Sodium ions, calcium ions, blood pressure regulation, and hypertension: a reassessment and a hypothesis

Blaustein, Mordecai P. Sodium ions, calcium ions, blood pressure regulation, and hypertension: a reassessment and a hypothesis. Am. J. Physiol. 232(3): C165–C173, 1977 or Am. J. Physiol: Cell Physiol. 1(3): C165–C173, 1977. – An attempt is made to elucidate the cellular mechanisms which may account for the well-documented correlation between sodium metabolism and peripheral vascular resistance. As a starting point, the evidence that the Na electrochemical gradient across the vascular smooth muscle cell plasma membrane (sarcolemma) plays an important role in cell calcium regulation is reviewed. Because there is significant resting tension ("tone") in most resistance vessels, the ionized Ca²⁺ level ([Ca²⁺]i) in the smooth muscle fibers in these vessels must be maintained above the contraction threshold. Consequently, the Ca transport system in the sarcolemma, presumably an Na–Ca exchange mechanism, must be set so as to hold [Ca²⁺]i at this suprathreshold level. Any change in the Na gradient will then be reflected as a change in [Ca²⁺]i and, therefore, in steady vessel wall tension and peripheral resistance. The correlation between Na metabolism and hypertension could then be accounted for if a circulating agent, perhaps the "natriuretic hormone," affects the Na gradient (across the sarcolemma) and, therefore, [Ca²⁺]i and tension.

peripheral vascular resistance; sodium-calcium exchange; vascular smooth muscle

The association between sodium ions and hypertension has been well documented in the biomedical literature. For example, hypertension may be induced or exacerbated by a large sodium intake (22, 46, 60, 61) and can frequently be treated by limiting sodium intake (20, 51) and/or by administering natriuretics (1, 51). Hypertension can also be induced by (sodium retaining) mineralocorticoids in experimental animals (60) and in man (as consequence of primary aldosteronism (65) or Cushing's syndrome (61)). Despite this widely recognized correlation between Na metabolism and hypertension, the underlying mechanisms have escaped elucidation. However, a number of recent observations appear to provide some important clues to these mechanisms. The fundamental concepts are: 1) that Ca ions are the immediate trigger for contraction in vascular smooth muscle (28, 55), as in other types of muscle (21, 66); and 2) that Na ions play a critical role in the maintenance of Ca balance in vascular smooth muscle. The influence of Na ions on Ca regulation will be briefly reviewed, with emphasis on the data from vascular smooth muscle. This information will then be incorporated into a model which may help to explain the significance of Na in the maintenance of arterial tone and, consequently, the relationship between Na ions and hypertension.

Sodium-Calcium Exchange and Regulation of Intracellular Ca in Smooth Muscle

An early clue to the relationship between Na ions and tension stems from the work of Leonard (47), who found that removal of external K, or treatment with cardiac glycosides, causes an increase in tension in arterial strips. Even in normal man, peripheral vascular resist-
ance is directly increased by low (therapeutic) doses of cardiac glycosides (48). One common factor in these manipulations (K depletion and treatment with cardiac glycosides) is an inhibition of cell membrane sodium pumps, leading to a net gain of Na by the cells (34).

The first direct observation of a correlation between Na ions and muscle tension was that of Wilbrandt and Koller (70), who found that cardiac ventricular muscle tension depended on the ratio $[Ca^{2+}]_o/[Na^{+}]_o$ (where the square brackets refer to the respective ion concentrations; subscripts o and i will be used to denote the extracellular and free sarcoplasmic concentrations, respectively). This phenomenon was explored in more detail by Niedergerke (50) and by Reuter and his colleagues (33, 54); in sum, their observations indicated that net Ca entry in cardiac muscle was promoted by lowering $[Na^{+}]_o$ and/or raising $[Na^{+}]_i$. Reuter and Seitz (54) also noted that a significant fraction of the Ca efflux required the presence of Na in the bathing medium.

Similar observations were subsequently made in isolated arterial smooth muscle: the replacement of external Na (by Li, choline, or sucrose) was found to induce reversible contractures (8, 40, 53, 57). These contractures are associated with a net gain of Ca by the tissue (53) and are a result of both a decrease in Ca efflux (53) and an increase in Ca influx (53, 64), which occur on withdrawal of external Na.

