**Brief Review**

**Flow Regulation of Vascular Tone**

Its Sensitivity to Changes in Sodium and Calcium

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All hypotheses concerned with the basis of human or animal models of hypertension must provide an explanation of the increase in peripheral vascular resistance—the common attribute of the hypertensive state. They must also provide experimental evidence for, or at least contain a reasonable suggestion regarding the basis of, the decreased diameter of the small arteries and possibly small veins seen in this condition. Furthermore, these causative processes should be of sufficient magnitude to account for the decreased diameter. Possible causative mechanisms have frequently been investigated in isolated blood vessels. Usually, the vascular tissues studied—in vitro preparations, cultured vascular smooth muscle cells, or subcellular biochemical fragments—have originated from the larger, usually elastic arteries (see below). Research has emphasized the effects of contractile agonists of various types, cellular depolarization, perivascular nerve activation, and various experimental manipulations of the ionic environment.

**Resistance Artery Tone: Ionic Sensitivity**

During the past decade, in part because of advances in technology, it has been established that blood vessel properties related to vascular tone change as vascular diameter gets smaller. Furthermore, changes that occur in the arteries from one bed as they subdivide are not necessarily indicative of the changes that occur in another. There are differences in the density and nature of the innervation, in the subtype of a number of smooth muscle and endothelial cell surface receptors, and in their coupling mechanisms. Quantitative changes in the influence of endothelium-derived factors on tone also occur. Of major functional significance, the influence of intraluminal pressure and flow on vascular wall tone becomes increasingly important, perhaps even dominating other vascular tone-regulating systems in some regional beds. An increase in intravascular pressure by stretching the vascular wall initiates myogenic constriction. The dominant response to intraluminal flow observed by all who have investigated it is dilation (for review, see References 1 and 5 through 9). Two laboratories studying a number of arteries and veins find that flow under certain circumstances can also cause contraction. In most reports, when it has been investigated, flow-induced dilation is prevented by procedures designed to selectively destroy the endothelium or inactive endothelial processes (for review, see References 1 and 7 through 9). One laboratory reported that flow-induced dilation in a variety of beds is only partly obtunded by morphologically confirmed endothelium removal. The rarely reported response of flow contraction can be elicited undiminished after endothelium removal. The reasons for these differences in observations, whether they are due to technical or diameter, regional, or species differences, await resolution.

In contrast to large arteries, small arteries exhibit sizable levels of intrinsic tone in vivo, which is roughly inversely proportional to their diameter. Pressure and flow represent important contributors to and regulators of this tone at rest. Longitudinally conducted excitation in arteries of all sizes also probably contributes. Because of these differences in the basis and regulation of tone in large and small arteries, it would seem prudent when investigating the functional basis of the increase in peripheral resistance in hypertension to include in those features examined experimentally the tone-regulating mechanisms thought to be significant in smaller arteries.

Many proposals have been made regarding the possible roles of sodium ($Na^+$) and calcium ($Ca^{2+}$) in hypertension, and most experiments on blood vessels related to these roles have been made on large arteries (see below). In a number of instances, the magnitude of the manipulations in the concentrations of $Na^+$ and $Ca^{2+}$ used to investigate these possibilities has been well outside the range encountered in vivo. This experimental strategy has been adopted on the presumption that the functional changes resulting from small changes in ion concentration particularly over a long period of time can be understood by making larger experimental changes over shorter periods of time and then extrapolating the effect of the change to smaller alterations. In general, the ionic dependence of the unique mechanisms that produce or influence small artery tone—pressure, flow, and conduction—has escaped serious attention.

The objective of this commentary is to compare the sensitivity of flow-induced alterations in tone to changes in extracellular $Na^+$ and $Ca^{2+}$ to the sensitivity of specific ionic mechanisms that have been proposed to contribute to or participate in the regulation of vascular tone. It is not the purpose of this article to try to relate the reported sensitivity of hypertension to dietary levels...
of Na\(^+\) and Ca\(^{2+}\) to the cationic sensitivity of flow-related tone but to argue that this vascular response deserves at least consideration in relation to this condition.

