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Role of potassium in regulating blood flow and blood pressure

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Haddy, Francis J., Paul M. Vanhoutte, and Michel Feletou. Role of potassium in regulating blood flow and blood pressure. *Am J Physiol Regul Integr Comp Physiol* 290: R546–R552, 2006. doi:10.1152/ajpregu.00491.2005.—Unlike sodium, potassium is vasoactive; for example, when infused into the arterial supply of a vascular bed, blood flow increases. The vasodilation results from hyperpolarization of the vascular smooth muscle cell subsequent to potassium stimulation by the ion of the electrogenic Na^+-K^+ pump and/or activating the inwardly rectifying Kir channels. In the case of skeletal muscle and brain, the increased flow sustains the augmented metabolic needs of the tissues. Potassium ions are also released by the endothelial cells in response to neurohumoral mediators and physical forces (such as shear stress) and contribute to the endothelium-dependent relaxations, being a component of endothelium-derived hyperpolarization factor-mediated responses. Dietary supplementation of potassium can lower blood pressure in normal and some hypertensive patients. Again, in contrast to NaCl restriction, the response to potassium supplementation is slow to appear, taking ~4 wk. Such supplementation reduces the need for antihypertensive medication. "Salt-sensitive" hypertension responds particularly well, perhaps, in part, because supplementation with potassium increases the urinary excretion of sodium chloride. Potassium supplementation may even reduce organ system complications (e.g., stroke).

endothelium-derived hyperpolarization factor; Na^+-K^+-ATPase; potassium channels

POTASSIUM IS THE MOST ABUNDANT intracellular ion, and its preeminence there is guaranteed by Na^+-K^+-ATPase in the plasma membrane (also known as the sodium pump or Na^+-K^+ pump). Indeed, the sodium pump is the active transport system that is responsible for maintenance of the transmembrane gradients of Na^+ and K^+. Because these gradients provide energy for several essential cellular functions (e.g., control of membrane potential, cell volume, and pH), it is not surprising that this transport protein is present in all animal cells. This includes the cells in blood vessels (e.g., endothelial cells, smooth muscle cells, and adrenergic nerves) and in the tissue that surrounds them (e.g., myocardial muscle, skeletal muscle, brain).

NA$^+$-K$^+$-ATPase AND BLOOD FLOW

Na^+-K^+-ATPase is composed of noncovalently linked α and β subunits. Four different isoforms of the α subunit ($\alpha 1$ to $\alpha 4$) and three isoforms of the β subunit ($\beta 1$ to $\beta 3$) have been identified in mammalian cells. The enzymatic function has been totally assigned to the α subunit, which also contains the

binding sites for ATP and the cardiac glycoside ouabain. The β subunit serves as a chaperone molecule to facilitate the appropriate insertion of the α subunit in the plasma membrane. In addition, the β subunit modulates the affinity of Na^+-K^+-ATPase for cations. Each combination of α and β subunit produces a functionally active enzyme that possesses distinct affinities for Na^+ and K^+ and different sensitivities for ouabain (46). A third protein, member of the FXYD protein family, which includes the γ-subunit, is stochiometrically associated with the α-β complex and influences the apparent affinity of the enzyme for Na^+ and K^+, as well as to ouabain. In mammalian arteries, both vascular smooth muscle and endothelial cells express the $\alpha 1$ subunit, the housekeeping form of Na^+-K^+-ATPase. However, depending upon the species and/or vascular bed studied, both the endothelial and vascular smooth muscle cells can express the $\alpha 2$ and/or $\alpha 3$ isoforms. In rodents, these isoforms are markedly more sensitive to the inhibitory action of ouabain than the $\alpha 1$ isoform and are activated by an increase in extracellular concentrations of potassium over the physiological range (37, 46, 89). In other

mammal species, the various α isoforms have a high affinity for potassium and would be expected to be near saturation by 5 mM external K^+ concentration. However, the Na^+-K^+-ATPase should not be assimilated to a monotonic regulator of ion transport, the multiple α- and β-isoforms are heavily regulated in a tissue-specific manner, not only by the associated γ-subunits, but also by intracellular messenger-dependent phosphorylations of the α-subunit (2, 9).