The tracer data clearly show that the smooth muscle fibers are permeable to Ca: therefore, because a large electrochemical gradient for Ca, favoring inward movement, is normally maintained across the plasma membranes of these fibers (cf. ref 7, 8, and equation 1), the fibers must be capable of extruding Ca by an “active” (energy requiring) process. Certain crucial experiments (18, 53) indicate that external Na plays an important role in this extrusion process: when tension has been increased by Ca loading (e.g., by treatment with norepinephrine or with Na-deficient, Ca-containing media), complete and rapid relaxation requires the presence of Na in the bathing medium.

Comparable observations on the effects of internal and external Na on Ca fluxes have been made in a variety of other tissues from both vertebrates and invertebrates (7). Nevertheless, it is only fair to mention that the consensus of opinion regarding the role of Na-Ca exchange is not unanimous. For example, van Breemen and his colleagues (19, 63) have concluded that Na-Ca exchange does not play a role in Ca transport in taenia coli (but compare ref 47a)—despite their observation that lowering external Na (Fig. 4 of ref 19) or raising internal Na (Fig. 10 of ref 63) causes these muscle fibers to gain Ca.

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**Fig. 1.** Effect of external Na on relaxation of vascular smooth muscle. Tension in a rabbit aortic strip (record A) was raised by a 24-min exposure to Na-free choline-Tyrode solution (all 137 mM NaCl replaced by choline chloride) containing 1.8 mM CaCl₂; beginning of record A indicates tension during last 8 min of this treatment period. Then, at a, bathing medium was replaced by a similar, but Ca-free choline solution containing 0.5 mM EGTA (ethylene glycol-bis(β-aminoethyl ether)-N,N'-tetraacetate); tissue slowly began to relax, but relaxation was only about 75% complete after 20 min. At this point (b), tissue was again exposed to choline-Tyrode containing 1.8 mM CaCl₂. Tension rose (starting at b) to level shown at beginning of record B (a continuation of record A; there is an 8-min gap between c and beginning of record B). At d, choline-Tyrode was replaced by standard Na-Tyrode, which contained 137 mM NaCl and 1.8 mM CaCl₂. Note more rapid and complete relaxation with Na (and Ca) present in bathing medium. Dashed line indicates base-line tension level; resting load was 0.5 g. Two records were photographically superimposed; artifacts in records (at 4-min intervals) were caused by solution changes. Temperature = 37°C (M. P. Blaustein and H. Reuter, unpublished experiment).

**Fig. 2.** Model of a countertransport “carrier” mechanism which simultaneously exchanges 3 Na⁺ for 1 Ca²⁺. Y form of carrier denotes configuration with Na-binding sites exposed to external medium and Ca-binding site exposed to sarcoplasmic fluid; Z form of carrier has Na sites on sarcoplasmic side and Ca site facing external medium. Carrier can rotate through plane of membrane only when free (i.e., fully unloaded), as Y or Z, or when fully loaded, as Na₃YCa or CaZNa₃.
The kinetics of the Na-coupled Ca transport system have been studied primarily in squid axons (3, 5, 9, 10, 12, 14) and in giant barnacle muscle fibers (2, 16, 26, 56), because of the conveniently large size of the individual cells (nerve and muscle fibers, respectively) in these preparations. The general conclusion (11) is that the Na-dependent Ca extrusion mechanism evolved fairly early on in the history of the animal kingdom and has been retained, with minimal modification, through the subsequent evolution of the higher animals, including man. The kinetic data indicate that the probable stoichiometry of the Na-Ca exchange is: one Ca\(^{2+}\) ion extruded in exchange for three entering Na\(^{+}\) ions (11, 14, 56). The kinetic data also indicate that the transport mechanism requires simultaneous loading of internal and external ion binding sites (5, 9, 10). A hypothetical model of this simultaneous exchange system is diagramed in Fig. 2; it may be contrasted with the more frequently discussed sequential or shuttle mechanism (14, 56).

