Influence of Extracellular K⁺ Concentration on Cable Properties and Excitability of Sheep Cardiac Purkinje Fibers

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ABSTRACT

Conduction velocity was increased from 3.5 m/sec to 4.1 m/sec in sheep cardiac Purkinje fibers when the superfusing Tyrode solution was changed from 2.7 mM K⁺ to 4.0 mM K⁺. Further increase to 7.0 mM K⁺ resulted in a fall in conduction velocity to 3.3 m/sec. To understand the nature of the cellular change responsible for this effect, cable analyses were made. With increases in extracellular K⁺ concentration membrane resistance decreased and membrane capacitance did not change. Resistance of the myoplasm tended to fall in 7.0 mM [K]₀. Since these effects did not explain the change in conduction velocity, excitability was studied by strength-duration curves using intracellular microelectrodes for current passage and recording. Increase in K⁺ from 2.7 to 4.0 mM resulted in a shift of the entire curve to the left, with a fall in rheobasic current from 121 to 104 nanoamperes and a fall in the time constant from 2.79 to 2.4 msec. Normalized plotting of stimulating current over rheobasic current (I/Iₘₑₜ) against duration of stimulating current over the time constant (t/τ) suggested that the curves were not basically different. The increase in K⁺ from 2.7 to 4.0 mM was associated with a depolarization of the resting membrane, consistent with alteration in the potassium equilibrium potential, but no change in the absolute membrane potential for threshold. In this way, the changes in membrane voltage and charge necessary for excitation were reduced in 4.0 mM [K]₀.

ADDITIONAL KEY WORDS

- electrophysiology
- strength-duration curves
- membrane properties
- conduction velocity

Several investigators have observed that an increase in extracellular potassium ion concentration ([K]₀) can increase conduction velocity of the action potential in heart muscle (1-3). Generally, they have found that up to 7 mM [K]₀ the conduction velocity increases, but that with further elevation of [K]₀ conduction velocity falls and the fiber finally becomes inexcitable. Since an increase in [K]₀ tends to depolarize the cell by changing the potassium equilibrium potential, loss of excitability is probably adequately explained by inactivation of the voltage-dependent sodium entry system (4). The changes in conduction speed that occur at lower potassium concentrations than those required to interfere with excitability have been more difficult to understand.

Siebens et al. (5) first reported an increase in excitability by modest increases in [K]₀. There is no reason to believe that this effect is related to an alteration in the voltage dependence of the sodium entry system, which Weidmann showed to be independent of [K]⁺, in the range under consideration (4). The most widely accepted explanation for enhanced excitability is that the increase in [K]₀ depolarizes the membrane to a potential nearer its voltage threshold without...
significantly inactivating the sodium entry system, thereby reducing the current required for threshold depolarization. The reduced current necessary for excitation might be expected to favor more effective conduction by local circuit currents. This suggested mechanism seems inconsistent with the known effect of increased $[K^+]_o$ to lower resting membrane resistance (6, 7), an effect which would result in an increased current requirement for excitation for a given threshold depolarization.

In the experiments reported here, cable properties and strength-duration curves were measured in cardiac Purkinje fibers. The strength-duration curves showed that there was a reduced current requirement for excitation in experiments in which increased $[K^+]_o$ produced an increase in conduction velocity. Cable analysis confirmed the fall in membrane resistance with increased $[K^+]_o$.

**Methods**

Sheep hearts were obtained from the slaughter house and brought to the laboratory in cold Tyrode's solution. Purkinje fibers were excised on arrival at the laboratory and stored in oxygenated Tyrode's solution until use. All experiments were done on long, unbranched fibers superfused with Tyrode's solution containing NaCl, 137 mM; KCl, 2.7 to 7 mM; NaHCO$_3$, 2.38 mM; K$_2$HPO$_4$, 1.8 mM; glucose, 5 mM; and MgCl$_2$, 1.05 mM; NaH$_2$PO$_4$, 13.4 mM; NaHCO$_3$, 2.38 mM; CaCl$_2$, 1.8 mM; glucose, 5 mM; and KCl, 2.7 to 7 mM. The solutions were gassed with 95% $O_2$ and 5% $CO_2$ to produce a pH of 7.2 to 7.3 and kept at a temperature of 34 to 35°C.

