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Time Course and Mechanisms of the Acute Effects of Hypokalemia and Hyperkalemia on Vascular Resistance[1] (38020)

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The local effects of altering plasma [K^+] have been examined in several systemic vascular beds. In general, slight to moderate increases in the plasma [K^+] of the blood perfusing a vascular bed produce vasodilation, whereas decreases in arterial plasma [K^+] produce vasoconstriction. However, the details of the cellular mechanisms which produce these changes in vascular resistance with altered plasma [K^+] are not well-established. Generally, changes in vascular resistance are associated with changes in membrane potential of the vascular smooth muscle cells, i.e., depolarization is associated with vasoconstriction and hyperpolarization with vasodilation. If either the Nernst or Goldman equation is used to calculate change in membrane potential when [K^+] is altered between 0 and approximately 10 mEq/liter, the predicted change in vascular resistance is opposite to that experimentally observed. We have proposed that this difference between predicted and observed change in vascular resistance is due to the effects of the altered [K^+] on the electrogenic Na–K pump and on its contribution to membrane potential (1, 2). In addition, we have recently developed a computer model for calculating initial and transient changes in resting membrane potential due to altered active (electrogenic Na–K pump) and passive ion fluxes (3). Calculations with this model suggest that if the proposed mechanism is correct, then a definite pattern should be observed in the gradual changes in vascular resistance following a step change in the arterial plasma [K^+]. Specifically, there should be a slight decrease in resistance following the initial increase during hypokalemic perfusion of a vascular bed and the initial decrease in resistance during hyperkalemic perfusion should wane and become a net increase in vascular resistance in approximately 5 min.

The purposes of this report are to investigate the changes in local vascular resistance following a step increase or decrease in plasma [K^+] of the blood perfusing an isolated vascular bed and compare the observed changes in resistance with the calculated changes in membrane potential as well as discuss the mechanisms of these changes.

Methods. Experimental. Mongrel dogs of either sex were anesthetized by intravenous injection of sodium pentobarbital (33 mg/kg), ventilated with a mechanical respirator via an intratracheal tube, and anticoagulated by intravenous sodium heparin (5 mg/kg). In one series of experiments, the right hindlimb gracilis muscle was isolated except for the main gracilis artery, vein, and nerve as previously described (4). In a second series of experiments, the right forelimb was isolated at approximately 3–5 cm above the elbow except for the brachial artery, forelimb nerves, and brachial and cephalic

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veins. In both series of experiments, a constant-flow blood pump and hemodialyzer were interposed in the arterial blood supply of the isolated vascular beds. Blood flow was initially adjusted so that arterial perfusion pressure was approximately equal to systemic pressure and this rate was maintained throughout the experiment. Thus variations in vascular resistance were reflected via changes in perfusion pressure.

During a control period, the blood perfusing the experimental vascular bed was dialyzed against an isotonic Ringer's solution which had an ionic composition essentially the same as plasma (K^+, 4 mEq/liter; Na^+, 146; Mg^{2+}, 2; Cl^-, 131; Ca^{2+}, 5; HCO_3^-, 21; osmolality, 300; pH, 7.3). After perfusion pressure had become constant, the $[K^+]$ in the perfusing blood was altered by switching to a dialysate solution in which the $[K^+]$ was either increased or decreased by isoosmotic substitution for Na^+. After 2–10 min, the dialysate was returned to the control Ringer's solution and perfusion pressure was allowed to become constant. Each preparation was exposed to either one or two abnormal plasma K^+ concentrations.

Theoretical. The effects of altered extracellular potassium ion concentration ($[K^+]_e$) on the resting membrane potential of a hypothetical vascular smooth muscle cell (Table I) were calculated with a previously described computer model (3). In brief, the model uses passive transmembrane fluxes of K^+, Na^+, Cl^-, and H_2O and active fluxes of Na^+ and K^+ to calculate continuous changes in resting membrane potential in response to altered extracellular concentrations.

TABLE I. Hypothetical Vascular Smooth Muscle Cell.[a]

	Concentrations (mEq/liter)		Permeability (cm/sec)
	Extracellular	Intracellular	
Na^+	140	10	4.8×10^{-9}
K^+	4	145	2.2×10^{-8}
Cl^-	120	18	2.2×10^{-8}
Total	300	300	

[a] Resting potential −50 mV; pump exchange ratio 1.7 Na^+:1 K^+.