Because the Na^+-K^+-ATPase pumps sodium and potassium unequally (three Na^+ for every two K^+), the transport is electrogenic, and thus it produces changes in the membrane potential. It was proposed some time ago that this has important effects on the contractile state of vascular smooth muscle, which can, in turn, influence blood flow and blood pressure (32). For example, when skeletal muscle is activated, the depolarized skeletal muscle cells immediately release potassium into the interstitial space surrounding the arterioles. This stimulates the Na-K pump in the vascular smooth muscle cells and, because of the unequal pumping of sodium and potassium, results in hyperpolarization of the cells, reduced calcium influx into the smooth muscle cells, hence, relaxation and dilatation of the arteriole. The result is increased blood flow to, in part, meet the increased metabolic needs of the contracting skeletal muscle. The sympathetic nerve fibers may also be involved. Potassium increases the uptake of norepinephrine into the sympathetic nerve terminals, leaving less in the cleft. This also promotes relaxation of the vascular smooth muscle and increases blood flow. The concentration range over which potassium exerts these effects is small, a matter of only 0.5 to 4.0 meq/l above resting levels. K^+ also has an inhibitory effect on the exocytotic release of norepinephrine from the adrenergic nerve endings, thus helping to disconnect the working tissues from the homeostatic control exerted by the sympathetic nervous system (73, 78, 87, 88). Similarly, when brain tissue is activated (e.g., spontaneous depolarizations as during seizures), the depolarized cells release potassium into the interstitial fluid and increase brain blood flow by the same mechanism. Functional hyperemia, as seen with salivary gland activation, may share a similar mechanism.

It is easy to demonstrate that potassium is a vasodilator. If it is applied locally, blood flow increases. For example, if an isoosmotic solution of potassium chloride is infused into the brachial artery of the dog at a rate that raises potassium concentration in the arterial blood by 0.5 to 4.0 meq/l, blood flow increases in the area supplied by the brachial artery (20). Similar changes are seen when potassium is infused into the coronary and renal arteries (77). The increase is prompt, substantial, and sustained but does not compare in magnitude to that which can be produced by exercise hyperemia. The appearance of potassium in the venous blood during exercise is prompt and correlates with blood flow, suggesting a more important role in the initiation than during the maintenance of exercise hyperemia, when other factors (e.g., adenosine) may become involved.

Lowering the potassium concentration in blood produces vasoconstriction, but this is more difficult to demonstrate because it requires the interposition of a hemodializer in the arterial blood supply to reduce the concentration (6). Reductions as little as 1 meq/l produce vasoconstriction, and the onset and the offset of the response is prompt. The magnitude of the vasoconstriction is not great, however, and does not

compare to that produced by norepinephrine or angiotensin, for example. The mechanism underlying the constriction involves Na^+-K^+-ATPase inhibition, electrogenic depolarization, increased calcium influx into the vascular smooth muscle cell, and decreased uptake of norepinephrine into sympathetic nerve endings.

Dietary supplementation and restriction of potassium also influence resistance to blood flow through vascular beds, for example, cerebral and renal vascular beds (54). The responses are not prompt and well defined, particularly during supplementation, presumably due to temporal delays and systemic compensatory responses.

Both the vasodilatations and vasoconstrictions produced by potassium in the dog gracilis muscle can be blocked by ouabain (6), indicating that the two responses are related to activity of the Na^+-K^+ pump. In other species and vascular beds, ouabain may not completely block the potassium-induced vasodilatation, suggesting the participation of mechanisms other than electrogenic Na^+-K^+ pumping. Here, the response may be blocked by barium or barium plus ouabain, suggesting the participation of inwardly rectifying K^+ channels.

