Hypertension

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Membrane Mechanisms in Arterial Hypertension

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SUMMARY   The purpose of this review is to focus on alterations in vascular muscle membrane potentials (E_m), ionic permeabilities, and ionic transport systems which may either contribute to or be a consequence of the hypertensive state. Three models of hypertension are discussed: 1) deoxycorticosterone-salt (DOCA-salt)-induced hypertension; 2) low-renin (presumably volume expanded) renal hypertension (LRRH); and 3) the spontaneously hypertensive rat (SHR) of the Okamoto-Aoki Kyoto-Wistar strain and its normotensive genetic control (WKY). The importance of studying all possible mechanisms of increased contraction in vascular smooth muscle is stressed.
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KEY WORDS • DOCA-salt hypertension • low-renin renal hypertension • spontaneously hypertensive rat • vascular smooth muscle • ionic permeability • transport systems • blood pressure regulation • membrane potential

ALTHOUGH neural and humoral factors influence both central and peripheral sites to regulate arterial pressure (Brody,[1] Abboud[2]), the final common pathway for the control of vascular reactivity, and ultimately peripheral vascular resistance, lies at the level of the vascular smooth muscle cell. Thus, knowledge of the membrane processes responsible for vascular muscle cell activation is crucial in understanding the complete scope of blood pressure regulation. Furthermore, it is important to recognize the differences found in different blood vessels (Hermsmeyer,[3, 4] Harder et al.[5]). For valid conclusions to be drawn, the same vessel should be compared in hypertensive and normotensive animals. Mechanisms worked out in a particular blood vessel can be rigorously applied only to that particular vessel, unless others of interest have also been vigorously investigated. For a comprehensive theory of altered vascular muscle membrane function, the same measurements should be carried out on each vessel of interest. As data from different blood vessels are only available for some of the alterations found, it is difficult to draw more than qualified conclusions about the generality of differences.

This overview will encompass the following concepts regarding the vascular muscle cell membrane and its control over force development in the hypertensive vs normotensive state: differences between in vivo and in vitro membrane potential (E_m), including the effects of an intact sympathetic innervation; altered ionic permeabilities in hypertensive vascular smooth muscle and the concomitant effect on vascular reactivity; and alterations in energy-dependent electrogenic ion transport as a function of humoral factors, innervation, or intrinsic muscle properties in vascular muscle cells from animals with hypertension of three different origins.

In Vivo vs In Vitro Membrane Potentials in Vascular Muscle Cells of Spontaneously Hypertensive Rats

Extensive literature has accumulated demonstrating that sympathetic control of the vasculature in spontaneously hypertensive rats (SHR) is altered at many levels (Okamoto et al.,[6] Yamori,[7] Dietz et al.,[8] Folkow et al.,[9] Takahashi and Bunag,[10] Abboud[2]). Furthermore, alterations in release and uptake of norepinephrine (NE) may produce effects similar to increased neural input and may contribute to the maintenance of the hypertensive state (Abboud[2]).

It is only in the SHR that both in vivo and in vitro data are available because of the great difficulty in measuring E_m, especially in vivo. The E_m of small mesenteric veins of SHR compared to WKY differ markedly when measured in vivo, but not when measured in vitro (Harder et al.[11]). The difference in E_m between SHR and WKY in vivo is abolished if neural input is blocked by tetrodotoxin (Harder et al.[11]) or if α-adrenergic receptors are blocked by phenoxybenzamine (Willems et al.[12]). These differences are summarized in table 1. Such findings strongly suggest that the adrenergic excitation of the vascular muscle cell membrane is markedly elevated in mesenteric veins of SHR. It is unlikely that such differences in E_m between SHR and WKY mesenteric veins are due to increased stretch (preload) since the in vivo pressure within mesenteric veins of SHR is only several millimeters of mercury higher than that recorded in WKY (unpublished observations). Differences in E_m are also absent in isolated portal veins (Hermsmeyer and Walton[13]).

Such in vivo studies use the E_m of vascular muscle cells as a sensitive indicator that sympathetic stimulation of individual vascular muscle cells is stronger in SHR. The usefulness of this technique lies in the fact that the membrane response is the "final common pathway" indicator of neurotransmitter access to vascular muscle, combining the following influences: impulse activity in sympathetic nerve fibers, amount of NE released per impulse, uptake and inactivation of NE, and vessel wall thickness and connective tissue influencing NE diffusion. Recording of intracellular potential demonstrates that there is elevated sympa-

thetic influence on mesenteric veins of SHR (Harder et al.,[11] Willems et al.[12]). Furthermore, by using specific blockers of α- and β-receptors, it is possible to demonstrate an endogenous hyperpolarizing influence (possibly epinephrine) which appears to be masked in SHR mesenteric veins by the predominance of α adrenergic response (Willems et al.[12]).

