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HEART MUSCLE CELLS AS PREDICTED BY THE
ASSOCIATION-INDUCTION HYPOTHESIS *

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Reprinted from
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Volume 204, Pages 534-537
March 30, 1973

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Experiments concerning the accumulation of potassium, rubidium, and cesium ions (K^+ , Rb^+ , Cs^+) in the perfused guinea-pig heart had demonstrated that the transport mechanism into the cells of these ions is similar.^{2, 3} The influx V_i of an alkali ion i could be described by the following equation:

$$V_i = \frac{V_{i\max} \cdot k_i \cdot c_{i1}}{1 + k_i c_{i1} + k_j c_{j1}} \quad (1)$$

$V_{i\max}$: maximum influx of the alkali ion i ; c_{i1} , c_{j1} : extracellular concentrations (mM/l) of the alkali ions i , j ; k_i , k_j : constants; i, j : K^+ , Rb^+ , Cs^+ ; k_{K^+} : 0.19; k_{Rb^+} : 0.28; k_{Cs^+} : 0.10

It is well known that this equation can be interpreted by different models. But all models in question must assume from this finding (Equation 1) that K^+ , Rb^+ , and Cs^+ influence the resting potential (RP) of the muscle cell in a similar manner. Thus, the question arises: Is it possible to predict the influence of Rb^+ and Cs^+ on the RP compared with K^+ , if only the ion fluxes are known? This question should be considered from two points of view: the membrane theory and the association-induction hypothesis.

Membrane Theory. According to the membrane theory the RP (ψ) is a diffusion potential caused primarily by the extra- and intracellular concentrations of sodium and potassium ions ($[Na^+]_{ex}$, $[Na^+]_{in}$, $[K^+]_{ex}$, $[K^+]_{in}$) and by the mobilities of these ions in the cell membrane, as expressed by the following equation:

$$\psi = \frac{RT}{F} \ln \frac{P_K [K^+]_{in} + P_{Na} [Na^+]_{in}}{P_K [K^+]_{ex} + P_{Na} [Na^+]_{ex}} \quad (2)$$

R, T and F have their usual meaning; P: permeability coefficient

The chloride portion of the Goldman-Hodgkin-Katz equation⁷ is omitted because it is widely accepted that chloride is passively distributed across the cell membrane as a function of the RP.^{1, 6} Assuming an additional steady state of extra- and intracellular Rb^+ or Cs^+ , corresponding terms of these ions must be added to Equation 2. From Equation 2 it can be seen that it is not possible to predict the influence of Rb^+ and Cs^+ in relation to K^+ on the RP from known fluxes, as the permeability coefficients cannot be evaluated without potential measurements. If the extra- and intracellular concentrations of an

* This work was supported by Deutsche Forschungsgemeinschaft, Bad Godesberg, Sonderforschungsbereich 38 (Membranforschung), Federal Republic of Germany.

ion are known, the permeability coefficient must be evaluated, for example, from influx and potential measurements according to the constant field approximation: ⁵

$$V_i = P_i \cdot \frac{F}{RT} \cdot \frac{\psi}{(1 - e^{-\psi F/RT})} \cdot c_{i1} \quad (3)$$

V: influx; P: permeability coefficient; c_1 : extracellular concentration; i: K^+ , Rb^+ , Cs^+ ; V and P in relative units

Association-Induction Hypothesis. According to Ling's association-induction hypothesis,^{8,9} the RP (ψ) is a phase boundary potential caused by an adsorption of potassium ions to anionic sites of the cell surface. This is expressed by the equation:

$$\psi = \frac{RT}{F} \ln \frac{\text{const.}}{[K^+]_{\text{ex}}} \quad (4)$$

Assuming that the influx of K^+ starts from adsorption sites at the cell surface, the influx would be proportional to the number of occupied sites at the surface. Therefore it should be possible to evaluate the quantity (in relative units) of surface-adsorbed K^+ , Rb^+ and Cs^+ from Equation 1:

$$N_i/N_0 = k_i c_{i1} / (1 + k_i c_{i1} + k_j c_{1j}) \quad (5)$$

N_i : number of adsorption sites which are occupied by the i th ion; N_0 : total number of adsorption sites; i, j: K^+ , Rb^+ , Cs^+ ;
 k_{K^+} : 0.19; k_{Rb^+} : 0.28; k_{Cs^+} : 0.10

Equation 5 describes a mixed adsorption of the Langmuir type. The preference in occupying the adsorption sites would be in the order $Rb^+ > K^+ > Cs^+$. Now it should be possible to predict the influence of Rb^+ and Cs^+ in relation to K^+ on the RP. Assuming a given relationship between the extracellular K^+ concentration and the RP, one calculates from Equation 5 the K^+ concentration c'_{1K^+} that produces the same RP as produced by two given extracellular alkali ion concentrations c_{1K^+} and c_{1j} (j: Rb^+ , Cs^+) according to:

$$N'_{K^+}(c'_{1K^+}, c_{1j} = 0) = N_{K^+}(c_{1K^+}, c_{1j}) + N_j(c_{1K^+}, c_{1j}) \quad (6)$$

N_{K^+} and N_j are calculated from Equation 5; j: Rb^+ , Cs^+

Potential measurements on isolated guinea-pig papillary muscles were performed as described in an earlier paper⁴ (3 M KCl-filled microelectrodes, tip potentials < 5 mV, resistances between 5 and 20 megohms). The results are given in FIGURE 1, which demonstrates the influence of extracellular K^+ , Rb^+ , and Cs^+ on the RP. All measurements started with an extracellular K^+ concentration of 5 mM/liter, then K^+ , Rb^+ , or Cs^+ were added. The RP had reached its final value about two minutes after addition of K^+ , about 25 minutes after addition of Rb^+ , and about 60 minutes after addition of Cs^+ . All changes of the RP were reversible! The resting potentials measured with an extracellular K^+ concentration of 5 mM/liter (80–95 mV) were normalized to 100%. Each symbol in FIGURE 1 represents the average of 4 to 6 experiments.