POTASSIUM CHANNELS AND BLOOD FLOW

Potassium channels help determine the resting membrane potential and regulate cell volume. Because cells maintain a much higher intracellular concentration of potassium than that present in the extracellular medium, the opening of potassium channels induces a change in membrane potential toward more negative values (repolarization or hyperpolarization). They play a key role in many cellular signaling events, including the regulation of smooth muscle tone and blood flow (79). Potassium channels are classified in four subgroups (according to Nomenclature Compendium—International Union of Pharmacology subcommittee on potassium channels): the voltage-gated (K_V), the calcium-activated (K_{Ca}), the two-pore-domain (K_{2P}), and the inward rectifier (Kir) potassium channel families (35).

The inward rectifier family of potassium channels is divided into seven subfamilies (Kir1.0 to Kir7.0), but the following section will only address the Kir2.0 subfamily, which is most relevant to the blood vessel wall. The inward rectification means that the channel conducts potassium current more readily in the cells than out of the cells over a wide range of potentials. When the membrane potential is negative compared with the equilibrium potential for K^+ (E_K), the driving force for the flux of K^+ is in the inward direction. However, for positive membrane potentials (compared to E_K), the outward flow of K^+ through Kir is smaller. Under physiological conditions, the membrane potential of vascular cells is always positive compared with E_K, so it is the relatively small efflux of K^+ that plays a role (24, 64, 69). In the vascular wall, Kir channels are expressed in both the endothelial and the smooth muscle cells (14, 68). The expression of the Kir channel is more abundant in the smooth muscle of autoregulatory vascular beds such as the coronary and cerebral circulations (68, 75). In the general circulation, the expression of the Kir channel appears to increase as the diameter of the artery decreases (39, 67). Kir channels are blocked by micromolar concentrations of barium and certain imidazoline compounds (21, 71).

A unique feature of Kir channels is the effect of extracellular potassium on its gating. A moderate increase in potassium concentration, in the range of 1 to 15 mM, enhances potassium efflux through Kir at physiologically relevant potentials (40, 71). In some arterial smooth muscle cells, this moderate increase in extracellular potassium concentration leads to hyperpolarization and relaxation. This observation is counterintuitive, as the Nernst equation would predict a depolarization of the cells as a result of such an increase in the extracellular K^+ concentration. As the depolarization of vascular smooth muscle cells produces the opening of voltage-dependent calcium channels, a contraction of these cells should follow. However, small increases in the extracellular concentration of K^+ by activating Kir (64) and/or the Na^+-K^+ pump (see above) overcomes the small depolarizing effects linked to the increase in K^+ per se. The net result is hyperpolarization and thus relaxation of the smooth muscle cells. In agreement with the pattern of expression of Kir channels in smooth muscle, potassium-induced Kir channel-dependent relaxations or vasodilatations are prominent in cerebral (16, 59) and coronary arteries (40), as well as in the microcirculation (15), including skeletal muscle arterioles (36, 40). The contribution of Kir channel has also been observed in potassium-induced relaxation of isolated human peripheral arteries, as well as in vivo during potassium-induced forearm vasodilatation (7, 11, 60). The Kir channel most likely involved in potassium-induced relaxation is composed of the Kir2.1 α-subunits, as these relaxations disappear in mice with deletion of Kir2.1 (91). In some arteries, potassium-induced relaxation involves the contribution of endothelial Kir (10).

Therefore, the Kir channel, like the Na^+-K^+ pump, can be regarded as a metabolic sensor producing vasodilation and increases in blood flow when potassium accumulates in the extracellular fluid, for instance, during neuronal activity or exercise.

POTASSIUM AS AN ENDOTHELIUM-DERIVED HYPERPOLARIZING FACTOR

The endothelial cells control the tone of the underlying vascular smooth muscle cells by releasing various relaxing and contracting factors, the former including nitric oxide (NO), prostacyclin, and epoxyeicosatrienoic acids. In addition, the endothelium can regulate the diameter of blood vessels via another pathway that involves the hyperpolarization of vascular smooth muscle. The mechanism of endothelium-dependent hyperpolarizations, once attributed to an elusive endothelium-derived hyperpolarizing factor (EDHF), is understood better. EDHF-mediated responses are triggered by an increase in the endothelial intracellular calcium concentration that is followed by the opening of two populations of potassium channels, the calcium-activated potassium channels of small and intermediate conductance (SK_{Ca} and IK_{Ca}), which results in the hyperpolarization of the endothelial cells. This response is transmitted to the smooth muscle cells by direct electrical coupling through myoendothelial junctions and/or by the accumulation of potassium ions in the intercellular myoendothelial space (3) (Fig. 1).