Intracellular micropipettes of the Ling-Gerard type (18) were filled with $144$ KCl and had $\Delta$-c resistances of 5 to 8 MO. Cable analysis was performed with hyperpolarizing currents as previously described (18), with one pipette placed at the end of the cell column for current passage and one or two others at various distances along the column. Each transmembrane potential was recorded as the difference between two pipettes, one inside the cell and the other just outside. Resting potential was measured by withdrawal of an intracellular pipette during quiescence and therefore represented the steady potential rather than the maximal diastolic potential. Conduction velocity was calculated from the conduction time of the action potential between two widely separated pipettes. These pipettes were kept impaled at the same points throughout the changes in $[K^+]_o$. Conduction time was measured at 2-minute intervals for the first 10 minutes after a change in $[K^+]_o$. During the rest of the experiment it was measured at about 5-minute intervals. The first derivative of the upstroke of the action potential was obtained electronically with an operational amplifier (Tektronix Type O). Apparent capacitance filled by the foot of the action potential was calculated according to the method of Tasaki and Hagiwara (9). The diameter of the cell column was measured with a micrometer eyepiece. Frozen sections were also made and stained with Safranin O to confirm the presence of a single column of cells in the false tendon.

Strength-duration curves were measured by passage of square pulses of depolarizing currents through one intracellular pipette located at one end of the fiber and recording of the voltage response at a second pipette placed within 50 μm of the first. Current was measured by an operational amplifier (Tektronix Type O) that kept the bath at virtual ground. The current requirement and the minimal voltage change necessary to provoke an action potential were measured for current pulses varying from 0.1 msec to 40 msec in duration.

**Results**

Conduction Velocity.—In 25 experiments, the potassium ion concentration was altered in various steps between 2.7 and 7.0 mM. Increase in $[K^+]_o$ to 4.0 or 5.4 mM resulted in a modest increase in conduction velocity, but an increase beyond 5.4 mM usually resulted in a fall in conduction velocity. A typical time course of change in conduction velocity is seen in Figure 1. Part of the delay in establishment of a new steady state was the 1 to 2 minutes required for complete change of solution. In two experiments moderate increases in $[K^+]_o$ failed to increase conduction velocity; these observations will be discussed later.

Cable Analysis with 2.7 and 4.0 mM $[K^+]_o$.—Five experiments were performed with cable analysis, first in 2.7 mM $[K^+]_o$, and then in 4.0 mM $[K^+]_o$. In two of these, it was possible to return to 2.7 mM $[K^+]_o$, and obtain a repeat cable analysis. In one (expt. 5), a sequential change was made to 7.0 mM $[K^+]_o$, and then back to 2.7 mM $[K^+]_o$. The fibers were modestly depolarized. The overshoot of the action potential did not change, although there was usually a small increase in the maximal rate of change of voltage during the upstroke. Input resistance...
FIGURE 1

Change in conduction velocity of the propagated action potential upon change of [K⁺]o from 2.7 to 4.0 mM and back to 2.7 mM. The lower line indicates time of exposure to 4.0 mM [K⁺]. The upper line indicates successive measurements of conduction velocity determined by recording action potentials from two intracellular microelectrodes. The onset of change in conduction velocity may have been even faster than indicated, since more than a minute was required for complete washout of the chamber.

fell in every case, with a shortening of the space constant and the time constant. These measurements were used to calculate the specific cable values. In three of the five experiments Rₘ (specific resistance of the myoplasm) decreased slightly but the change was not large enough to be convincing. Rₘ (membrane d-c resistance) fell consistently and substantially. Cₘ (specific membrane capacitance) probably did not change. The time constant of the action potential foot decreased slightly, but the change was consistent with the rise in conduction velocity, so that calculated capacitance filled during the upstroke of the propagated action potential was not changed.

Cable Analysis with 4.0 and 7.0 mM [K⁺].—Five additional experiments were performed to study the effect of increasing [K⁺] from 2.7 to 7.0 mM (Table 2). In each of these studies the conduction velocity fell. The overshoot of the action potential was reduced and the maximal rate of change of voltage declined. Input resistance declined, and the space constant and time constant were both reduced, effects similar to those seen on increasing [K⁺] from 2.7 to 4.0 mM. The resulting calculations revealed a modest fall in Rₘ, a substantial fall in Rₘ and a suggestive fall in Cₘ. The increase in the time constant of the action potential foot was proportional to the fall in conduction velocity, so that there was probably no change in the calculated capacitance filled during the propagated action potential upstroke.