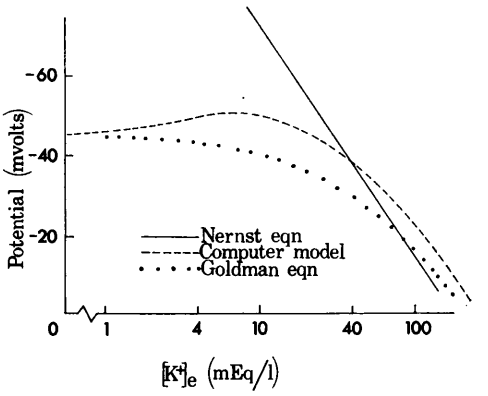

FIG. 1. Effects of varying $[K^+]_e$ on resting membrane potential of a vascular smooth muscle cell.

Results. Figure 1 shows the membrane potential calculated for the vascular smooth muscle cell of Table I when the extracellular $[K^+]$ is varied about the normal 4 mEq/liter by isoosmotic substitution with Na^+. It is important to note that, with an electrogenic Na–K pump (exchange ratio of 1.7 Na^+:1 K^+ assumed constant), there is a calculated hyperpolarization as the $[K^+]$ is increased from zero up to about 10 mEq/liter, in contrast to the depolarization calculated with the Nernst (K^+ equilibrium potential) or Goldman (electroneutral Na–K pump) equation.

Figure 2 shows the initial change (after approximately 1–5 min) in perfusion pressure of the canine gracilis muscle of 31 animals produced by locally altering the arterial plasma $[K^+]$ about the normal 4 mEq/

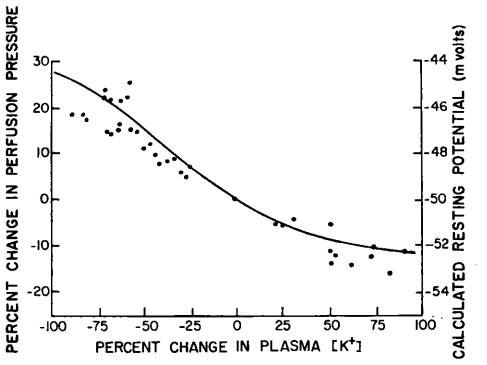

FIG. 2. Experimental changes in resistance produced by altered plasma $[K^+]$ (dots) compared with calculated resting membrane potential.

liter via hemodialysis (data previously reported in part in Refs. 1 and 2). Note that the greater changes in vascular resistance were produced by the larger changes in [K+]. These changes in resistance are compared (on an arbitrary scale) with the calculated resting membrane potential of a vascular smooth muscle cell which has an electrogenic Na–K pump (line redrawn from Fig. 1). It is seen that the experimental changes in vascular resistance have the same pattern as the calculated change in membrane potential.

The calculated effects on the membrane potential of a vascular smooth muscle cell in response to a 10-min exposure to hyperkalemia and hypokalemia are shown in Fig. 3. (The initial potential changes have been slightly smoothed to simulate the time lag associated with flow and diffusion of K^+ to and from the cell membrane in contrast to the step change in concentrations used in the model calculations.) Initially, the cell membrane hyperpolarizes in response to an increase in extracellular [K+] and this is followed by a gradual waning of potential. By the end of approximately 5 min, the hyperpolarization disappears and is converted into a net depolarization. Returning [K+] to normal after 10 min produces a further depolarization before membrane potential returns to the control value. On the other hand, there is only a slight waning of the initial depolarization accompanying a reduction in [K+] by the end of 10 min. Increasing [K+] to normal at this time causes the membrane to hyperpolarize beyond the

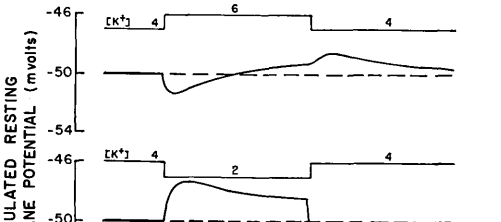

FIG. 3. Calculated time course of the changes in resting potential with elevated and reduced [K+].

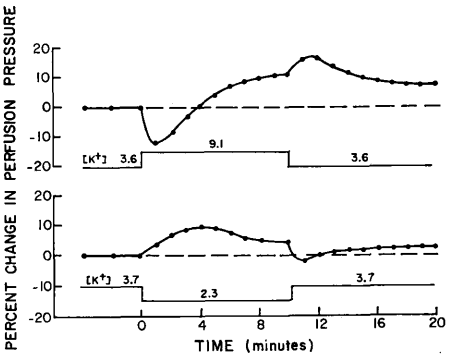

FIG. 4. Typical transient changes in forelimb perfusion pressure produced by hypo- and hyperkalemic perfusion during constant flow.

initial −50 mV before returning to the control value.