The endothelium is a cell monolayer, and it would be expected that an efflux of potassium in the lumen of the blood vessel from this small cell mass would be washed away by the flowing blood and be most likely without physiological consequences. However, an efflux of potassium toward the abluminal side can accumulate in the intercellular space between endothelial and smooth muscle cells and reach sufficient levels to activate Kir and the Na^+-K^+ pump on the smooth muscle cells in the immediate vicinity of the endothelial cells releasing K^+. Therefore, K^+ could be an EDHF or contribute to the mechanism of EDHF-mediated responses. This hypothesis was demonstrated successfully in the hepatic and mesenteric arteries of the rat by Edwards et al. (17). These authors provided evidence that IK_{Ca} and SK_{Ca} channels are located on the endothelial cells and that after their activation, K^+ accumulate in the intercellular space between endothelial and smooth muscle cells. The potassium efflux associated with the opening of endothelial K^+ channels, in turn, produces hyperpolarization of the smooth muscle by activating both Kir and the Na^+-K^+ pump on the smooth muscle (17). The contribution of K^+ in EDHF-mediated responses was confirmed in many other arteries (13, 18, 53), including human arteries (4, 85).

In rat arteries, RT-PCR and immunohistochemistry studies indicate that the Kir channel, which is most likely involved in the endothelium-dependent hyperpolarization (relying K^+), is composed of the Kir2.1 α-subunits (19), consistent with the results obtained in the knockout mice (89). The Na^+-K^+ pump activated during these EDHF-mediated responses is not likely composed of α1 subunits, as this isoform is nearly fully activated at the physiological concentration of extracellular potassium, but most likely is formed with α2 and/or α3 isoforms, which in the rat are activated by a rise in extracellular concentrations of potassium from 1 to 15 mM (37, 89) (Fig. 1).

However, in some blood vessels potassium does not evoke, or inconsistently produce, relaxations and hyperpolarizations (8, 12, 70, 92). Therefore, in these blood vessels, the contribution of K^+ in EDHF-mediated responses must be, if anything, minimal.

