Vascular Muscle Membrane Cation Mechanisms and Total Peripheral Resistance

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SUMMARY Passive and active carrier-mediated transport of sodium across vascular muscle membranes has been suggested to be important in the increased total peripheral resistance found in genetic hypertension. Using manipulations of ion gradients and recordings of ion currents, membrane potentials, and tension, I have found evidence for calcium regulation as the central pathophysiological mechanism in spontaneously hypertensive rats. Increased sodium pump activity, which may be a partial compensation for the increased sodium influx in hypertension, may thus be secondary to altered calcium channel regulation in hypertension. The calcium channel, and the membrane potentials governing it, seem to be the most immediately important membrane mechanisms for hypertension research. (Hypertension 10 [Suppl I]: I-20–I-22, 1987)

Key Words • membrane potential-tension relationship • sodium pump • sodium-calcium countertransport • calcium channels

Evidence exists for several ion transport alterations in vascular muscle in different animal and human forms of hypertension, as has recently been reviewed.1,2 Reviews by Canessa3 and MacGregor and de Wardener4 on ion transport factors affecting red blood cells and kidneys of humans also support the hypothesis that alterations in ion transport due to circulating inhibitors of the Na+-K+ pump can be used in the diagnosis and investigation of hypertension. While the association of intracellular sodium with hypertension has been strong conceptually, the fundamental mechanistic question about their relationship is unanswered.

This report is addressed to reviewing three possible contributors to hypertension. The first is increased passive sodium transport, which may contribute to the increased total peripheral resistance in hypertension by causing intracellular calcium to increase. The second is the active (adenosine 5'-triphosphate-consuming) transport of sodium and potassium that is the main regulatory control mechanism for intracellular sodium. The third is changes in intracellular calcium, either through decreased transport or increased influx through calcium channels, that would directly cause increased arterial contraction and thus hypertension.5,7

Passive Sodium Transport

The possibility that passive sodium transport contributes to the increase in total peripheral resistance found in spontaneously hypertensive rats (SHR), as reflected by the isolated caudal artery segments, was studied recently.8 At present, the most likely among the passive sodium flux mechanisms is Ca2+-Na+ countertransport, as proposed for vascular muscles by Reuter et al.9 and hypothetically linked to hypertension in subsequent publications by Blaustein.10–12

According to the Ca2+-Na+ countertransport hypothesis, the increase in intracellular sodium would be translated into an increase in intracellular calcium because part of the continuous calcium efflux from the resting cell is by way of the countertransport carrier, which depends energetically on the influx of sodium down its electrochemical gradient. Therefore, an increase in intracellular sodium would lead to an increase in intracellular calcium by decreasing the sodium gradient, and therefore decreasing the rate of movement of calcium out of the cell. Furthermore, the hypothesis suggests how a circulating ouabainlike substance contributes to hypertension by leading to an increase in intracellular sodium.13,14

Several important properties and predictions of the Ca2+-Na+ countertransport allow the test of its importance in hypertension. First, the process is passive in all cells where it has been studied. Otherwise, consumption of adenosine 5'-triphosphate would be in excess of what is available.8 Second, the process must be electrogenic (even though it is passive) or it would...
predict a resting intracellular free calcium ion concentration of greater than 200 μM at rest. Third (and important), the Ca\(^{2+}\)-Na\(^{+}\) countertransport mechanism predicts a reversal potential, negative to which the process extrudes calcium (the condition at rest), and positive to which the process results in calcium uptake. The unique predictions of the mechanism are 1) that sudden 90% reduction of extracellular sodium would cause a transient hyperpolarization-contraction, and 2) that return to normal sodium would lead to a transient depolarization-relaxation. Notice that the membrane potential and tension association is opposite to the usual sense. This unique prediction of Ca\(^{2+}\)-Na\(^{+}\) countertransport mechanism makes it possible to test the hypothesis.

In cardiac muscle, the Ca\(^{2+}\)-Na\(^{+}\) countertransport process is prominent and easily demonstrated. Transition from the normal extracellular sodium of 145 to 10 mM leads to a transient hyperpolarization of 5 to 8 mV and an increase in diastolic tension (equivalent to about half the tension generated by a cardiac action potential). In contrast, arterial muscle cells from muscular arteries (caudal and basilar) show neither a hyperpolarization nor a contraction on transition into 10-mM sodium solution, thus failing to show any indication of a Ca\(^{2+}\)-Na\(^{+}\) countertransport mechanism. A similar conclusion was recently reached for regulating arteries (contrasted with aorta) by Mulvany et al., who were able to find Ca\(^{2+}\)-Na\(^{+}\) countertransport only after extremely high sodium loading requiring hours in high concentrations of ouabain. It thus appears likely that the Ca\(^{2+}\)-Na\(^{+}\) countertransport mechanism may not play an important role in the increased total peripheral resistance found in at least the SHR form of hypertension. However, it remains possible that passive sodium influx may be abnormally increased through other mechanisms (e.g., sodium leak influx).