The effects of a 10-min hyperkalemic and hypokalemic perfusion of a canine forelimb on initial and secondary changes in perfusion pressure are shown in Fig. 4. These changes in vascular resistance agree very closely with those expected from the calculated membrane potential of Fig. 3.

The effects of a 10-min hyperkalemic and hypokalemic perfusion of the forelimb are summarized in Fig. 5 and compared (arbitrary scale) with calculated changes in resting membrane potential of a vascular smooth muscle cell. In all animals, resistance initially decreased ($P < 0.01$) upon increasing plasma [K+] and then began to increase within 1–2 min. Resistance rose above control by the end of 10 min of hyperkalemia

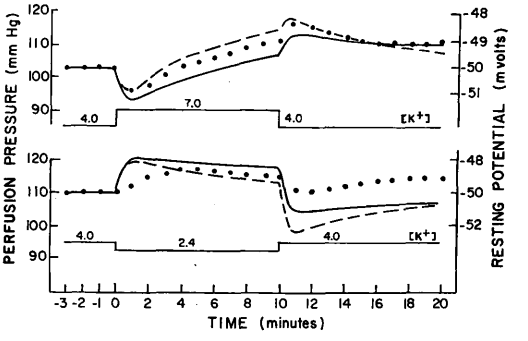

FIG. 5. Comparison of average changes in forelimb perfusion pressure (dots) with calculated membrane potential. Dashed line, initial $[Na^+]_i$ = 5 mEq/liter; solid line, initial $[Na^+]_i$ = 10 mEq/liter.

in 7 of 8 animals ($P < 0.01$). In one animal, resistance returned to the prehyperkalemic value at the tenth min. There were further increases in perfusion pressure in all animals upon returning [K+] to normal, followed by a gradual waning of resistance toward the prehyperkalemic value.

The initial response to a decrease in arterial plasma [K+] was an increase in forelimb perfusion pressure ($P < 0.001$), and in 6 of 7 animals, the initial increase was followed by a slight decrease by the end of 10 min of hypokalemic perfusion ($P < 0.05$). In one animal, resistance initially rose during the low [K+] perfusion and then remained constant. Upon returning the inflowing plasma [K+] to the control value, perfusion pressure rapidly decreased and then gradually increased in all animals. In 2 of 7 animals, resistance initially decreased below the control value ($P > 0.4$) upon reinstituting the normal arterial [K+]. Perfusion pressure became constant after 10 min of perfusion with normokalemic blood; however, at a pressure greater than the prehypokalemia value ($P < 0.01$). It can be seen that these initial and gradual changes in perfusion pressure agree with the calculated potential in every respect, except for the elevated perfusion pressure following hypokalemia.

In two-forelimb preparations, a small artery and a small vein of the skin and skeletal muscle were cannulated and pressure monitored to determine which vascular segment produced the changes in resistance observed during perfusion with abnormal [K+]. In both preparations, the changes in skin and skeletal muscle arterial pressures paralleled each other and there were no changes in venous pressures, indicating that the observed changes in resistance occurred in the arterioles and/or precapillary sphincters and that skin and skeletal muscle resistances changed essentially the same.

Discussion. This study shows that the direction and pattern of the initial changes in vascular resistance produced by locally altering arterial plasma [K+] between 0 and 8 mEq/liter can be predicted from calculated changes in resting membrane potential. In addition, the time course of the changes in vascular resistance during hyperkalemic and hypokalemic perfusion is the same as calculated membrane potential. The significance of these results is that it is possible to discuss the cellular mechanisms which produce the changes in vascular resistance with altered arterial plasma [K+].

There are many complicated intermediate events which lead to change in vascular resistance with altered resting membrane potential, most notable is probably a change in frequency of action potentials. However, since there is such good agreement between observed changes in vascular resistance and calculated changes in membrane potential (Figs. 2 and 5), it appears that the assumed linear relationship between resistance and membrane potential is reasonable. Thus, this *discussion* will consider the mechanisms which produce the changes in cell membrane potential in response to changes in $[K^+]_e$ as well as other data which support the proposed mechanisms.

By comparing Figs. 1 and 2, it is seen that the observed changes in vascular resistance could be predicted only if the Na–K pump is electrogenic. This requirement causes no problem since there is extensive evidence which indicates that probably every Na–K pump is electrogenic. In a recent review, Thomas (5) concluded that the Na–K pump in many types of nerve and muscle (including vascular smooth muscle) cells is electrogenic and there is little if any direct evidence that it is electroneutral. It appears that a truly neutral Na–K pump may not, in fact, exist (6).

