth muscle may also be present in other membranes in hypertension.\(^10,11\) Most of these studies have been carried out in the red blood cell. Postnov et al.\(^17\) have observed similarly elevated ion permeability of the plasma membrane of adipocyte of SHR.

Another index of plasma membrane function that has been studied extensively in vascular smooth muscle in hypertension is its Na-K-ATPase activity. Although there is some evidence to the contrary,\(^14\) most investigators have indicated that this system is more active in vascular smooth muscle from the hypertensive animal than in that from the normotensive control.\(^14,15\) The more common interpretation of this finding is that the hyperactivity of the pump in vascular smooth muscle in hypertension is caused by stimulation of the pump by a greater influx of sodium resulting from a more permeable plasma membrane.

In 1973, Holloway and Bohr\(^22\) observed that a higher concentration of calcium is required to produce relaxation of vascular smooth muscle from various types of hypertensive animals than is required to cause relaxation of the vascular smooth muscle from normotensive controls. They hypothesized that this observation could have reflected a lesser number of calcium-binding sites on the plasma membrane of the vascular smooth muscle from the hypertensive vessels. Jones\(^24\) observed parallel differences when he studied the effects of calcium concentration on the rate of potassium efflux from the vascular smooth muscle cell. Recently Postnov et al.\(^14\) directly confirmed these interpretive differences when he found a deficit in a high-affinity calcium binding site of the plasma membrane of red blood cells of SHR.

There may be a genetic defect in membrane synthesis which is responsible for this deficit in calcium binding and hence for the increase in membrane permeability in hypertension.

Neurogenic Influence on Vascular Effector System

Change in a vascular regulatory center in hypertension may alter vascular smooth muscle sensitivity by either humoral or neurogenic pathways. Although extensive evidence can be mustered in support of humoral factors,\(^28\) the goal of this review is to cite observations that support the possibility that there are abnormal neurogenic influences that cause changes in vascular smooth muscle sensitivity in hypertension. Vanhoutte et al.\(^27\) have recently surveyed findings that characterize differences in nerve terminals in hypertension. Alterations in norepinephrine release and uptake have been documented in SHR. Both functional\(^29,30\) and structural\(^31,32\) studies have demonstrated an increased vascular innervation in hypertension.

Recent studies by Campbell et al.\(^32\) have furnished definitive evidence relating membrane changes that occur in vascular smooth muscle of the SHR to a neurogenic influence. A segment of caudal artery from a donor rat was transplanted to the iris of an adult recipient. These transplants were maintained in their new environment for 5 or 6 weeks at which time resting membrane potentials were determined at 16°C. At this temperature, electrogenesis from the sodium pump is turned off so that the resting membrane potential reflects the passive diffusion potentials. (Hermsmeyer\(^22\) had observed previously that this resting membrane potential of the caudal artery of the SHR was approximately 8 mV less than that of the normotensive control.) Transplants obtained from an adult animal retained the membrane potential of the donor animal (fig. 5). On the other hand, if the transplant was obtained from a 2-week-old rat (prior to innervation), it developed the membrane potential of the host animal.

In an extension of these observations (Hermsmeyer, personal communication), caudal artery segments were transplanted to irises of animals from which the ipsilateral superior cervical ganglion had been removed (fig. 6). Although the donor rats in these experiments were 2 weeks old, the membrane potential of the transplant was not influenced by the characteristics of the host, demonstrating that the low membrane potential of the SHR must be mediated through neurogenic influences.

A similar age-dependence has been reported in the ability of 6-OH dopamine administered in the lateral cerebral ventricle to protect against arterial pressure elevation in the SHR. If treated at a prehypertensive level, the animal does not become hypertensive. If treated following the development of hypertension, the elevated pressure will not be reversed.\(^6\)

In the light of these observations, it is tempting to speculate that both genetic and mineralocorticoid hypertension have their origin in a specific center such as that in the AV3V region, which has been studied by Brody et al.\(^33\) This temptation leads to the hypothesis that there is impaired calcium binding to membrane sites of the cells of the center. Resultant changes in membrane fluxes alter effenter activity of the center, initiating the elevation of arterial pressure. An ex-
Transplants from ADULT

Transplants from 2 WEEK OLD

**Figure 5.** Membrane potentials of caudal artery smooth muscle. Wide stippled bars are measurement from host caudal artery, narrow clear bars are from donor arteries growing in the anterior eye chambers of adult host. KNR = Kyoto-Wistar normotensive rat, SHR = spontaneously hypertensive rat. Transplants from adult donors retain the membrane potential of the strain of origin. Transplants from 2-week-old rats acquire the membrane potential of the adult host.

**Figure 6.** Membrane potential of caudal artery of 2-week old rats transplanted into anterior chamber of sympathectomized eye of adult donor rat. Membrane potentials of the transplants are not influenced by the host when the eye is denervated. (Data replotted by permission from Campbell et al. and Hermansmeyer et al., personal communication.)

trapulation beyond current observations is required for this hypothesis, namely, that the abnormal membrane properties already observed in the red blood cell, the vascular smooth muscle cell, and other tissues, also occur in the membrane of the cells of this pressure-regulating center.

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