Active Sodium Transport

If the explanation for increased total peripheral resistance is not Ca\(^{2+}\)-Na\(^{+}\) countertransport, what is the relationship of intracellular sodium to contraction? The active Na\(^{+}\),K\(^{+}\)-adenosine triphosphatase (ATPase), which is the known principal regulator of intracellular sodium, is a candidate. The Na\(^{+}\),K\(^{+}\)-ATPase, also known as the sodium pump, is active (consuming adenosine 5'-triphosphate) and electrogenic (contributing several millivolts of membrane potential) in vascular muscle. The sodium pump is inhibited by ouabain and ouabainlike substances. While the membrane potential-tension relationship is normal, the two related defects in SHR vascular muscle cells that could lead to abnormally increased total peripheral resistance are 1) abnormal (increased) norepinephrine sensitivity and 2) abnormal sodium pump. The sodium pump alteration is related to contraction experimentally by the increased magnitude of hyperpolarization on return to potassium after exposure to 0 potassium. The fluxes of sodium, potassium, and chloride are all known to be increased. The importance of the sodium pump for tension appears to be through membrane potential in response to higher than normal rates of sodium influx. The pump in hypertensives operates at an increased activity level, contributing more than normal to resting membrane potential. Concurrently, intracellular potassium is diminished. The increased electrogenicity of the sodium pump under these conditions might suggest an altered ratio of sodium to potassium transport. Such a suggestion, made to account for electrophysiological data, has recently been supported by ion flux data.

This membrane potential alteration leads to exaggerated contraction because the sodium pump can maintain membrane potential negative enough to remain in the relaxed state only when membrane resistance is relatively high. Because the sodium pump generates its potential by current (in the form of ions) driven across the cell membrane resistance (which equates with voltage by Ohm's law), the pump's contribution to membrane potential becomes less under the influence of norepinephrine (which decreases membrane resistance). The smaller potassium gradient in SHR arterial muscle cells becomes evident as membrane resistance is decreased. The increase in sodium pump activity in hypertension can thus explain the greater reactivity found in SHR, despite the fact that hyperpolarization itself is in the opposite direction to explain increased contraction.

The sodium pump could be a compensation for membrane alterations of hypertension, even though sodium is not the most damaging abnormality. The dissociation of contraction from intracellular sodium levels recently was reported by other workers. For example, Aalkjaer et al. reported that tension in small arteries is highly correlated with membrane potential but shows no significant correlation with intracellular sodium. That report argues against a direct causal relationship between intracellular sodium and arterial muscle contraction.

Calcium Channel Regulation

What is the major factor important for contraction? The answer to the question, which is also fundamental to excitation-contraction coupling in vascular muscle, is likely to involve calcium. Alterations in calcium entry or exit might well lead to changes in tension without intervention by another ion. Calcium enters the cell through voltage- and time-dependent calcium channels, which we studied recently using tight-seal pipettes. Among several interesting properties of isolated single cells from rat mesenteric arteries was the indication that calcium channels may be modulated. That is, in the presence of a calcium agonist, such as BAY k 8644, calcium currents become greater than can be found with norepinephrine, possibly suggesting that further modulated calcium channels are present. Perhaps the modulation, which may be caused by interactions with calcium channel protein, is deficient in SHR. The resulting excessive influx of calcium increases total intracellular levels, which may in turn induce an increase in the opening of potassium chan-
nels (through the calcium-induced potassium conductance mechanism). Furthermore, if calcium influx were great enough to cause depolarization, there would also be sodium influx, perhaps causing the increased sodium present in vascular muscle and circulating blood cells in certain stages of human and animal hypertension. The increased influxes of all other cations would also be explained as secondary to depolarization caused by excess opening of calcium channels.

Conclusions

With the data so far available, the most important modulators of tension in arterial muscle (and therefore total peripheral resistance) would appear to be a membrane potential and intracellular calcium levels. The many correlations of hypertension with increased intracellular calcium have been reviewed recently. There is no known noncorrelation between intracellular calcium and increased total peripheral resistance. Furthermore, it has been demonstrated that calcium antagonists appear to normalize blood pressure not just decrease it, suggesting that the calcium channel variable might be central to understanding the pathophysiology of hypertension.

With the recent evidence that hypertension is not always associated with increased intracellular sodium and the evidence for calcium as an undeniable central element, it seems reasonable to suggest that the focus of research should be shifted to studies of membrane regulation of intracellular calcium levels. It is the focus of research should be shifted to studies of membrane regulation of intracellular calcium. It is perhaps causing the increased tension development in arterial smooth muscle. Philos R Soc Lond [Biol] 1973;265:87–94

References

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