It is interesting to note that, even after neural blockade via tetrodotoxin, the E_m measured in the same vessel in vivo is about 6 mV less negative than when in vitro in both SHR and WKY when the vessels are studied under identical conditions in an organ bath (Harder et al.[11]) (table 1). This finding might demonstrate that blood-borne substances exert a degree of control over vascular muscle cells, if the stretch and other isolation procedures can be taken to have minimal effect.[11]

When the vascular muscle cell E_m of SHR and WKY are measured in vitro, no significant difference in the resting value can be found, even though conditions are optimized for each vessel. No difference in resting in vitro E_m between SHR and WKY was found in mesenteric veins (Harder et al.[11]) caudal artery (Hermsmeyer[14]), portal vein (Hermsmeyer and Walton[13]), or middle cerebral artery (Harder et al.[5]). In both caudal and middle cerebral arteries, however, we have found alterations in membrane electrical properties that suggest altered electrogenic ion transport, which are unmasked only after inhibition of ion transport.

Membrane Control Over Force Development: Abnormalities in Hypertensive States

E_m and Tension

Membrane control over force development in vascular muscle is defined by corresponding changes in E_m and mechanical events, but all of the variables allowing the relationship to be changed are unclear (Hermsmeyer et al.[15]). However, there exists substantial literature demonstrating that a high degree of the activation state at the level of the plasma membrane is associated with contraction (Harder[16]). Briefly, depolarization of vascular muscle cells increases the influx of Ca^{2+} with resultant force development (Johansson and Somlyo[17]) and agonist stimulation depolarizes E_m and thus increases ionic conductances, including Ca^{++}, through voltage sensitive channels (Haeusler,[18] Harder and Sperelakis[19]). The level of E_m prior to agonist stimulation largely determines the sensitivity to that agonist (Hermsmeyer[20]) because the distributions and conductances of ions across the vascular muscle plasma membrane are influenced by E_m. Ion gradients and conductances thus determine and are influenced by E_m in a complex interaction. E_m is a major control of the mechanical properties of the blood vessel within a given vascular bed, thereby ultimately controlling peripheral vascular resistance in the intact animal (Hermsmeyer,[3] Hermsmeyer et al.,[15] Harder[5]). Although there is no evidence that the relationship between E_m and contraction is shifted in hypertensives vs normoten-

TABLE 1. *Effect of Tetrodotoxin on Transmembrane Potentials Measured in Vascular Muscle Cells of Small Mesenteric Veins*

	WKY E_m		SHR E_m	
	n/a	mV	n/a	mV
In situ measurements				
Control PSS	90/20	-49 ± 1.3	37/14	-34 ± 0.8*
PSS +TTX	64/10	-48 ± 1.4	35/10	-45 ± 1.7†
(1 μg/ml)				
In vitro measurements				
Control PSS	71/13	-54 ± 1.1‡	114/12	-51 ± 1.0‡
PSS + TTX	53/4	-54 ± 1.1‡	22/3	-52 ± 1.4‡
(1 μg/ml)				

Each E_m value is the mean $\pm$ SE calculated from n impalements, with external suffusion solution (PSS) as zero reference. a = no. of animals used to obtain the total number of impalements. WKY = Wistar-Kyoto rats; SHR = spontaneously hypertensive rats; E_m = transmembrane potential; PSS = physiological saline solution; TTX = tetrodotoxin.

*In control PSS, magnitude of in situ E_m in SHR is significantly smaller than that of WKY.

†Significant hyperpolarization produced in situ in SHR only during TTX suffusion.

‡Magnitude of in vitro E_m in WKY or SHR is significantly greater than corresponding in situ value. (From Harder et al., see ref. 11, reproduced by permission of the American Physiological Society.)

sives, ionic mechanisms leading to increased contraction through changes in E_m under certain conditions have been identified. These include alterations in ion gradients, passive ionic conductances, and energy dependent ion transport, any one of which can alter the response to an agonist as will be considered below.

The previous section alluded to the involvement of the sympathetic nervous system in increased peripheral resistance. The following sections will focus on altered ionic permeabilities and transport systems in steroid, renal, and genetic models of hypertension.