EDHF AND Kir in DYSFUNCTION

EDHF-mediated responses have been demonstrated unequivocally in various blood vessels from different species, including human, and may play a role in the local control of blood flow especially in the coronary circulation and in the microvasculature (22). Mice with deletion of Kir2.1 die shortly after birth because of a cleft palate and associated respiratory problems (91). Therefore, the potential effect of this deletion on arterial blood pressure cannot be assessed, and conditional knockouts for Kir2.1 will be required to determine whether or not Kir channels play a role in the setting of peripheral vascular resistance and in the physiological control of arterial blood pressure. However, in mice with germ line deletion of endothelial nitric oxide synthase and cyclooxygenase-1 (double knockout), the females are normotensive, while the males have high blood pressure (76). The endothelium-dependent relaxations in resistance arteries taken from female mice are preserved because an EDHF-mediated response compensates fully for the disappearance of endothelial NO and prostacyclin. In the resistance arteries of these female mice, the activation of Kir channels and Na^+-K^+ pump contributes to the EDHF-mediated responses. In contrast, in the corresponding male mice, this compensatory EDHF-mediated mechanism is absent, leading to a severe impairment of the endothelium-dependent
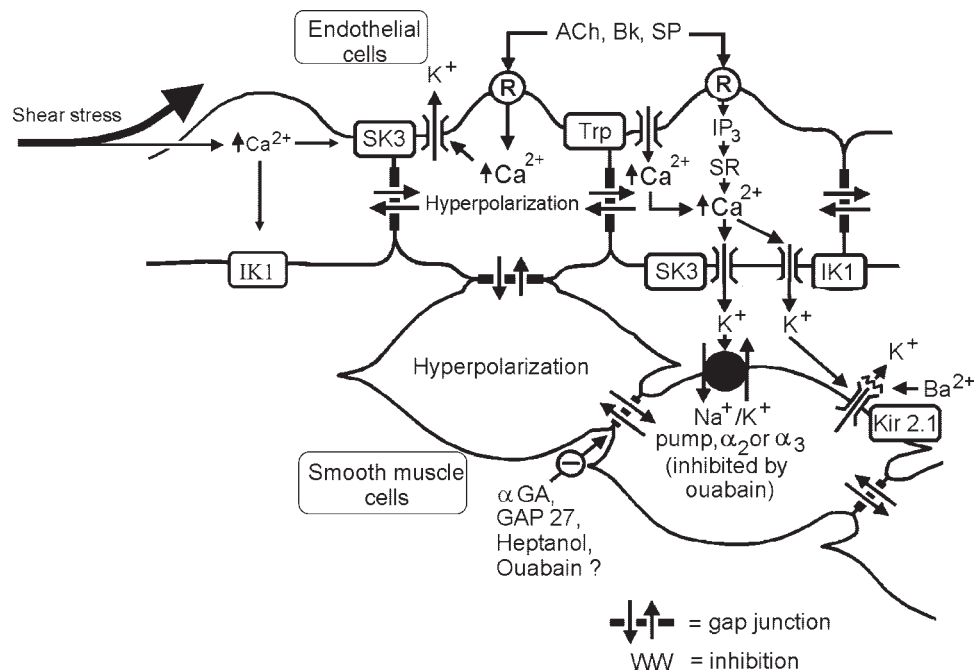
Fig. 1. Potassium and endothelium-derived hyperpolarization factor-mediated responses. Neurohumoral mediators such as ACh, bradykinin (BK), or substance P (SP) activate their respective endothelial receptors (R) that produce an increase in intracellular calcium (Ca^{2+}) via the inositol-trisphosphate- (IP_3) dependent release of Ca^{2+} from the sarcoplasmic reticulum (SR) and an increase in Ca^{2+} entry via the activation of nonspecific cationic channels, most likely from the transient receptor potential channel family (Trp). Physical stimuli, such as shear stress forces, also increase endothelial intracellular calcium concentration. This increase in endothelial intracellular free Ca^{2+} concentration activates calcium-activated potassium channels of small (SK3) and intermediate (IK1) conductance, which hyperpolarizes the endothelial cells. The activation of endothelial potassium channels produces not only the hyperpolarization of the endothelial cells but also an efflux of potassium ions, which accumulate in the intercellular space. The endothelial cell hyperpolarization can be conducted through myoendothelial gap junctions to the underlying vascular smooth muscle cells. The accumulation of potassium ions in the intercellular space can hyperpolarize the smooth muscle cells by activating inwardly rectifying potassium channels (Kir2.1) and Na^+-K^+-ATPase, which are inhibited by barium and ouabain, respectively. The two mechanisms—transmission of the hyperpolarization via gap junction and the accumulation of K^+ (potassium being in essence an EDHF)—are not necessarily mutually exclusive and, in a given blood vessel, they can occur simultaneously, sequentially, or even synergistically. The relative proportion of each mechanism almost certainly depends on numerous parameters, including the state of activation of the vascular smooth muscle, the density of myoendothelial gap junctions, and the level of the expression of the appropriate isoforms of Na^+-K^+-ATPase and/or Kir (3). αGA (glycyrrhetinic acid derivative), Gap 27 (a peptide with a sequence identical to a portion of an extracellular loop of connexins), and heptanol are inhibitors of gap-junction communication. Ouabain at elevated concentrations is no longer a specific inhibitor of Na^+-K^+-ATPase but can also inhibit gap junctions.

relaxations (76). These results suggest that EDHF-mediated responses contribute to the overall regulation of arterial blood ressure and that Kir channels are involved in this phenomenon.