Regardless of the precise details of the underlying mechanism, the main feature of this exchange is that the Na entering the cell moves down its electrochemical gradient and the energy, which is thereby released, can then be harnessed, through the coupled exchange, to move Ca out of the cell against its electrochemical gradient. As already indicated, the transport mechanism can also apparently operate in the reverse direction: that is, it can move Na out and Ca into the cell if the ion gradients are appropriately set (3). With a stoichiometry of three Na\(^{+}\) for one Ca\(^{2+}\), a coupled exchange of this type could maintain a Ca concentration gradient across the plasma membrane (sarcolemma) given by:

\[
\frac{[\text{Ca}^{2+}]_{i}}{[\text{Ca}^{2+}]_{o}} = \frac{[\text{Na}^{+}]_{o}^3}{[\text{Na}^{+}]_{i}^3} \exp \frac{-V_{M}F}{RT}
\]

where \(V_{M}\) is the membrane potential, and \(F\), \(R\), and \(T\) are Faraday's number, the gas constant, and absolute temperature (degrees Kelvin), respectively. The inclusion of the exponential term is a consequence of the net entry of one positive charge when three Na\(^{+}\) ions enter and one Ca\(^{2+}\) exits (12, 13, 15, 49). With a Na gradient ([Na\(^{+}\)]\(_o)/[Na\(^{+}\)]\(_i\)) of about 15 and a membrane potential of about \(-40\) mV, the Na-Ca exchange mechanism could, in principle, maintain a limiting Ca gradient ([Ca\(^{2+}\)]\(_o)/[Ca\(^{2+}\)]\(_i\)) of about \(10^4\) without benefit of direct energy input from ATP. Although ATP does affect the kinetics of Na-Ca exchange in squid axons (4, 5, 9, 10, 27), it is not absolutely required (9, 14, 27) and may not, in fact, power the exchange (10). Consequently this problem need not concern us here, and the direct contribution of ATP (if any) to the maintenance of the Ca gradient (equation 1) will, therefore, be ignored in the ensuing discussion.

Role of Na Ca Exchange in Maintenance of Vascular Smooth Muscle Tone

The sensitivity of vascular smooth muscle to changes in [Na\(^{+}\)]\(_o\) and [Na\(^{+}\)]\(_i\) is indicated by the fact that tension in this tissue increases measurably within 1–2 min of removal of external Na (Fig. 1 and Fig. 3A and B) or K (Fig. 3C) or of exposure to ouabain (Fig. 3D and cf. ref 47, 48). By way of contrast, invertebrate (barnacle) skel-

FIG. 3. Effect of cations and of ouabain on tension of rabbit aortic strips. Resting load was 0.5 g in all cases. A: increase in tension due to exposure (at a) to Na-free Li-Tyrode solution (all 137 mM NaCl replaced by LiCl). Tissue relaxed promptly when returned to standard (Na-containing) Tyrode (at b). B: between records A and B, aortic strip was incubated for 30 min in K-free Ca-free Na-containing Tyrode to load muscle with Na. Exposure to K-free Na-free Li-Tyrode (with 1.8 mM CaCl\(_2\)) at c, caused a more rapid and greater rise in tension than seen in A. Standard Tyrode was reintroduced at d. C: data from another aortic strip showing effect of external K removal (at e and e') on tension; solutions all contained 1.8 mM CaCl\(_2\). Strip promptly relaxed when external K was added back (at f). Temperature = 37°C. Calibration (A–C): vertical (tension) = 2 g (A and B) or 1 g (C); horizontal (time) = 1 min. D and D': data from a third aortic strip illustrating effect of 10 \(^{-6}\) M ouabain, introduced into bathing solution at g, on tension. Between h and h' (9.3 min), ouabain was washed out with four changes of fresh Tyrode solution. Calibration: vertical (tension) = 1 g; horizontal (time) = 1 min. (M. P. Blaustein and H. Reuter, unpublished experiments).
etal muscle and quiescent cardiac muscle take many minutes or hours to develop contractures when treated with ouabain; and harnecine muscle fibers do not develop contractures when external Na is removed unless the fibers have been previously loaded with Na (16; unpublished data). The \([\text{Ca}^{2+}]_{\text{i}}\)-tension diagram in Fig. 4 provides an important clue to the explanation for this marked difference in sensitivity to alteration of the \([\text{Na}^+]_{\text{i}}/[\text{Na}^+]_{\text{i}}\) ratio. Cardiac muscle, of course, relaxes completely between beats, and barnacle muscle can also relax completely when incubated in an appropriate "normal" physiological salt solution (38). Under these circumstances, \([\text{Ca}^{2+}]_{\text{i}}\), must be well below \(10^{-7}\) M, the threshold concentration for contraction (cf. Fig. 4); even if lowering \([\text{Na}^+]_{\text{i}}\), or raising \([\text{Na}^+]_{\text{i}}\), moves Ca into the fibers, a considerable amount of Ca will have to enter before the contraction threshold is reached, especially if the sarcoplasmic reticulum in these fibers buffers the \([\text{Ca}^{2+}]_{\text{i}}\), near the normal resting level (i.e., well below \(10^{-7}\) M).