Deoxycorticosterone-Salt (DOCA-Salt) Hypertension

The early history describing electrolyte abnormalities and proposing low salt diets as a treatment in hypertension has been reviewed by Tobian.[21] Bohr[22] and others have since demonstrated several properties likely to be explained by altered ion permeabilities and/or transports. For example, femoral artery strips from DOCA hypertensive rats develop spontaneous mechanical oscillations upon elevation of $[Ca]_o$, a phenomenon observed much less frequently in normotensive controls. Alterations in the ionic permeabilities and turnover of aortic arterial muscle of DOCA hypertensive animals were also found by Jones and Hart,[23] who demonstrated increases in K^+ and Cl^- fluxes across plasma membranes. Similarily, Jones[24] observed increased Na^+ flux in aortas of DOCA hypertensive rats.

There is no agreement on whether the altered responsiveness of arteries from DOCA hypertensive animals are the result of an elevated cell volume or primary changes in the ionic composition (Cox,[25] Cohen et al.[26]). What does appear to be clear, however, is that changes in ionic permeabilities and/or transmembrane gradients can change both sensitivity and reactivity to an agonist (Cox,[25] Cohen et al.[26]). In the DOCA-salt hypertensive animal model, it has been suggested that the increase in vascular reactivity may initiate the increase in mean arterial blood pressure (Berecek and Bohr[27]). If so, the change in ion permeabilities may be transient because the work of Hermsmeyer and colleagues[28] demonstrated no difference in resting E_m or mechanical response to norepinephrine in caudal arteries of DOCA-salt hypertensive rats. However, Webb[29] found increased relaxation in vitro on return to K^+ in pig femoral and tail arteries of DOCA hypertensives. The DOCA-salt model may well be dependent on a circulating ouabain-like factor that would not be detected in vitro (Pamnani et al.[30]). Friedman[31] has suggested that aldosterone-stimulated Na^+ transport is greater in rat caudal arteries in DOCA-salt hypertension, and that perhaps mineralocorticoid activity contributes to other humoral factors to cause a net increase in intracellular Na^+. Vasopressin also appears necessary to the development of hypertension in the DOCA-salt rat (Berecek et al.[32]).

Renal Hypertension (LRRH)

Vascular muscle has a sizeable electrogenic component to its resting E_m contributed by ion transport,

probably through Na-K ATPase. This electrogenic component can range from 8 to 20 mV depending upon the artery (Hermsmeyer,[14] Harder[16]). The Na-K pump suppression appears to increase responsiveness in vascular smooth muscle cells of animals with experimental low renin, presumably volume-expanded hypertension (Overbeck[33]). The evidence for reduced Na-K pump activity includes decreased K^+-induced vasodilation and decreased ouabain-sensitive ^{86}Rb uptake by hypertensive blood vessels (Overbeck et al.,[34] Pamnani et al.[35]), and decreased Na-K ATPase activity in cardiac microsomes (Clough et al.[36]). The immediate result of electrogenic Na-K pump inhibition by an endogenous, ouabain-like substance on vascular muscle would be membrane depolarization. Indeed, such a mechanism has been supported in hypertensive arterial muscle (Pamnani et al.[30]). The resulting depolarization of E_m would lead to a smaller threshold to reach the contraction range of E_m in response to vasoconstrictor agents in renal hypertensive animals, unless other ionic mechanisms were also altered.

Spontaneously Hypertensive Rats (SHR)

Several investigators have demonstrated that aortas from SHR contract to the divalent cations Sr^{++}, Co^{++}, and Mn^{++}, while their genetically normotensive controls do not (Shibata et al.,[37] Bohr,[22] Greenberg and Bohr,[38] Noon et al.,[39] Webb and Bohr[40]), suggesting that SHR arterial muscle cells are "leaky" to divalent cations. However, muscular arteries do not contract in Sr^{++}, Co^{++}, or Mn^{++} (Hermsmeyer and Walton[13]). Why aortas would be contracted by foreign cations is not established, but it probably is the consequence of an increased cell permeability to Ca^{++}, thereby augmenting the hypertensive state.