EDHF-mediated responses are altered under various pathological conditions (22). In the spontaneously hypertensive rat, the decrease of the EDHF-mediated conducted vasodilatation has been associated with the suppression of the facilitating role of Kir channels (27). Various other pathological processes decrease the expression and/or the functionality of Kir channels, such as ischemia-reperfusion, diabetes, or chronic alcohol consumption (55, 58, 66, 83), suggesting that the dysfunction of Kir channels can contribute to the alteration of EDHF-mediated responses (when the K^+ is a mediator of these responses) and, therefore, to the overall endothelial dysfunction.

POTASSIUM AND BLOOD PRESSURE

Blood pressure is influenced by the dietary potassium intake, both in normal subjects and hypertensive subjects. The international cooperative INTERSALT study (81) showed that blood pressure tends to be related to urinary potassium excretion and to the ratio of urinary sodium excretion to potassium excretion. Earlier, more localized studies, for example, in Evans County, Georgia, showed that African American subjects consumed less potassium than Caucasian subjects and that high blood pressure in African American subjects is associated with low potassium intake (1, 23, 29, 30, 44, 45, 50, 81, 82). The increased prevalence of high blood pressure in the African American subjects does not appear to be related to greater dietary intake of sodium chloride, as the intake of sodium appears similar in African and Caucasian Americans (23). Dietary potassium depletion raises blood pressure in normal humans (43), and this is associated with a blunted ability to handle an acute sodium load and sodium retention (42). In borderline hypertensive patients, a low-potassium diet (16 mmol/day) for 10 days increases systolic and diastolic pressures by 7 and 6 mmHg, respectively, relative to 10 days on a high-potassium diet (96 mmol/day) (41).

Furthermore, dietary potassium supplementation lowers blood pressure in established hypertension (5, 25, 57, 86). In one report (57), dietary potassium supplementation (65 mmol/day) in 32 African American women with mild to moderate essential hypertension caused a small fall in blood pressure, significant for both systolic and diastolic pressure after 4 wk. The authors also reviewed the findings in seven other published studies. Despite differences in patient age, amount and duration of potassium supplementation, and sodium intake, the findings

were similar and consistent, that is, a small decrease in systolic and diastolic pressures after 10 days to 6 wk of potassium supplementation. According to another report, potassium supplementation also appears to reduce pressure in hypertensive patients with hypokalemia due to diuretics (41). It also reduces the need for antihypertensive medication (80). A high intake of potassium from dietary sources may also protect against stroke-associated death (38).

Studies in animals with established hypertension lead to similar conclusions. The rat with reduced renal mass-saline hypertension, for example, responds to increased dietary potassium intake with a reduction in blood pressure (65). The Dahl salt-sensitive rat receiving a 1% sodium chloride diet has a minimum blood pressure when eating 1.6% KCl and responds to either a reduction in KCl intake or an elevation in KCl intake with an increase in pressure relative to the pressure on 2.6% KCl (54). In the spontaneously hypertensive rat, potassium intake also significantly reduces arterial blood pressure, a phenomenon associated with a restoration of the EDHF-mediated responses in the mesenteric vascular bed (90).

In normal human subjects, dietary sodium excess increases urinary potassium excretion, and this is associated with a small fall in plasma potassium concentration. Blood pressure also increases, and this can be attenuated by dietary potassium supplementation (49, 51, 52, 84). Dietary potassium supplementation also attenuates the blood pressure increase seen in diabetic children on a high-sodium diet (61). The findings in animals are similar. In the common laboratory rat, a small increase in dietary potassium confers some protection against the effects of excess dietary sodium, attenuating the increase in pressure and increasing longevity (26, 47, 62, 63), mainly by preventing strokes (84).