A very different situation is encountered in vascular smooth muscle, however. Some resting tension (tone) is normally maintained in most resistance vessels (30, 55, 64). This implies that \([\text{Ca}^{2+}]_{\text{i}}\), must be constantly maintained above \(10^{-7}\) M (cf. Fig. 4) because there is no reason to suspect that other factors such as the intracellular Mg or ATP (adenosine-5'-triphosphate) concentrations are limiting (e.g., 42, 55). Under these circumstances, because the contractile tissue is balanced on the rising phase of the \([\text{Ca}^{2+}]_{\text{i}}\)-tension curve, even a small change in \([\text{Ca}^{2+}]_{\text{i}}\), will be manifested as a change in tension. Consequently, if \([\text{Ca}^{2+}]_{\text{i}}\), is constant, and if Na-Ca exchange plays an important role in regulating the Ca gradient across the sarcolemma, as implied above, changing the \([\text{Na}^+]_{\text{i}}/[\text{Na}^+]_{\text{i}}\), ratio should rapidly alter \([\text{Ca}^{2+}]_{\text{i}}\), and, therefore, tension. The relatively sparse sarcoplasmic reticulum (24) (as compared to frog skeletal muscle), which must normally buffer \([\text{Ca}^{2+}]_{\text{i}}\), in the range of \(10^{-7}\) to \(10^{-6}\) M delimited by the rising portion of the curve in Fig. 4, may be able to compensate only partially for the entering Ca (see below). These considerations lead to the conclusion that Ca transport across the sarcolemma, by means of Na-Ca exchange, may play a critical role in the maintenance of \([\text{Ca}^{2+}]_{\text{i}}\), and resting vascular smooth muscle tone.

**Sodium Balance, Na Ca Exchange, and Hypertension**

It is generally recognized that most forms of hypertension are associated with an increased peripheral resistance due to maintained abnormal constriction of the small "resistance vessels" (29; but see ref 37). Thickening of the vessel walls and consequent narrowing of the lumina may contribute to the maintenance of the chronic hypertensive state. However, Tobian (59) has stressed the fact that increased vascular smooth muscle tone must play an important role: hypertension is usually present before the vessel wall changes occur and, in some forms of renal hypertension, the blood pressure can return to normal after treatment, even though the vessel walls throughout the body remain thickened. There is no evidence, to date, that alterations in the vascular smooth muscle contractility (i.e., a change in the shape of the \([\text{Ca}^{2+}]_{\text{i}}\)-tension curve of Fig. 4 or a shift of the curve to the left along the \([\text{Ca}^{2+}]_{\text{i}}\), axis) are involved. In the absence of such evidence, the most straightforward assumption is that changes in tone reflect changes in \([\text{Ca}^{2+}]_{\text{i}}\), and that a rise in the mean \([\text{Ca}^{2+}]_{\text{i}}\), may be the "final common path" by which most, if not all, hypertension is produced. This assumption is consistent with the conclusion of Greenberg and Bohr (36) that the altered reactivity of smooth muscle fibers in the veins of spontaneously hypertensive rats is a consequence of elevated \([\text{Ca}^{2+}]_{\text{i}}\),. In view of the aforementioned association between Na ions and hypertension, the next step is to explore, in semiquantitative terms, the interrelationship between Na ions and the Ca gradient.