**Sodium and Calcium Dependence of Flow-Dependent Dilation**

In this section, the findings by this author contained in a recent\(^{16}\) and in other published articles\(^{17,18}\) on the sensitivity of flow-induced dilation to Na\(^+\) and Ca\(^{2+}\) are summarized. As mentioned above, there is abundant evidence—from both in vivo and in vitro experimentation, with vessels from both the arterial and venous side of the circulation, from a number of species, and from a considerable number of laboratories—that intraluminal flow can influence vascular tone. This possibility has been known since the observations of Schretzenmayer\(^{19}\) on the vasculature of skeletal muscle. There are differences in some experimental findings, particularly related to the cellular mechanisms involved, but common agreement that intraluminal flow through a local action on the blood vessel can regulate vascular tone.

Flow-initiated dilation is diminished by reduction in extracellular Na\(^+\) in the physiological saline solution from normal levels of 150 to 119 mmol/L. Proportional lowering of Ca\(^{2+}\) from 1.60 mmol/L, which is commonly found in physiological saline solution, to 1.28 mmol/L results in a quantitatively similar reduction (Fig 1a and 1b). It is argued that, because flow-induced contraction has a similar sensitivity to Na\(^+\) and there is evidence that flow-induced effects may be related to the Na\(^+\)-Ca\(^{2+}\) ratio,\(^{16}\) these effects of changes in these ions reflect characteristics of an extracellular flow sensor. The immediate thrust of the present commentary is to demonstrate that the observed sensitivity to changes in cationic concentration is not found in other mechanisms in which Na\(^+\) and Ca\(^{2+}\) play a regulatory role.

**Dependence of Some Vascular Wall Processes on Extracellular Sodium and Calcium Concentration**

In this section, the effects of changes in extracellular sodium and calcium concentrations on some ion transport, flux, and exchange mechanisms and on intracellular ion concentrations, many of which have been proposed to be involved in vascular tone regulation, are summarized. Original published data have been redrawn to a common horizontal scale to facilitate comparison of their sensitivity to particular changes in ionic concentration. For the most part, these studies were carried out on in vivo vascular preparations, tissue culture systems, and biochemical preparations from large arteries. The effects of changes in sodium below 150 mmol/L and in Ca\(^{2+}\) over the range of 0 to 10.0 mmol/L are shown. It is relatively rare that sodium concentrations in excess of 150 mmol/L are examined experimentally because of the problem in maintaining the constancy of osmotic pressure and ionic strength.

**Changes in Extracellular Sodium**

**Sodium-calcium exchange.** Sodium-calcium exchange has been variously assessed—by studying ion exchange in sarcoplasmic vesicular preparations and in tissue culture and as presumably reflected in changes in various parameters of wall force development.

Fig 1 includes the results of several in vitro studies of changes in arterial wall force to alteration in extracellular sodium concentration. Using the rat aorta, Blaustein et al\(^{20}\) (Fig 1c) have documented changes in rates of contraction and relaxation with an alteration in extracellular Na\(^+\). Contraction rate decreased and relaxation increased as sodium concentration was experimentally increased to physiological levels. For both processes, the maximum rate of change occurred at approximately 25 mmol/L. There was little alteration in these responses with changes in Na\(^+\) concentration close to approximately normal levels. The relaxation rate of the artery rings of Wistar-Kyoto rats changed little with extracellular sodium alteration between 50 and 150 mmol/L. Greater changes were seen in the contraction rate, but they were comparatively small between 100 and 140 mmol/L Na\(^+\). The size of the change in both parameters was greater in the spontaneously hypertensive rat.\(^{21}\) In this context, Mulvany et al\(^{22}\) found that decreases in sodium to 100 mmol/L had no significant effect on the rate of agonist relaxation of rat mesenteric resistance artery. Effects of changes in sodium between 50 and 150 mmol/L on the increased calcium- and potassium-induced (after its prior absence) relaxations of rat tail arteries were trivial.\(^{23}\)