The antihypertensive effect of the Dietary Approaches to Stop Hypertension (DASH) diet (54) may result mainly from increased consumption of fruits and vegetables, which are high in potassium. The extent to which potassium participates in the beneficial antihypertensive effect of the DASH diet is difficult to assess since the dietary changes that occur on initiation of the diet are multiple.

It is recommended that the average daily potassium intake of roughly 2 g be increased to about 5 g (54). This seems appropriate in the management of hypertension and the prevention of stroke, but excessive potassium intake should be avoided, particularly in the presence of renal disease. Perhaps the intake should be graded, depending upon the circumstances. Patients receiving angiotensin-converting enzyme (ACE) inhibitors or ANG II receptor antagonists, particularly when combined with an aldosterone blocker, on a background of poor renal function, sometimes become hyperkalemic, while others who have hyperaldosteronism or are receiving certain diuretics, frequently become hypokalemic. Plasma potassium values above 5.5 meq/l in the former and below 3.5 meq/l in the latter situation are not unusual. Effects on the heart were long ago frequently documented (31). We now should consider whether these changes in potassium concentration have important effects on human blood vessels as well. Studies in animals indicate important changes in vascular resistance when these levels are produced in the inflowing blood of an organ (6, 20, 77). Thus the hypokalemia of primary aldosteronism may participate in the hypertension, and the the hyperkalemia of ACE inhibitor, ANG II receptor

blocker, and aldosterone antagonist therapy may participate in the vasodilatory and antihypertensive effects of these agents. Likewise, the hypokalemia of diuretic therapy may limit the antihypertensive effect of the diuretic. Dietary potassium supplementation does reduce pressure in hypertensive subjects with hypokalemia due to diuretic therapy (41). The incidence of primary aldosteronism is probably greater than previously thought; almost all hypertensive patients respond to spironolactone with a blood pressure decrease.

The antihypertensive effect of dietary potassium supplementation may be due to more than one mechanism. One likely possibility is stimulation of Na^+-K^+-ATPase in vascular smooth muscle cells and adrenergic nerve terminals, resulting in vasodilatation (32, 33). Dietary potassium supplementation potentiates endothelium-dependent relaxation (73). In the long run, this may relate to more than a simple increase in turnover of Na^+-K^+-ATPase; it may also relate to an increase in the number of enzyme molecules, that is, "potassium adaptation."

Long-term, high intake of potassium induces an increased capacity for potassium secretion in the colon, as well as in a segment of the collecting duct of the kidney (34). The stimulus for this change has been attributed to aldosterone [long-term potassium loading increases adrenal production of aldosterone (56)]. Both long-term potassium loading and chronic hyperaldosteronism induce similar changes in epithelia in the colon and kidney, capable of potassium secretion. In addition to increased potassium secretion, these changes include an increase in the number of Na^+-K^+-ATPase pump sites in basolateral cell membranes and, in epithelial segments, an increase in the transepithelial voltage.

If the number of Na^+-K^+-ATPase pump sites also increases in the plasma membrane of vascular smooth muscle cells, a cellular mechanism would be in place to attenuate the vasoconstriction seen in various hypertensive states. Increased pumping can result from increased turnover of the pumps (acute administration of K^+) or increased number of pumps (chronic administration of K^+) or both. It would be of interest to measure vascular (e.g., rat tail artery) Na^+-K^+-ATPase activity and Na^+ and K^+ pumping during acute and chronic oral administration of K^+. Potassium adaptation could account for the stability of plasma potassium concentration in the face of altered potassium intake and also for the delay in the antihypertensive response to dietary potassium supplementation in hypertensive subjects (the delay is ~4 wk vs. 1 to 2 days in the case of sodium restriction).

Thus increased dietary potassium can lower blood pressure in animals and humans, particularly if they have "salt-sensitive" hypertension. It also decreases the need for antihypertensive medication. Reduced potassium intake can raise blood pressure, and it seems possible that the hypokalemia of primary aldosteronism and other conditions contributes to the hypertension seen in these states. The onset of these effects is slow, perhaps partly due to the stabilizing effect of new pump sites ("potassium adaptation").

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