On the other hand, even smaller muscular arteries of SHR show greater contraction in high Ca^{++} solutions than WKY (Webb and Bohr[41]). This increased sensitivity to divalent cations in vascular muscle cells of hypertensives has also been attributed to the inability of structures within the cell to bind and/or extrude intracellular Ca^{++} (Webb and Bhalla,[42] Shibata et al.,[37] Noon et al.,[39] Moore et al.,[43] Kwan et al.[44]). There is also indirect evidence that Ca^{++} permeability is greater in arteries from essential hypertensive individuals (Hulthén et al.[45]) as well as SHR (Lederballe Pedersen et al.[46]).

It has been well documented that arterial muscle cells from the SHR have an elevated ion transport activity (Jones,[47] Hermsmeyer,[14] Hermsmeyer and Walton,[13] Webb and Bohr,[48] Harder et al.,[5] Friedman[31]). This enhanced pump activity in SHR caudal arterial muscle membranes increases the electrogenic component to the resting E_m by 5 to 7 mV over those of WKY (Hermsmeyer[14]). It has been hypothesized that an elevated electrogenic component partially compensates for a reduced K^+ equilibrium potential (E_K) in the hypertensive vascular muscle plasma membrane (Hermsmeyer[3, 14]). A reduced E_K in arterial muscle would increase the sensitivity to vasoactive agents which mediate their action through membrane depolar-

ization because it would bring the diffusion potential closer to mechanical threshold. In moderate to high concentrations of NE, the SHR cells would be more depolarized and contracted (Hermsmeyer[3, 14]).

Although an enhanced electrogenic component to the arterial muscle E_m in SHR appears to be a property of arteries from several different vascular beds, a reduced E_K does not. Middle cerebral arterial muscle cells treated with ouabain to block electrogenic ion transport are depolarized more in SHR than in WKY rats, suggesting an enhanced electrogenic ion transport similar to other arteries; however, when E_m vs log $[K]_o$ curves are used to determine the E_K, there is no difference (Harder et al.[5]). The difference between the E_m even with electrogenic pumping inhibited in SHR and WKY cerebral arteries is due to a difference in E_m-$[K]_o$ slope, suggesting a difference in Na^+/K^+ permeability. Perhaps a related phenomenon is the consistent finding of spontaneous electrical and mechanical activity in cerebral arteries from SHR (Harder et al.[5]).

One influence that does not appear important in SHR is that of the humoral factors that seem to be involved in DOCA-salt and renal forms of hypertension. The first evidence is that, unlike in SHR, the E_m of DOCA-salt rats in solutions at 16°C or in 0 K^+ solutions were not different from controls. This suggests that the SHR have an altered ion transport mechanism that persists even in vitro (after the humoral factors would have been washed out). The second bit of evidence is that the SHR form of hypertension is the only one so far tested that is not prevented by the lesion of the anteroventral region of third ventricle (AV3V) developed by Brody and colleagues (Brody[1]). It thus appears that, in SHR, neural factors and the trophic influence of the sympathetic nervous system are more important factors. The trophic influence is suggested because it was possible to demonstrate by cross-innervation experiments that the altered membrane NE sensitivity and $\dot{E}_m$ electrogenesis follow the innervation, rather than the source animal for the caudal arteries (Abel and Hermsmeyer[49]). There does not appear to be evidence that the SHR is dependent upon a humoral ouabain-like factor.

Conclusions

Consideration of evidence that has been proposed to give cellular mechanisms leading to altered NE sensitivity and contraction in DOCA-salt, renal, and SHR forms of hypertension suggests that different mechanisms are involved, and are worthy of separate exploration. Although ion transport systems seem implicated in each of the forms of hypertension, the precise forms of ion transport that are altered, and the dependence of the alterations on neuronal, humoral, or inherent vascular muscle properties, might be quite different. The most important point in studying all of these types of hypertension is to identify and understand thoroughly each altered mechanism that can contribute to increased contraction. It has long been understood that hypertension is a multifaceted disease. Comparison of these differently induced forms of hypertension only emphasizes the importance of finding all possible mechanisms leading to abnormally high tension development by vascular muscle cells.