As sodium was varied around the upper ranges of concentration studied—close to physiological levels—calcium uptake into sarcoplasmic vesicles from rat myometrium\(^{24}\) enriched in plasma membranes did not change significantly. The concentration of sodium (by inspection) at which calcium uptake was half-maximal was approximately 6 mmol/L. There were comparable results in dog mesenteric arteries,\(^{25}\) when the concentration was 16 mmol/L (Fig 1d), and comparable results have been published by Nachsch and Kongsmunt.\(^{26}\)

Changes in extracellular sodium influenced the peak rate of calcium efflux that occurs in response to angiotensin II in cultures of rat aorta. The relation was hyperbolic, with a dissociation constant (K\(_{d}\)) of 32 mmol/L.\(^{27}\) These results suggested little change with sodium increases of more than 100 mmol/L.

Changes in extracellular sodium in the region of its physiological level had little effect on cytoplasmic free calcium in primary and passaged cultures of rat aortic muscle cells, whether or not they were treated with ouabain, or on their calcium content\(^{28}\) (Fig 1e). The latter observations are consistent with the absence of change in the size of norepinephrine-induced contraction of small artery segments in vitro with change in extracellular Na\(^+\).\(^{27}\) By the same token, there was little change in the maximum serotonin-evoked tension in rat aorta and (not shown) mesenteric artery segments\(^{28}\) over higher sodium concentrations (Fig 1f).

**Sodium-hydrogen exchange.** Several different measurements considered to reflect sodium-hydrogen exchange activity have been used after acid load: the initial rate of recovery of pH in Sprague-Dawley rat aortic vascular smooth muscle,\(^{30}\) the rate of pH recovery of human smooth muscle cells\(^{31}\) (Fig 1g), and the rate of change of pH in aortic cells of Wistar-Kyoto and stroke-prone spontaneously hypertensive rats\(^{32}\) using the fluorescence dye 2',7'-bis(2-carboxyethyl)-5(6)-carboxyfluorescein (BCECF). In all instances, the curves relating these measurements to external sodium show little or no alteration when concentration changes were...
Bevan Vascular Tone Sensitivity to Sodium

Figure 1. Panels a and b: Plots show relations between flow-induced contraction (a) and dilation (b) of resistance artery branches of rabbit central ear artery and sodium concentration in physiological saline solution (PSS). Responses are expressed as percentage of tone increase to norepinephrine (NE, $10^{-6}$ mol/L). Relaxation was elicited in arteries precontracted to this NE concentration. Sodium in PSS was changed by substitution of NaCl by either sucrose or n-methyl-d-glucamine (see Reference 17). Panel c: Plot shows relation between $[\text{Na}^+]_o$, and relative rate of tension development contraction in rat aorta A (•) (see Reference 20). Panel d: Plot shows changes in rate of $\text{Ca}^{2+}$ uptake in sarcoplasmic vesicles loaded with different concentrations of Na$. Data represent mean±SEM of 3 to 9 experiments (see Reference 25). Panel e: Plot shows effect of varying $[\text{Na}^+]_o$ on $\text{Ca}^{2+}$ uptake and constant into monolayers of cultured rat aortic vascular smooth muscle cells exposed to varying $[\text{Na}^+]_o$. Each point represents mean±SEM of seven determinations (see Reference 28). Panel f: Plot shows effect of $[\text{Na}^+]_o$ on contractile response of aortic rings to 30 μmol/L 5-hydroxytryptamine (5-HT). Error bars indicate ±SEM where errors extend beyond symbols (see Reference 29). Panel g: Plot shows dependence of recovery of human smooth muscle cells from 15 mmol/L NH$_4$Cl-induced intracellular acidosis in CO$_2$/HCO$_3$-buffered PSS (pH 7.4) on extracellular Na concentration ($[\text{Na}^+]_o$). Each point represents average of eight rats; SEM is indicated by verticals. Redrawn assuming normal values of $[\text{Na}^+]_o$ of 142 mmol/L (see Reference 37). For further details, please consult original articles.
in excess of 100 mmol/L. The concentration of sodium (by inspection) at which recovery from a load was half-maximal was 15 to 25, 10 to 5, and 25 to 30 mmol/L, respectively.