If Na-Ca exchange does underlie net Ca transport, a simple calculation may serve to illustrate the importance of the Na gradient in maintaining \([\text{Ca}^{2+}]_{\text{i}}\),. Taking approximate values for \([\text{Na}^+]_{\text{i}}\), \([\text{Na}^+]_{\text{i}}\), and \([\text{Ca}^{2+}]_{\text{i}}\), of 150, 10, and 2.5 mM, respectively, and a resting membrane potential of \(-40\) mV, the value of \([\text{Ca}^{2+}]_{\text{i}}\), calculated from equation 1 is \(1.5 \times 10^{-7}\) M, which corresponds to a tension of about 14% of maximum tension (cf. Fig. 4). Let us now assume that the Na pump is partially inhibited (e.g., with a low concentration of ouabain) so that \([\text{Na}^+]_{\text{i}}\), increases by, for example, 5%, to a new steady value of 10.5 mM; if \([\text{Ca}^{2+}]_{\text{i}}\), \([\text{Na}^+]_{\text{i}}\), and \(V_{\text{M}}\) remain constant, \([\text{Ca}^{2+}]_{\text{i}}\), will increase by 15% to \(1.7 \times 10^{-7}\) M (equation 1). According to the \([\text{Ca}^{2+}]_{\text{i}}\)-tension diagram in Fig. 4, these new values (summarized in Table 1) correspond to a tension of about 21% of maximum—an increase of about 50%, when \([\text{Na}^+]_{\text{i}}\), is in

![FIG. 4. Effect of concentration of free (ionized) Ca2+ on tension developed by glycerinated vascular smooth muscle fibers from hog carotid artery. Conditions: temperature, 20°C; 150 mM KCl, 20 mM histidine buffer (pH 6.6), 5 mM ATP, and 5 mM Mg, 4 mM EGTA in control. Free [Ca2+] was varied by changing ratio Catotal/EGTAtotal appropriately. Curve was redrawn from Fig. 1 of Filo et al. (28). A virtually identical curve was obtained with individual glycerinated psoas (striated) muscle fibers (28).](http://ajpcell.physiology.org/ by 10.220.33.1 on August 27, 2017)
creased by only 5% (an increment which cannot be accurately detected with currently available methods).

Although recent studies (18, 32, 53) have explored the role of Na-Ca exchange in Ca regulation and tension development in vascular smooth muscle, this exquisite sensitivity to changes in [Na+]i has not been emphasized.

The preceding calculations ignore the possible contribution of the sarcoplasmic reticulum to intracellular Ca regulation. A model which may provide a more realistic picture of Ca distribution in vascular smooth muscle fibers is diagramed in Fig. 5. For convenience, all of the intracellular Ca buffering (sarcoplasmic reticulum, mitochondria, sarcoplasmic proteins, etc.) is lumped into the compartment labeled sarcoplasmic reticulum because all of the Ca buffers may be expected to behave in similar fashion except for quantitative differences in buffering capacity. Of course, only those buffers (or sequestering sites) with a very high affinity for Ca will play a significant role here.

The model (Fig. 5) also shows the main routes of entry and exit of Na and Ca across the sarcolemma. The k's refer to the apparent rate coefficients (23) for the Na and Ca movements: Na and Ca influx from the external medium, primarily through the voltage-sensitive conductance pathways of the action-potential mechanism (6, 44, 45, 64), are indicated by k1 and k2, respectively. The Na-K exchange pump (1 in the diagram) is responsible for Na extrusion (with Na rate coefficient k-,) while Ca exits primarily via Na-Ca exchange (transport system 2), with Ca rate coefficient k2. (Note that Na movements via Na-Ca exchange probably account for only a minor fraction of the total Na fluxes. For simplicity, only the predominant pathways for Na and Ca movements are shown, although the k's actually refer to the total unidirectional movements of the respective ion species.)