References

1. Brody MJ: New developments in our knowledge of blood pressure regulation. Fed Proc 40: 2257, 1981
2. Abboud FM: The sympathetic system in hypertension. State-of-the-art review. Hypertension 4 (suppl II): II-208, 1982
3. Hermsmeyer K: Membrane potential mechanisms in experimental hypertension. In New Trends in Arterial Hypertension, INSERM Symposium No. 17, edited by Worcel M. Amsterdam; Elsevier/North Holland Biomedical Press, 1981, pp 175–187
4. Hermsmeyer K: Integration of mechanisms in single vascular muscle cells. Fed Proc 42: 269, 1983
5. Harder DR, Brann L, Halpern W: Altered membrane electrical properties of smooth muscle cells from small cerebral arteries of hypertensive rats. Blood Vessels 20: 154, 1983
6. Okamoto K, Nosaka S, Yamori Y, Matsumoto M: Participation of neural factor in the pathogenesis of hypertension in the spontaneously hypertensive rat. Jpn Heart J 8: 168, 1967
7. Yamori Y: Neurogenic mechanisms of spontaneous hypertension. In Regulation of blood pressure by the central nervous system, edited by Onesti G, Fernandes M, Kim K. New York; Grune, Stratton, 1976, pp 65–76
8. Dietz R, Schomig A, Haebana H, Mann J, Rascher W, Luth JB, Grunherz N, Gross F: Studies on the pathogenesis of spontaneous hypertension in rats. Circ Res 43 (suppl I): 98, 1978
9. Folkow B, Hallback M, Noresson E: Vascular resistance and reactivity of the microcirculation in hypertension. Blood Vessels 15: 33, 1978
10. Takahashi H, Bunag RD: Augmentation of centrally induced alpha-adrenergic vasodepression in spontaneously hypertensive rats. Hypertension 2: 198, 1980
11. Harder DR, Contney SJ, Willems WJ, Stekiel WJ: Norepinephrine effect on in situ venous membrane potential in spontaneously hypertensive rats. Am J Physiol 240: H837, 1981
12. Willems WJ, Harder DR, Contney SJ, McCubbin JW, Stekiel WJ: Sympathetic supraspinal control of venous membrane potential in spontaneous hypertension in-vivo. Am J Physiol 243: C101, 1982
13. Hermsmeyer K, Walton S: Specificity of altered electrogenesis of membrane potential in hypertension. Circ Res 40: 153, 1977
14. Hermsmeyer K: Electrogenesis of increased norepinephrine sensitivity of arterial vascular muscle in hypertension. Circ Res 38: 362, 1976
15. Hermsmeyer K, Trapani A, Abel PW: Membrane-potential dependent tension in vascular muscle. In Vasodilatation, edited by Vanhoutte PM, Leusen I. New York: Raven Press, 1981 pp 273–284
16. Harder DR: Heterogeneity of membrane properties in vascular muscle cells from various vascular beds. Fed Proc 43: 253, 1983
17. Johansson B, Somlyo AP: Electrophysiology and excitation-contraction coupling. In Handbook of Physiology, Section 2: The Cardiovascular System, vol II, edited by Bohr DF, Somlyo AP, Sparks, Jr HV. Bethesda, Maryland; American Physiological Society, 1980 pp 301–323
18. Haeusler G: Relationship between noradrenaline-induced depolarization and contraction in vascular smooth muscle. Blood Vessels 15: 46, 1978
19. Harder DR, Sperelakis H: Action potentials induced in guinea-pig arterial smooth muscle by tetraethylammonium. Pflugers Arch 378: 111, 1979
20. Hermsmeyer K: Electrogenic ion pumps and other determi-

nants of membrane potential in vascular muscle (the 1982 Henry Pickering Bowditch lecture). Physiologist **25:** 454, 1982

21. Tobian L: Interrelationship of electrolytes, juxtaglomerular cells, and hypertension. Physiol Rev **40:** 280, 1960

22. Bohr DF: Reactivity of vascular smooth muscle from normal and hypertensive rats: effect of several cations. Fed Proc **33:** 127, 1974

23. Jones AW, Hart RG: Altered ion transport in aortic smooth muscle during deoxycorticosterone acetate hypertension in the rat. Circ Res **37:** 333, 1975

24. Jones AW: Kinetics of active sodium transport in aortas from control and deoxycorticosterone hypertensive rats. Hypertension **3:** 631, 1981

25. Cox RH: Time course of arterial wall changes with DOCA plus salt hypertension in the rat. Hypertension **4:** 27, 1982

26. Cohen DM, Webb RC, Bohr DF: Nitroprusside-induced vascular relaxation in DOCA hypertensive rats. Hypertension **4:** 13, 1982

27. Berecek KH, Bohr DF: Whole body vascular reactivity during the development of deoxycorticosterone acetate hypertension in the pig. Circ Res **42:** 764, 1979

28. Hermsmeyer K, Abel PW, Trapani AJ: Norepinephrine sensitivity and membrane potentials of caudal arterial muscle in DOCA-salt, Dahl, and SHR hypertension in the rat. Hypertension **4:** 1149, 1982