Sodium, potassium, and chloride cotransport. In one series of experiments designed to assess this mechanism, potassium influx into cultured human fibroblast cells changed relatively little with alterations in external sodium greater than 100 mmol/L. The sodium concentration at which the rate of change was half-maximal was 40 to 60 mmol/L (Fig 1h). To our knowledge, comparable experiments have not been undertaken in vascular smooth muscle.

Other parameters in relation to change in extracellular sodium. In monolayers of rat aortic vascular smooth muscle, intracellular sodium changes only a little, approximately 3 mmol/L, with an increase of external sodium from 100 to 140 mmol/L. Probably the change is not significant in chick embryo fibroblasts. The latter investigators found no variation in sodium incorporation into leukocytes over this range. Replacing external sodium had little effect at concentrations of 100 mmol/L and higher on the angiotensin-evoked calcium efflux from cultured rat aortic cells. The potassium-induced relaxation of strips of rat tail artery, after potassium-free conditions, was unchanged over the range of 50 to 150 mmol/L NaCl. K+-stimulated Na+ efflux from aortas of rats changed little over a similar range.

Friedman has long argued that the cellular transmembrane distribution of sodium is a major determinant of blood pressure. In a recent study, he and coworkers both increased and decreased plasma sodium in mice by intraperitoneal dialysis of various solutions. When corrected for changes in osmotic pressure, increases in plasma sodium resulted in increases in blood pressure, both systolic and diastolic (Fig 1l). The rise of pressure paralleled the change in plasma sodium. Lowering sodium had an opposite effect. The sodium gradient, defined as concentration difference across the cell membranes (defined differently from Friedman), increased as the sodium was raised and decreased as it was lowered. A most interesting feature of these results is the sensitivity of the vascular response to changes in plasma sodium.

Changes in Extracellular Calcium

Lowering extracellular calcium. The concentration of calcium in different physiological saline solutions varies but is of the order of 1.6 mmol/L. Flow-induced contraction and dilation increased as calcium was increased toward this physiologically equivalent concentration (Fig 2a). A somewhat comparable effect was seen for nitric oxide production by the rabbit thoracic aorta (Lopez-Jaramillo et al, Fig 2b). The similarity between the dependence of nitric oxide production and flow-induced dilation on calcium (the latter may result from the synthesis of an endogenous factor derived from muscle — muscle-derived relaxing factor) prompted the speculation that its production may also be calcium dependent. Over the calcium range of 0.16 to 2.5 mmol/L, the half-life of acetylcholine-induced hyperpolarization resulting presumably from endothelium-derived hyperpolarizing factor increased from less than 0.5 to almost 3 minutes (Fig 2c).

There is some inconsistency in the reported change in membrane potential with increasing calcium concentration up to the level found in physiological saline solution. The transmembrane potential of cultured rat aortic smooth muscle cells became more negative up to concentrations of 1.6 mmol/L (Fig 2d). Only three calcium levels were examined, however. By contrast, the membrane potential of rabbit carotid artery muscle cells became less negative, changing from levels of approximately -75 mV at concentrations of Ca2+ close to zero to less than -40 mV when it was 1.7 mmol/L (Fig 2c). This depolarization was associated with an increase in wall tension. In another study the membrane potential of the same artery with and without acetylcholine (10-5 mol/L) did not vary over a similar range of calcium (Fig 2c). Intracellular calcium did not change when external calcium was increased from 0.25 to 1.8 mmol/L. Intracellular sodium was found not to change when extracellular calcium was increased up to 1.8 mmol/L in cultured rat aortic smooth muscle cells. This was confirmed in cells cultured from the carotid artery of the same species.