Rate coefficient k3 refers to Ca sequestration by the ATP-dependent Ca pump of the sarcoplasmic reticulum (39) (3 in Fig. 5), while k4 is the rate coefficient for Ca leak from the sarcoplasmic reticulum to the sarcomplasm. The model does not provide for direct transfer of Ca from the sarcoplasmic reticulum to the extracellular fluid. The scanty evidence available (there is none for vascular smooth muscle) is inconsistent with a direct transfer of this type: release of Ca from the sarcoplasmic reticulum into the sarcomplasm, by caffeine, enhances the Na-dependent Ca efflux from barnacle muscle (56) — even though the Ca concentration in the sarcoplasmic reticulum is, presumably, reduced.

The steady-state conditions for the model of Fig. 5 are:

\[ J_{Na}^i = J_{Na}^o \]  

and, since \[ J_{Na}^i = k_1 [Na^+]_o \], then \[ k_1 [Na^+]_o = k_{-1} [Na^+]_i \]  

and \[ k_2 [Ca^{2+}]_o = k_{-2} [Ca^{2+}]_i \]  

and \[ k_{-3} [Ca^{2+}]_i = k_3 [Ca^{2+}]_{SR} \]  

where the \( J_{Na} \) and \( J_{Ca} \) terms are the unidirectional fluxes of Na and Ca, respectively, across the plasma membrane; the \( J_{SR} \) terms refer to the fluxes of Ca from sarcoplasm to sarcoplasmic reticulum (\( J_{SR}^o \)) and from sarcoplasmic reticulum to sarcoplasm (\( J_{SR}^i \)). The concentration of ionized Ca\(^{2+}\) in the sarcoplasmic reticulum is [Ca\(^{2+}\)]\(_{SR}\).

Returning to the example given above (cf. Table 1), the effects of inhibition of the Na pump can now be reexamined in greater detail. We will assume that a low dose of a cardiac glycoside is administered, sufficient to inhibit the Na pump (i.e., reduce \( k_{-1} \)) by about 5%. Then, since \([Na^+]_o/\[Na^+]_i = k_{-1}/k_1\), and since \([Na^+]_i\) is maintained constant (in the intact animal, primarily by renal regulatory processes), \([Na^+]_o\), will increase by about 5%— from 10.0 to 10.5 mM, according to the example summarized in Table 1. The increase in \([Na^+]_o\), will tend to increase Ca influx by "reversed" Na-Ca ex-
change) and decrease Ca efflux (by displacing internal Ca from the transport mechanism); in kinetic terms, these effects may be represented by an increase in $k_2$ and a decrease in $k_{-2}$. The new steady state will be reached when $[Ca^{2+}]_{SR}$ is correspondingly increased (see equation 3a), assuming that there is no change in $[Ca^{2+}]_{SR}$. Now, as $[Ca^{2+}]_{i}$ increases, some of the entering Ca will be taken up by the sarcoplasmic reticulum, in accordance with equation 4a. If the new steady-state values of $[Na^{+}]_{i}$ and $[Ca^{2+}]_{i}$ are, respectively, 10.5 mM and 1.7 $\times$ 10$^{-3}$ M (Table 1), $[Ca^{2+}]_{SR}$ will equal $([Ca^{2+}]_{i} - [Ca^{2+}]_{SR})$ (equation 4a), or about 0.9–9 $\times$ 10$^{-3}$ M if the ratio, $k_{-3}/k_3$, is about 500–5,000 as in skeletal muscle sarcoplasmic reticulum (39). Assuming that $k_3$ and $k_{-3}$ do not change significantly when $[Na^{+}]_{i}$ and $[Ca^{2+}]_{i}$ are increased slightly, the foregoing calculation implies that, if the sarcoplasmic reticulum accounts for only about 5% of the intracellular volume (24) in frog skeletal muscle the sarcoplasmic reticulum, including terminal cisternae accounts for about 18% of the intracellular volume (52)), total cell Ca will increase by about 4–40 mM fiber water. This increment, which may amount to, at most, about a 4%/M change in total cell Ca (about 1,000–1,500 M fiber water as measured by the "lanthanum method" (35, 53)), would be difficult to detect with currently available methods. Although the sarcoplasmic reticulum can buffer intracellular Ca, it is not an infinite sink for Ca. The long-term regulation of $[Ca^{2+}]_{i}$, must therefore be manifested in the sarcosome transport system, with the extracellular fluid serving as the "infinite" Ca source or sink. In vascular smooth muscle, with $[Ca^{2+}]_{i}$, maintained above the contraction threshold, this means that long-term regulation of tension is also manifested in the sarcosoma Ca transport system.