Excitability.—In four experiments, strength-duration curves were obtained first in 2.7 mM [K⁺], and then in 4.0 mM. In one experiment, the study was first made in 4 mM [K⁺], and then in 2.7 mM. A typical pair of curves is illustrated in Figure 2. The strength-duration curves show the same general shape as those found in nerve, with greatly increased current requirement for shorter pulses. The entire curve was shifted to the left—to less current for a given duration—when the fiber was exposed to higher [K⁺]. In addition, the rheobasic current was reduced. Data from the five experiments are given in Table 3. While there was some variation in the values from fiber to fiber, it can be seen that conduction velocity increased in four instances. The average values from the five experiments reflect the approximate magnitudes of the changes. As expected, increasing [K⁺] depolarized the fiber. Rheobasic current averaged 121 namp in 2.7 mM [K⁺], and decreased to 104 namp in 4 mM [K⁺]. In the one experiment in which conduction velocity did not increase, there was no change in rheobase.
Electrical Constants of Purkinje Fibers in 2.7 and 4.0 min (K+o)

| Exp. | (°C) | $V$ (m/s) | $V$ (V/m) | $V/df$ (K) | $A$ (mm) | $R_1$ (K ohm) | $X_0$ (Gm/cm) | $t_{AP}$ (msec) | $C_m$ (aF/m) | $C_{AP}$ (aF/m) | Fiber diameter (a) |
|------|------|----------|----------|------------|-------|-------------|------------|-----------|-------------|-------------|----------------|---------------------|
| 1    | 2.7  | 3.5      | -94      | 965        | 155   | 3.8         | 74         | 2300      | 23          | 10.0        | 9.0             | 5.0                  |
| 2    | 4.0  | 6.1      | -92      | 890        | 313   | 3.3         | 65         | 1550      | 21          | 11.4        | 8.8             | 3.7                  |
| 3    | 2.7  | 4.1      | -94      | 650        | 160   | 3.46        | 77         | 2060      | 21          | 10.5        | 9.8             | 2.4                  |
| 4    | 2.7  | 3.8      | -100     | 525        | 117   | 3.1         | 120        | 2020      | 19          | 9.4         | 9.6             | 2.8                  |
| 5a   | 2.7  | 3.6      | -92      | 109        | 92    | 3.0         | 92         | 1850      | 50          | 14.0        | 12.5            | 50                   |
| 4    | 2.7  | 3.8      | -92      | 107        | 99    | 3.0         | 99         | 1810      | 20          | 12.0        | 12.5            | 3.8                  |
| MEAN | 2.7  | 3.5      | -98      | 390        | 169   | 1.4         | 280        | 1340      | 26          | 16.0        | 19.0            | 110                  |
| 5a   | 2.7  | 3.8      | -93      | 300        | 95    | 3.0         | 130        | 880       | 311         | 17.5        | 17.5            | 3.0                  |

[K+o] = concentration of potassium ions in the superfusing solution; $\delta$ = propagation velocity of the action potential; $V_m$ = the steady diastolic potential; $V$ = the maximum rate of change of voltage during the action potential; $V/df$ = the d-c input resistance of the fiber; $A$ = the space constant; $R_1$ = the specific resistance of the myoplasm; $R_m$ = the membrane d-c resistance; $r_m$ = the membrane time constant; $C_m$ = the specific membrane capacitance as measured by the square-wave method; $t_{AP}$ = the time constant of the foot of the propagated action potential; $C_{AP}$ = the capacitance as calculated from the foot of the action potential.
### TABLE 2

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<th>$V$ (v/sec)</th>
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<th>$\lambda$ (mm)</th>
<th>$B_1$ (m/sec)</th>
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<th>$T_1$ (msec)</th>
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*The values for 4.0 mM $[K^+]_o$ are listed also in Table 1, since the observations were sequential. Symbols are defined in Table 1.
The classical description of the strength-duration curve for nerve was first derived by Lapicque (10):

\[ I = I_{\text{th}} / (1 - e^{-t/T}) \]  

where \( I \) is the current required for excitation, \( I_{\text{th}} \) is rheobasic current, and \( T \) is defined as

\[ T = \lim_{t \to 0} T_{\text{th}} \]  

In each experiment the product \( I/T \) for pulses less than 1 msec in duration was plotted against pulse duration and extrapolated to the zero time axis. From this value and the rheobasic current, a calculation of \( T \) was made. In each experiment \( T \) fell as \([K^+]_o\) was increased from 2.7 to 4.0 mM (Table 3).^{3}

As suggested by Cole (11), the characteristics of the strength-duration curve can sometimes be illustrated by the use of a normalized plot, using \( I/I_{\text{th}} \) and \( T/R \). The data plotted in Figure 2 are reshow in Figure 3 using these dimensionless coordinates. The similarity of the curves in different potassium concentrations suggests that their basic form was not altered and that the changes can be accurately indicated by the measures \( T \) and \( I_{\text{th}} \).