Increases of calcium up to approximately 2 mmol/L caused constriction of cannulated first- or second-order arterioles from the hamster cheek pouch in response to extracellular K+ (40 mmol/L) (Fig 2f). However, most of the change occurred between calcium concentrations of 0 and 0.5 mmol/L. The peak response to calcium was observed at even lower calcium levels in the presence of phenylephrine. The relative absence of change in α-adrenergic receptor-mediated agonist response with changes in calcium close to the physiological range is consistent with our own findings. Hanson and Bohr did not study Ca2+ concentrations less than 1.6 mmol/L but determined that active tension developed by femoral arteries from a variety of rat preparations changed very little with concentration increases up to 4.0 mmol/L. The calcium-activated vascular reactivity dose-response relation has been assessed in normotensive and various models of hypertensive rats. There was relatively little change as a function of calcium concentration. The same authors found that the relaxation to potassium (after its prior absence) increased up to a Ca2+ concentration of 4 mmol/L. K+ efflux from aortas of normotensive rats fell as Ca2+ was raised to 1.0 mmol/L, a level that was maintained with further Ca2+ elevation. In vascular smooth muscle cultures from Sprague-Dawley rats, carotid artery sodium and potassium contents remain constant for calcium increases up to 4 mmol/L.

Raising extracellular calcium. A variety of vascular smooth muscle cell parameters diminish as external calcium is increased above the levels considered to be physiological. The concentration at which this decrease occurs is variable. Flow-induced dilation decreases at concentrations greater than 1.6 mmol/L at levels that do not influence the relaxation to acetylcholine (Fig 2a). Siegel and colleagues described parallel changes in hyperpolarization and relaxation with Ca2+ increases up to approximately 2.5 mmol/L, which then reversed with further increases (see Fig 2e for membrane potential changes). The contraction of normotensive but not hypertensive rat aortas to 40 mmol/L potassium fell off at calcium concentrations of 4 mmol/L and higher. As mentioned above, K+ efflux and carotid artery sodium and potassium contents did not change as external calcium was raised to 4 mmol/L. The relaxation to K+...
In summary, changes in sodium and calcium close to the "physiological range" appear to have little influence on mechanisms in the blood vessel wall reported to be involved in the establishment of vascular tone and its regulation. Exceptions to this in the case of calcium include the effect of its increase up to 1.6 mmol/L on flow-induced and acetylcholine dilation, nitric oxide production, and possibly membrane potential. With respect to the sodium changes, only flow-induced responses are altered with modest alterations in this ion concentration close to physiological levels. One laboratory has reported the exquisite sodium sensitivity of mouse blood pressure.

**Theory of Extracellular Effects of Changes in Sodium and Calcium**

The data presented above support the contention that flow-induced influences on vascular tone are particularly sensitive to changes in extracellular sodium, at least close to physiological levels. Other vascular smooth muscle cell parameters, including intracellular sodium and calcium, are seemingly well maintained in the face of small deviations in extracellular sodium (Figs 1 and 2). One possible implication of this finding is that the sodium-dependent feature—the one on which flow depends—is not associated with recognized intracellular or transplasmalemmal ionic events but could be primarily associated with mechanisms outside the cell.

The majority of sodium in the blood vessel wall, variously estimated to be 70% to 90%, is extracellular (Jones and Siegel et al). Friedmann adapted ion-exchange methods to quantitatively estimate sodium distribution and found that 55% to 70% of the wall sodium is extracellular and probably bound to glycosaminoglycans. Siegel described four sites of location of sodium: in the extracellular fluid, at two distinct extracellular binding sites, and as a rapid exchanging fraction that may vary with flow conditions.
represent the ion in pinocytic vesicles. Sodium, calcium, and other cations are mostly bound to extracellular polyionic cations—the glycosaminoglycans in the vessel wall that form an enveloping sheath around each cell. This sheath covering has connections through the cell membrane to the cytoskeleton and with the extracellular supporting vascular matrix. Sodium competes with other monovalent and divalent ions for sites on the sulfated and carboxylated polysaccharides that are intrinsic components of the polyanionic macromolecules.