29. Webb RC: Potassium relaxation of vascular smooth muscle from DOCA hypertensive pigs. Hypertension **4:** 609, 1982

30. Pamnani MB, Harder DR, Hout SJ, Bryant HJ, Kutyna FA, Haddy FJ: Vascular smooth muscle membrane potentials and the influence of a "ouabain-like" humoral factor in caudal arteries of rats with one-kidney, one clip hypertension. Clin Sci **63:** 31, 1982

31. Friedman SM: Evidence for an enhanced transmembrane sodium (Na^+) gradient induced by aldosterone in the incubated rat tail artery. Hypertension **4:** 230, 1982

32. Berecek KH, Murray RD, Brody MJ, Gross F: Vasopressin (VP) and vascular reactivity in the development of deoxycorticosterone hypertension in rats with hereditary diabetes insipidus (DI). Circulation **62:** 111, 1980

33. Overbeck HW: Vascular responses to cations, osmolarity, and angiotensin in renal hypertensive dogs. Am J Physiol **223:** 1358, 1972

34. Overbeck HW, Pamnani MB, Akera T, Brody TM, Haddy FJ: Depressed function of a ouabain-sensitive sodium-potassium pump in blood vessels from renal hypertensive dogs. Circ Res **38:** 48, 1976

35. Pamnani MB, Clough DL, Haddy FJ: Altered activity of the sodium-potassium pump in arteries of rats with steroid hyper-

tension. Clin Sci **55:** 415, 1978

36. Clough DH, Pamnani MB, Overbeck HW, Haddy FJ: Decreased myocardial Na, K-ATPase in rats with one-kidney Goldblatt hypertension (abstr). Fed Proc **36:** 491, 1977

37. Shibata S, Kurahashi K, Kuchii M: A possible etiology of contractility impairment of vascular smooth muscle from spontaneously hypertensive rats. J Pharmacol Exp Ther **185:** 406, 1973

38. Greenberg S, Bohr DF: Enhanced contractility of portal veins from spontaneously hypertensive rats. Circ Res **36** and **37:** 208, 1975

39. Noon JP, Rice PJ, Baldessarini RJ: Calcium leakage as a cause of the high resting tension in vascular smooth muscle from spontaneously hypertensive rat. Proc Nat Acad Sci USA **75:** 1605, 1978

40. Webb RC, Bohr DF: Vascular reactivity in hypertension: altered effect of ouabain. Experientia **36:** 220, 1980

41. Webb RC, Bohr DF: Mechanism of membrane stabilization by calcium in vascular smooth muscle. Am J Physiol **235(5):** C227, 1978

42. Webb RC, Bhalla RC: Altered calcium sequestration by subcellular fractions of vascular smooth muscle from spontaneously hypertensive rats. J Mol Cell Cardiol **8:** 651, 1976

43. Moore L, Hurwitz L, Davenport GR, Landon EJ: Energy-dependent calcium uptake activity of microsomes from the aorta of normal and hypertensive rats. Biochim Biophys Acta **413:** 432, 1975

44. Kwan CY, Belbeck L, Daniel EE: Abnormal biochemistry of vascular smooth muscle plasma membrane as an important factor in the initiation and maintenance of hypertension in rats. Blood Vessels **16:** 259, 1979

45. Hulthén UL, Bolli P, Amann FW, Kiowski W, Bühler FR: Enhanced vasodilation in essential hypertension by calcium channel blockade with verapamil. Hypertension **4** (suppl II): II-26, 1982

46. Lederballe Pedersen O, Mikkelsen E, Anderson KE: Effects of extracellular calcium on potassium and noradrenaline induced contractions in the aorta of spontaneously hypertensive rats. Increased sensitivity to nifedipine. Acta Pharmacol Toxicol (Copenhagen) **43:** 137, 1978

47. Jones AW: Altered ion transport in vascular smooth muscle from spontaneously hypertensive rats: influences of aldosterone, norepinephrine, and angiotensin. Circ Res **33:** 563, 1973

48. Webb RC, Bohr DF: Potassium relaxation of vascular smooth muscle from spontaneously hypertensive rats. Blood Vessels **16:** 71, 1979

49. Abel PW, Hermsmeyer K: Sympathetic cross-innervation of SHR and genetic controls suggests a trophic influence on vascular muscle membranes. Circ Res **49:** 1311, 1981