Effect of Electrolytes on Arterial Muscle Contraction

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The effect of specific electrolyte changes and of desoxycorticosterone on the responsiveness of vascular smooth muscle to epinephrine was studied using rabbit aortic strips. Low sodium increases, while high sodium decreases the epinephrine response. Conversely, low potassium decreases, while high potassium increases the epinephrine response. Desoxycorticosterone potentiates the epinephrine response in a manner qualitatively similar to that of high potassium, but different from that of low sodium potentiation.

The immediate cause of hypertension is an elevation in peripheral vascular resistance. In all probability this elevated resistance results from an increase in the tonus or contractility of vascular smooth muscle. Various experimental procedures initiate a chain of events which eventually lead to this increase in smooth muscle tonus and therefore to arterial hypertension. It is not known how such procedures actually produce this change in vascular smooth muscle nor whether a single mechanism of production is common to the different types of experimental hypertension. There is extensive evidence, however, that significant electrolyte abnormalities may exist in all types of experimental hypertension. In order to evaluate the possible role of such abnormalities, this study was designed to examine the relationship between specific electrolyte changes and the contractility of vascular smooth muscle.

Method

The method used for studying responsiveness of aortic smooth muscle was that of Furchgott. A spiral strip of rabbit aorta was mounted in a bath of Krebs bicarbonate solution. The strip was stimulated with epinephrine which was added at 20 minute intervals and allowed to remain in the bath for 5 minutes before being thoroughly flushed. Calcium versenate was present in the bath to bind traces of heavy metals which normally catalyze the oxidation of epinephrine. Isotonic contractions were recorded on smoked paper. Standard responses of the strip to epinephrine were obtained and compared with responses obtained when the electrolyte composition of the bath was altered and when desoxycorticosterone was added.

Results

The effects of several potassium concentrations in the bath were studied on 22 artery strips. The concentration of potassium was altered from physiologic (4.7 mEq.) to zero potassium and to double potassium (9.4 mEq.). The effects of these variations were consistent. The tracing from a typical experiment is shown in figure 1. There was a marked and progressive reduction in contractility when the bath surrounding the muscle was replaced by a potassium-free solution. Following return to a normal potassium concentration there was a gradual re-establishment of the control amplitude of contraction. The inadvertent addition of 10 times the intended concentration of epinephrine, in 1 experiment (fig. 1), gives an indication of the range of responsiveness of the vascular smooth muscle. Doubling the concentration of potassium chloride greatly increased the amplitude of contraction in response to epinephrine. Subsequent return of the strip to a normal concentration of potassium chloride was associated with gradual diminution of the amplitude of contraction to control levels.

Variations in sodium chloride concentration in the bath from a normal of 118 mEq. per L. to a high of 155 mEq. per L. and to a

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low of 85 mEq per L. produced consistent results in the 34 artery strips studied. In these experiments the osmolarity was maintained by varying the sucrose concentration to compensate for the changes in sodium chloride. Figure 2 illustrates typical responses of a strip in these sodium concentrations. A reduction in sodium chloride in the bath increased the amplitude of the contraction in response to epinephrine. The second response after the change to low sodium chloride concentration was not as great as the first and there was a reversal of the potentiation when the normal Krebs bath was replaced. This is in contrast to the continued potentiation in normal Krebs solution after high potassium chloride. An increase in the sodium chloride concentration caused an immediate decrease in the amplitude of response to epinephrine. When the normal Krebs bath was replaced, the initial response was often greater than the previous control responses. This recovery differs from that after low-potassium depression of the epinephrine response, in that the latter tends to persist for 1 or 2 contractions after normal Krebs solution is replaced.

A study of the effects of desoxycorticosterone carried out on 20 artery strips demonstrates that this steroid consistently potentiated the response to epinephrine in the manner illustrated (fig. 3). Here, as in the case of high potassium solution, some potentiation usually persisted for 1 or 2 contractions during the recovery period when the strip was returned to normal Krebs solution.

Studies were carried out on 12 muscle strips to determine the effects of superimposition of various electrolyte abnormalities. In all cases the individual effects of the electrolytes and of desoxycorticosterone were algebraically additive. In figure 4 it is seen that the high sodium reduced the potentiating effect of high potassium. The overcompensation during the recovery from high sodium is evident as is the maintained potentiation during the first response after removal from high potassium. In other experiments when desoxycorticosterone was added during a high potassium potentiation, there was a further enhancement of contraction amplitude.