Threshold voltages for the experiment shown in Figure 2 are plotted in Figure 4. With short current pulses, the required change

Table 3

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<th>( K ) (mM)</th>
<th>( I ) (msec)</th>
<th>( V_m )</th>
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<th>( I_{th} ) (amp)</th>
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\( \theta \) and \( V_m \) are defined in Table 1. \( V_{th} \) = membrane voltage value that was obtained in order to provoke an action potential, since the value was different depending on the duration of the pulse, the threshold for short pulses and for long pulses are both listed. \( I_{th} \) is rheobasic current and the \( \lim_{t \to 0} I/t \) is the value obtained by extrapolation of the relation between charge required and pulse duration to the zero time axis. \( \tau \) is the time constant of excitation as defined by \( \lim_{t \to 0} I/t \).
**K⁺ Effects on Cardiac Excitability**

**Figure 2**
Strength duration curves from cardiac Purkinje fibers measured in 2.7 and 4.0 mEq [K⁺]₀. Currents were passed into the fiber through one intracellular micropipette and recording was made through a closely adjacent one. Currents are those just adequate to provoke a propagated action potential at the end of the pulse.

**Figure 3**
Normalized strength-duration curve. The same experiment shown in Figure 2 is replotted with the ordinate as the ratio of current to rheobasic current (I/Iₜₙ) and the abscissa as ratio of pulse duration to tᵢₜₙ. In 2.7 mEq [K⁺]₀ the τ was 3.60 msec and in 4.0 mEq [K⁺]₀ the τ was 2.78 msec.

In membrane voltage was higher than with long pulses. With currents 1 msec or longer, the voltage threshold was quite constant, with a gradual drift upward by 40 msec. Very little difference could be seen in the actual membrane voltage required for threshold in 2.7 and 4.0 mEq [K⁺]. The transmembrane potential at the threshold for the shortest...
pulse observed and for pulses between 2 and 30 msec in duration are listed in Table 3 for each experiment. In most cases there was a small shift in threshold to less negative values with increase in \([K^+]_0\), but the change was not as large as the alteration in resting potential of the fiber. The only exception to this was the experiment in which conduction velocity failed to increase. In that case there was a large shift in threshold voltage.

A similar experiment was performed in two fibers with an increase in \([K^+]_0\) concentration from 4.0 or 5.4 mM to 7.0 mM. In both cases the strength-duration curve was shifted to the right, with a higher rheobasic current requirement and a large shift in voltage threshold. The pertinent measurements are listed in Table 3.

Discussion

In almost every experiment, an increase in \([K^+]_0\) in the superfusing solution from 2.7 to 4.0 mM resulted in an increase in conduction velocity. The passive factors related to conduction of an action potential at constant velocity are generally thought to be described by

\[
\theta = \frac{ka}{2Rc_m},
\]

where \(\theta\) is a constant conduction velocity, \(a\) is fiber radius, \(R\) is specific resistance of the myoplasm, \(c_m\) is membrane capacitance per unit surface area, and \(k\) is a constant related to the generator properties of the membrane. If alteration in \([K^+]_0\) influenced conduction by change in the passive membrane properties, it could increase \(\theta\) by a reduction in \(R\) or \(c_m\). As shown in Table 1 these values were not significantly altered upon changing from 2.7 to 4.0 \([K^+]_0\). It has been previously suggested that not all of the membrane capacity is filled by the propagating action potential (8, 12). The portion apparently being filled by the action potential may be estimated from the time constant of the foot of the action potential, and this capacitance also did not change significantly. A similar evaluation can be made of the fall in conduction velocity on transfer from 4.0 to 7.0 mM \([K^+]_0\). In this case (Table 2) there was a questionable fall in \(R\) and \(c_m\), but this would result in an increase in conduction velocity rather than the decrease that was found experimentally. Again there was only a small change in the capacitance apparently filled by the action potential, probably not enough to account for the change in \(\theta\). The only other notable change in cable values was the fall in membrane resting d-c resistance on increasing \([K^+]_0\). This is consistent with the
well known effect of \([K^+]_o\), on potassium conductance (6, 7).