Studies of water conductivity show that these glycosaminoglycan molecular systems, although they form only a relatively small percentage by weight of the extracellular matrix, contribute to the low value found in this type of tissue, presumably as a result of their interaction with collagen. Friedman graphically describes the blood vessel wall as containing “smooth muscle cells . . . laced together by a network of collagen fibers floating in a gel-like polysaccharide sac.” It is this sac that presumably has a high sodium content.

The cation binding capacity of the artery wall is not constant, and some causes of variation have been summarized by Simon. Extracellular sodium accumulates early in the course of experimental renovascular and steroid hypertension. Its concentration increases in the prehypertensive state in arteries and during hypertension in the veins. There are arguments that this non-pressure-dependent change may result from circulating factors. It has been speculated that the high sodium content in the vasculature can influence the effects of some constrictor factors and may be a predisposing influence in hypertension.

Changes in vascular wall sodium have commonly been presented or discussed in the context of hypertension. Presumably, there is some physiological variation in plasma sodium levels in this condition that would be reflected by changes in free sodium in the paracellular matrix. The sodium content in the vasculature can influence the effects of some constrictor factors and may be a predisposing influence in hypertension.

Changes in vascular wall sodium have commonly been presented or discussed in the context of hypertension. Presumably, there is some physiological variation in plasma sodium levels in this condition that would be reflected by changes in free sodium in the paracellular matrix. An increase in sodium would be associated with increased cellular water content. Tobian and Bunion referred to this excessive presence in hypertension as “water logging.” There would most likely be changes in arterial cellular and mechanical properties and thus, conceivably, a response to physical distorting stimuli, as well as in agonist sensitivity and contractility. Changes in free sodium in the paracellular matrix could alter the transmembrane sodium gradient and thus change reactivity to a number of agonists, including angiotensin (for discussion, see Reference 4). However, on the basis of our summary (see above), this change probably would not depend on presently recognized cellular mechanisms. Our proposal is that changes of sodium in the glycocalyx could change responsiveness of the vascular wall to flow and also possibly to pressure and that these changes might lead to secondary changes in response to agonists.

Sodium Binding and Charge Distribution

Manning (summarized in Comper and Laurent) has elaborated a theoretical framework to explain the electrostatic interaction of cations with anionic polysaccharides. Four phases of condensed counterions on the microion unit are envisaged. The first ("IV" in Fig 3) represents cation binding to specific ion sites; "I" represents the next outer zone of microion-microion interactions, when condensed counterions have little or no translational mobility relative to the polyelectrolyte; "II" represents a highly residual field due to the net charge of the polyelectrolyte modifying the behavior of "free ions"; and "III" represents some modification of interaction between mobile ions. Thus, for example, with sodium overload, not only would there be changes at the binding sites themselves but also in the influence exerted over varying distances beyond the polyanionic macromolecule.

Gustavsson et al have elaborated our ideas regarding the interaction of sodium and calcium and other cations with glycosaminoglycans. Using nuclear magnetic resonance techniques to study specific polyanionic proteoglycans, they have found that calcium can cause conformational changes in these molecules, resulting in change in the mobility of the polysaccharide chains possibly due to changes in intramolecular or intermolecular cross-linkage. This change in turn influences the binding of sodium. Thus, calcium is involved in more than a competitive interaction with sodium at the primary binding site; it can also influence the conformation of the polysaccharide complex.

The Flow Sensor and Sodium

Fig 4 summarizes the flow mechanism. In 1991 Bevan and Siegel proposed that the glycosaminoglycans may represent the essential element of the flow sensor in the blood vessel wall. This proposal was based on a number of parallel observations by Siegel and colleagues (and prior references) on the characteristics of sodium and calcium binding to multichain peptidoglycans using nuclear magnetic resonance and on our own observations on the ionic dependency of flow-induced changes in tone in resistance arteries (these are detailed in References 16, 18, 55, and 58).

(1) Flow-induced constriction and dilation are uniquely and equivalently dependent on extracellular sodium, suggesting that the sodium-dependent site is associated with a common pathway. The majority of sodium is extracellular, bound to the extracellular matrix, specifically the polyanionic mucopolysaccharides and associated cell-supporting systems, and is the main counterion. Other sodium-dependent systems do not share this sensitivity.