It is important to consider whether the computer model used for these calculations adequately represents the cell membrane. We have previously shown that initial and secondary changes in resting membrane potential in response to changes in extracellular [K+], [Na+], [Cl−], or osmolality of various cell types, including nerve, vascular smooth muscle, intestinal smooth muscle (3), and skeletal muscle cells (unpublished), can be calculated with this computer model. Thus, as a first approximation, the model calculations appear reasonably accurate.

In reference to the mechanisms which

produce the changes in membrane potential, consider the effects of increasing extracellular [K+] from an initial 4 mEq/liter to 6 mEq/liter on a cell with a potential of −50 mV (Table I). From the Goldman equation, it can be seen that the subsequent changes in passive ion fluxes would tend to depolarize the cell membrane. However, the increase in [K+] also speeds the electrogenic Na–K pump (7) and thus tends to hyperpolarize the membrane. The net change in potential depends, of course, on the sum of the changes in active and passive ion fluxes. In this case, there is a net hyperpolarization (Fig. 1). This type of behavior is characteristic only of cells with low resting potential and high Na^+ permeabilities (cf. Gorman and Marmor (8)).

As seen in Fig. 5, increases or decreases in arterial [K+] produce initial and secondary changes in resistance. These secondary changes are explainable in terms of the changes in $[Na^+]_i$ and subsequent effects on the electrogenic contribution to membrane potential. Consider, again, the effects of increasing $[K^+]_e$ from the normal 4 mEq/liter to 6 mEq/liter. As explained above, this results in an initial hyperpolarization and decreased resistance since the Na–K pump is stimulated. However, the $[Na^+]_i$ will now be gradually decreasing since Na^+ is being actively extruded at a much faster rate while the passive influx of Na^+ is only slightly increased. This fall in $[Na^+]_i$ results in a gradual slowing of the electrogenic pump, waning of potential, and increased resistance. In approximately 5 min, the $[Na^+]_i$ is sufficiently reduced to produce a net depolarization and increased resistance. Reducing $[K^+]_e$ to the initial 4 mEq/liter after 10 min causes a further depolarization and increase in resistance since this change in $[K^+]_e$ slows the electrogenic pump. Under these circumstances, there will now be a gradual gain of cellular Na^+ since the efflux has been reduced, producing a return toward initial resting potential and vascular resistance.

Reducing [K+] below normal has opposite effects on initial and secondary changes in potential and resistance, with the exception that the gradual gain of cell Na^+ produces only a slight waning of the initial response, instead of a complete reversal as with increased [K+].

Further support for this proposed mechanism comes from the effects of agents which inhibit the electrogenic Na–K pump. The cardiac glycoside ouabain is well-known and widely used for this purpose. Administration of ouabain into an isolated vascular bed causes vascular resistance to increase (1). This is expected since slowing the electrogenic pump depolarizes the cell membrane and leads to an increased resistance. Furthermore, altering arterial plasma [K+] after ouabain administration causes changes in vascular resistance which are opposite in direction to those before ouabain administration in skeletal muscle (1) and guinea pig heart (9). Again, these changes in resistance are expected since the Na–K pump has been slowed and the changes in membrane potential would be more in accord with those expected on the basis of passive ion fluxes, i.e., the Goldman equation.

Finally, the data of Fig. 5 indicate that K^+ does not participate in maintaining exercise hyperemia since hyperkalemia produces vasoconstriction after approximately 5 min. However, K^+ may be involved in the initiation of active hyperemia since the initial response to hyperkalemia is vasodilation.

Summary. The acute vascular effects of elevating and reducing arterial plasma [K+] in the canine gracilis muscle and forelimb have been compared with calculated changes in the resting membrane potential of a vascular smooth muscle cell. The direction, time course, and pattern of the changes in vascular resistance and calculated resting membrane potential agree very closely. Changes in calculated membrane potential are determined primarily by the effects of changes in $[K^+]_e$ and $[Na^+]_i$ on the rate of active transport by the electrogenic Na–K pump. This suggests that changes in arterial plasma [K+] alter vascular resistance via the direct effect of $[K^+]_e$ on the contribution of the electrogenic pump to resting membrane potential and secondarily by the effects of changes in $[Na^+]_i$. Further, the data indicate that K^+ does not play a role in maintaining exercise hyperemia.

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