Since the passive cable properties did not appear to change sufficiently to account for the effects on conduction velocity, it is necessary to consider alterations in the active generator properties of the membrane. Certain effects of potassium on sodium current inactivation have been observed in squid axons, leading to a fall in excitability (e.g. 13). But as mentioned previously, Weidmann (4) studied the effects of increased \([K^+]_o\) on the relation between membrane voltage and availability of sodium inward current in cardiac Purkinje fibers. He found no effect on the relation except that which could be accounted for by the resulting depolarization. To the extent that the fiber is depolarized by increased \([K^+]_o\), there is less sodium inward current available. This effect is probably sufficient to explain the fall in excitability with 7.0 mM \([K^+]_o\). However, the rise in conduction velocity between 2.7 and 4 mM \([K^+]_o\) could not be explained in this fashion.

The increase in excitability seen at 4.0 mM \([K^+]_o\), was documented by measurement of strength-duration curves. It is apparent that the entire strength-duration curve was shifted, with an accompanying fall in rheobasic current. These two effects are associated with only a small change in the voltage value of threshold. Since the fibers are depolarized by the increase in \([K^+]_o\), the change in voltage necessary to raise the membrane to threshold is less, and the current required is less. This effect is emphasized in the experiment in which no increase in conduction velocity occurred. In that case the voltage threshold changed as much as the fiber was depolarized, and the rheobasic current was not reduced. A similar effect of depolarization on excitability was shown in nerve by Hodgkin (14), who employed spread of electrotonus beyond a block, and in skeletal muscle by Jenerick and Gerard (15).

According to the local circuit theory of conduction, currents must flow from the excited portion of the fiber to the unexcited portion. If less current is required to excite the membrane, then it seems likely that it would be activated sooner, with a resulting increase in conduction velocity on changing \([K^+]_o\) from 2.7 to 4.0 mM.

There remain a number of factors relating excitability to conduction that are not clarified by these experiments. Flow of current from the active portion of the fiber to the inactive portion, producing the foot of the action potential, lasts only a part of a millisecond before threshold is reached. Therefore the rheobasic current is not the factor likely to be directly involved; responses of the fiber to short stimuli ought to be more important. Unfortunately, there is no direct way to compare results from studies using square current steps with the physiological stimulus of the exponentially increasing action potential foot.

The simple relationship between stimulation current and its duration stated in equation 1 appears to describe adequately the experimental results in nerve. Formally, this might represent the charging of a resistance-capacitance circuit to a constant voltage. Noble and Stein (16) have discussed some of the factors that should influence the shape of the strength-duration relationship for nerve. For example, they suggest that the voltage change required for very short pulses may be larger than for longer pulses, perhaps in order to hold the fiber above threshold until the excitatory process can be activated. That this is important in conduction is suggested by the fact that the exponential foot of the Purkinje fiber action potential rises from the resting potential to as high as \(-10\) or \(-20\) mv before a local response occurs. The higher voltages necessary for excitation with stimuli shorter than 1 msec in these experiments may have been a reflection of this latency. A second possible explanation for the higher voltage required for stimulation by short pulses could be related to charge distribution down the cable. A finite time is necessary for membrane charge to redistribute and alter voltage across a large enough area of membrane to permit excitation. If the stimulating pulse is short relative to this redistribution time, a higher
voltage would be recorded at the stimulation point.

The time constant of the strength-duration curve is markedly shorter than the membrane time constant determined by cable analysis. The strength-duration time constant was calculated by plotting the quantity \( I_0 \) against pulse duration and extrapolating to the zero time axis. In nerve, the quantity of charge \( I_0 \) becomes almost constant. In these experiments the quantity of charge required fell progressively with shorter pulses to the range of 100 \(^s\) seconds. For pulses shorter than this, the current applied was not sufficiently constant to permit exact analysis. The threshold charge might not be expected to be constant because the membrane equivalent circuit of the Purkinje fiber is probably not a simple resistance and capacitance (8, 17). The relevant time constant for comparison with that of the strength-duration curve might be approximated by the foot of the propagating action potential. Some support for this influence on the shape of the strength-duration curve in heart muscle can be found in the studies of Orias et al. (18). Using extracellular electrodes, they determined the diastolic strength-duration curve of dog ventricular muscle and found that the charge requirement for short stimuli was substantially less than for pulses of 1 or 2 msec. A similar complex membrane equivalent circuit for skeletal muscle has been described by Falk and Fatt (19) and might influence the strength-duration relation in skeletal muscle.

References
Influence of Extracellular K\(^+\) Concentration on Cable Properties and Excitability of Sheep Cardiac Purkinje Fibers

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