(2) Flow-induced effects can be elicited not only during intraluminal flow in the intact artery but also after endothelium removal and by flow over the external
artery surface. Thus, flow sensing is not limited to any one cellular layer. This conclusion is consistent with flow sensing by the vascular wall matrix.

(3) Enzymes that disrupt the extracellular matrix influence the flow effect. Pohl et al. demonstrated this in the intact coronary artery bed of the dog based on the use of neuraminidase.

(4) Flow-induced changes in tone seem to depend on the ratio of sodium to calcium concentrations; i.e., the response to flow does not reflect the expected physiological antagonism seen between these ions for binding sites. Over a comparable concentration range there is cooperativity and binding between sodium and calcium on proteoglycan systems.

(5) During nuclear magnetic resonance studies of ion binding at constant calcium concentrations, shaking of the solution, resulting in fluid movement and shear stress of the suspended molecules, resulted in a change in sodium binding.

Glycosaminoglycans have several interesting properties that make them candidates for flow-sensing molecules. They exhibit viscoelastic properties. External forces stretch these polymer chains, leading to molecular deformation. On removal of the applied force, they relax to their original state. In addition, these molecules not only have cationic binding sites—by virtue of their carboxylate, sulfate ester, and sulfamino groups, for which calcium and sodium are the prime contenders—but there is calcium cross-linking of the helical chains. Siegel et al. based on their nuclear magnetic resonance studies, have concluded that deformation leads to loss of intramolecular interactions and at the same time increases the number of cationic sites, which reflects the opening up of sites previously occluded.

But glycosaminoglycans are not the only candidate molecules. Extracellular matrix proteins involved in cellular adhesion have multiple epidermal growth factor-like repeats that appear to be sites for high-affinity calcium binding. Such proteins include laminin, thrombospondin, and tenascin. There is evidence that calcium binding to these proteins can cause local and also possibly global conformational changes in their structure (for review, see Reference 60).

The extracellular matrix is not only a structural system that connects with the cytoskeleton but appears to have the potential to influence a variety of cellular functions. Certain glycosaminoglycans, for example, proteoglycan, are constituents of the vascular smooth muscle cell membrane. Proteoglycan is a cell surface integrated protein. Some matrix proteins, for example the integrins, are not only adhesive molecules but also can function as a signaling mechanism, influencing cellular ionics processes through a variety of signaling systems.

Tenuous and speculative as these considerations are, they do represent possible mechanisms whereby shear stress acting on extracellular systems might influence cellular function through cationic-sensitive mechanisms.

**Summary**

Our hypothesis is that flow-through hydraulic drag or shear stresses the extracellular elements in the vascular wall. When the endothelium is intact, this results in the release of endothelium-derived relaxing factor and other substances, e.g., prostanoids, from the endothelium. As in some reports, after inhibition of nitric oxide synthase, flow effects are still observed although diminished; the shear effect is extended mechanically to the subendothelial tissues. Shear causes conformational changes in the glycosaminoglycans by extending them from a randomly coiled aggregated state to a more elongated condition along the line of flow. This elongation and the consequent exposure of an increased number of cationic binding sites on the glycosaminoglycans...
cans lead to changes in sodium binding. The extent of the conformational change is influenced by the concentration of calcium, an ion that both competes with sodium at specific binding sites but possibly cross-links the polysaccharide chains of the protein saccharide complex. These complex interactions might account for the cooperative, nonantagonistic interaction of sodium and calcium over the physiological concentration range. Sodium binding is influenced by changes in external sodium concentration, and this presumably accounts for the sodium sensitivity of the flow response. Although glycosaminoglycans are possibly the most studied in this regard, they are not the only candidates. Other extracellular proteins, either in conjunction with glycosaminoglycans or independently, might be involved. By mechanisms not yet identified, these changes are signaled to the cell. We have proposed that in part, at any rate, this may be related to the sodium concentration gradient. 18

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References


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