The anticipated response to a signal (perhaps depolarization (24)) to release Ca from the sarcoplasmic reticulum further illustrates why this organelle can regulate "short term," but not steady-state $[Ca^{2+}]_{i}$. When $k_3$ is suddenly increased (so that the ratio $k_3/k_{-3}$ is now greater than $[Ca^{2+}]_{i}/[Ca^{2+}]_{SR}$), there will be net movement of Ca from the sarcoplasmic reticulum to the sarcosome, and $[Ca^{2+}]_{i}$ will increase, as will tension (cf. Fig. 4). But now, because the original steady-state level of $[Ca^{2+}]_{SR}$ is exceeded, net extrusion of Ca across the sarcosome will occur, via Na-Ca exchange, and the Na which enters will be extruded by the sodium pump. Some of the Ca will also be recycled through the sarcoplasmic reticulum because of the Ca pump represented, in Fig. 5, by $k_{-3}$. If the increase in $k_3$ is brief, the original steady-state conditions will be reestablished—presumably within a few seconds or minutes. If, however, the increased level of $k_3$ ($= k_1$) is maintained, a new steady state will be established, with $[Ca^{2+}]_{SR} = k_3/k_{-3}$ (see equation 4a), and with $[Ca^{2+}]_{i}$ back at its initial level and $[Ca^{2+}]_{SR}$ at a reduced level; according to equations 1–4a, this is the obvious consequence of altering only rate parameter $k_3$, when the

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2 Even if the sarcoplasmic reticulum accounts for only half of the cell's Ca buffering capacity, the maximum expected change in total cell Ca would be only about 8%.

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extracellular pools of Na and Ca are very large, and $[Na^{+}]_{i}$, and $[Ca^{2+}]_{i}$, are held constant by renal and other regulatory processes. The time required to approach the steady state will, of course, be governed by the relative values of $k_{-2}$, $k_{-3}$, and $k_{-1}$. The foregoing considerations indicate that, because the Ca store in the sarcoplasmic reticulum and the Ca buffering capacity are limited, the rate-coefficient ratios, $k_3/k_{-3}$ and $k_2/k_{-2}$ play a critical role in the regulation of steady-state $[Ca^{2+}]_{i}$; factors which influence these ratios may, therefore, be important determinants of vascular smooth muscle tension (and blood pressure). The action potential is an example of one such factor: it may increase the permeability of the sarcosome to Na (44, 45) (primarily an effect on $k_1$) and perhaps to Ca (6, 45) (primarily an effect on $k_2$). With $[Na^{+}]_{i}$ and $[Ca^{2+}]_{i}$ constant, increased time-averaged values of $k_1$, and/or $k_2$, will tend to increase the mean $[Ca^{2+}]_{i}$, (cf. equations 1, 2a, and 3a). (In addition, of course, action potentials may raise $[Ca^{2+}]_{i}$, by triggering the release of Ca from the sarcoplasmic reticulum into the sarcosome (24).)

An interesting possibility is that some forms of hypertension may be the consequence of (pathologically) increased passive leak of Na into vascular smooth muscle fibers—equivalent to an increase in $k_1$, in the model of Fig. 5. There is evidence that in some hypertensive patients (67, 69), and in spontaneously hypertensive rats (31), the erythrocytes are excessively leaky to Na; it has been suggested that the plasma membranes of other types of cells, including vascular smooth muscle fibers (43, 68), may be similarly affected in these hypertensives. The hypertension of these patients and animals could then be accounted for by the Na and Ca interactions described in equations 1 and 2, increasing $k_1$, would cause an increase in $[Na^{+}]_{i}$, and, consequently, in $[Ca^{2+}]_{i}$, thereby inducing an increase in steady tension (Fig. 4). The striking sensitivity of the transport system to changes in $[Na^{+}]_{i}$, mentioned above, implies that a small change in $k_1$, may have a large effect on resting tone. Moreover, the amount of Ca sequestered in the sarcoplasmic reticulum would also increase (see equation 4a); the increased reactivity (17, 41, 43, 69) of vascular smooth muscle from hypertensive animals and man could then be explained by the release of a constant fraction, but increased amount (as compared to controls) of Ca from the sarcoplasmic reticulum, by vasoconstrictor agents.