Results summarized in figure 5 illustrate that: 1. Low sodium increases, while high sodium decreases, the epinephrine response. 2.
Fig. 5. Effects of electrolytes and desoxycorticosterone on response of aortic strip to epinephrine. 

Large arrows, increase or decrease in epinephrine response that occurred during exposure to the altered Krebs solution; small arrows, direction of change during recovery from the altered Krebs solution.

Conversely, low potassium decreases, while high potassium increases, the epinephrine response. 3. Desoxycorticosterone potentiates the epinephrine response. 4. There is a qualitative difference between the potentiation of low sodium and that of high potassium. This difference is illustrated by the fact that there is a rebound depression of the epinephrine response following low sodium potentiation, while the potentiation brought about by high potassium persists after the strip has been returned to normal Krebs solution. 5. The potentiating effect of desoxycorticosterone is qualitatively similar to that of high potassium and differs from low-sodium potentiation.

**DISCUSSION**

The following equations show a basic relationship demonstrated for nerve and skeletal muscle, and more recently confirmed for smooth muscle. If $K_i$ is intracellular, $K_o$ is extracellular potassium, and $C$ is a constant, then

$$\log \left( \frac{K_i}{K_o} \cdot C \right) = \frac{\text{resting threshold potential}}{\text{for response}}$$

$$\log \left( \frac{K_i}{K_o} \cdot C \right) = \frac{1}{\text{responsiveness}}$$

The relation shows a positive correlation between transmembrane potassium gradient, resting potentials and threshold of responsive-ness. As the ratio of internal to external potassium increases, the threshold for response increases. The responsiveness therefore decreases as this ratio increases. Csapo has demonstrated this relationship in uterine smooth muscle; Born and Bulbring have shown that loss of potassium from the intestinal smooth muscle cell is associated with a decrease in cell membrane potential and an increase in tone.

Observations in the current study suggest that a similar relationship exists between the potassium gradient and the aortic smooth muscle responsiveness to a physiologic stimulus. A decreased value of this ratio, $K_i : K_o$, caused an increased responsiveness of vascular smooth muscle: 1. When the potassium outside this smooth muscle cell was increased the magnitude of the gradient fell, and the response increased. 2. If desoxycorticosterone, which is known to interfere with potassium transport into the cell, lowers intracellular potassium in the vascular smooth muscle as it does in yeast, skeletal, or cardiac muscle, the resulting decrease in the $K_i : K_o$ ratio could account for the observed increase in response. This part of the picture is relatively clear, however, the relationship, or lack of relationship, of the effects of shifts in sodium to this potassium equilibrium is not.

It is reasonable to question the pertinence of findings in aortic smooth muscle to the mechanism of hypertension which is due to a change in the arterioles. However, since the relationships of the potassium gradient do apply not only to more remotely related smooth muscle (uterus and intestine), but also to skeletal muscle and nerve tissue, an extrapolation from aortic to arteriolar smooth muscle has some justification. Two types of observation relate these findings of the effect of potassium equilibrium on the tonus of isolated, normal smooth muscle to a possible mechanism in hypertension. In the first place Roseman, Freed and Friedman have observed that the hypertensive effect of desoxycorticosterone parallels the potassium intake in the rat. Also, there is both experimental and clinical evidence that a reduction in po-
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tassium intake will lower blood pressure.\textsuperscript{14, 15} The second type of evidence which links the current observation to the mechanism of hypertension is the suggestion that there may be an increase in aldosterone in hypertension.\textsuperscript{16}

SUMMARY

The current study indicates that a lowering of the K\textsubscript{1}:K\textsubscript{e} ratio increases the contractility of vascular smooth muscle. Regardless of other factors involved in the pathogenesis of hypertension, changes in this ratio must alter the responsiveness of vascular smooth muscle. Since it is known that factors which reduce this ratio exacerbate hypertension and that changes of this type may occur in hypertension, the possibility exists that a shift in this ratio may be an etiologic factor in hypertension.

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