### Hypothesis for Correlation Between Na Intake and Hypertension

The concepts mentioned above provide a basis for speculation about the correlation between Na balance and hypertension. The physiological response to a large salt load may be taken as an example: there is now considerable evidence that a circulating hormone, the so-called "third factor" or "natriuretic hormone," may promote Na excretion in response to an Na load (25). This hormone must either inhibit the active transport of Na from the renal tubular epithelial cells into the peritubular fluid or enhance the (passive) back flux of Na into the tubular lumen.
If the Na pumps in other cells, including those of vascular smooth muscle cells, are also influenced by this hormone then, at the same time that the renal epithelial cell Na pumps are inhibited, so, perhaps, are those of the vascular smooth muscle cells. In these cells, slightly reduced Na extrusion (corresponding to a decrease in $k_1$, of Fig. 5) would raise $[Na^+]_{i}$, and thus decrease the $[Na^+]_{m}/[Na^+]_{i}$ gradient across the plasma membrane (equation 2a). (Note that a comparable result would be expected if the hormone enhanced passive Na movements—and affected, primarily, $k_1$ in the model of Fig. 5.)

An inverted response might be anticipated in a hypotensive patient treated with a natriuretic drug (e.g., a thiazide) and a restricted-Na diet. The total body store of Na would fall, initially, in association with a reduction in blood plasma volume. The plasma Na concentration may remain fairly constant, however, and a steady Na balance may be achieved despite maintained therapy. This must mean that renal mechanisms which tend to conserve Na are called into play in order to counterbalance the natriuretic effect of the therapeutic agent. One important mechanism for Na conservation is a decrease in the glomerular filtration rate. In addition, however, we would expect the plasma concentration of the natriuretic hormone to be reduced; this should result in enhanced active Na transport (into the peritubular fluid) by the renal tubular epithelial cells, or decreased Na back flux (into the tubular lumen). In this case, again assuming that the hormone acts in a comparable manner on renal epithelial cells and vascular smooth muscle fibers, the $[Na^+]_{i}$ in the muscle fibers would be expected to fall, and the $[Na^+]_{m}/[Na^+]_{i}$ gradient across the sarcolemma would, therefore, rise (due to an increase in $k_1$, or a decrease in $k_1$).

In both situations, the changes in the Na gradient should alter $[Ca^{2+}]_{i}$ (equation 1) and tension (Fig. 4) and, thereby, influence peripheral resistance. An increase in peripheral resistance would be expected when the Na gradient across the sarcolemma of the vascular smooth muscle fibers is decreased. A decrease in peripheral resistance would be expected when the Na gradient is increased.

Conclusions

An effort has been made to account for the well-documented correlation between Na metabolism and peripheral vascular resistance in terms of known physiological mechanisms. The evidence that Na-Ca exchange plays a critical role in the Ca$^{2+}$-tension curve; even small changes in the Na gradient may, therefore, be reflected by corresponding changes in tension (cf. equation 1 and Fig. 4). By way of contrast, the sarcoplasmic reticulum may play an important role in transient tension changes, but not in steady tension regulation. These considerations imply that the study of Na (and Ca) permeability and transport in vascular smooth muscle may be a fruitful approach to the mechanisms underlying long-term blood pressure regulation and hypertension.

ADDENDUM

Haddy and Overbeck (37a) have recently provided a well-documented review of evidence that a humeral agent, perhaps the natriuretic hormone, may play an important role in the etiology of "volume expanded hypertensions" via an inhibitory effect on the sodium (i.e., Na-K exchange) pump of cardiovascular muscle. It should be readily apparent that this view dovetails very nicely with the hypothesis put forth in the present article. The ideas discussed in this article and an earlier one (8), concerning the role of the Na-Ca exchange in the regulation of intracellular Ca and tension in vascular smooth muscle, indicate how the Na pump in this tissue may be linked to tension regulation.

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