The membrane theory concept was tested as follows. It was assumed that the steady state alkali ion fluxes of the papillary muscle are similar to that of the perfused guinea-pig heart. The permeability coefficients were calculated according to Equation 3 and the expected RP was calculated according to

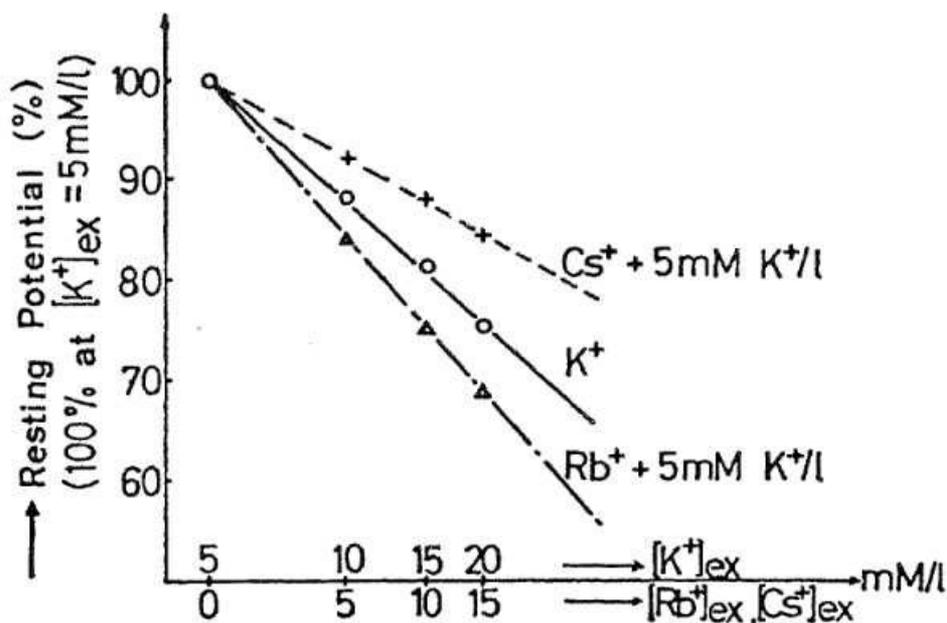


FIGURE 1. Influence of extracellular K^+ , Rb^+ and Cs^+ on the RP of guinea-pig papillary muscle cells (after Edelmann and Baldauf⁴).

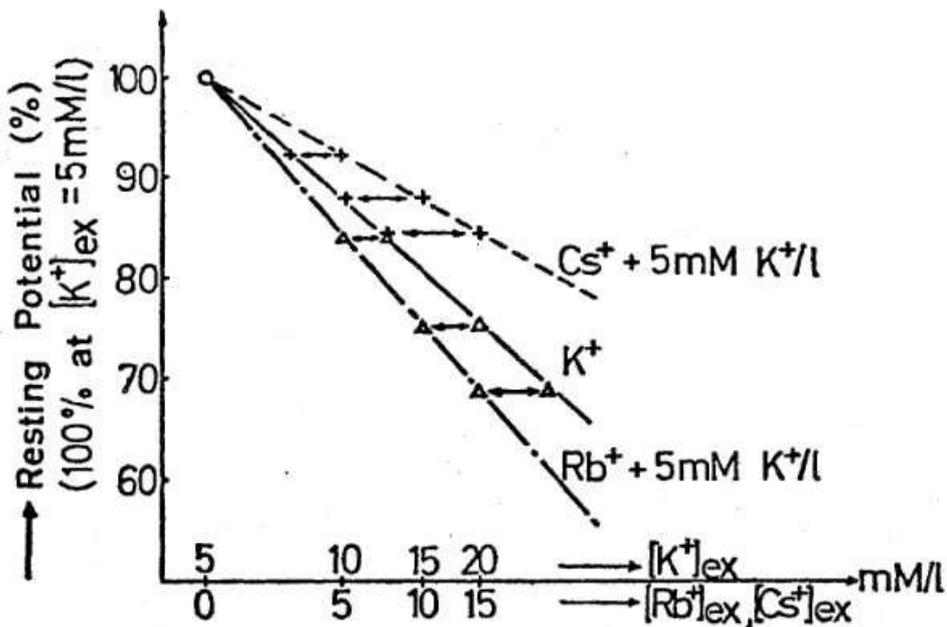


FIGURE 2. Influence of extracellular K^+ , Rb^+ , and Cs^+ on the RP of guinea-pig papillary muscle cells. The curves are equal to those of FIGURE 1. The symbols Δ and $+$ on the measured K^+ curve are calculated from the Rb^+ and Cs^+ symbols of FIGURE 1 and Equation 6 (after Edelmann and Baldauf⁴).

Equation 2, enlarged by Rb^+ or Cs^+ terms. No correspondence between theory and measurements could be found. The theoretically expected influence of Rb^+ was less than the influence of K^+ , and the expected effectiveness of Cs^+ was much less than the observed effectiveness. This discrepancy may be explained by a change of the permeability coefficient of Na^+ but this change seems to be very unlikely. Further investigations should reveal the influence of K^+ , Rb^+ , and Cs^+ on the permeability coefficient of Na^+ .

The predictions of the association-induction hypothesis were compared with the experimental results. FIGURE 2 demonstrates the correspondence between the prediction and the experiment. The symbols on the *measured* K^+ curve are calculated from the Rb^+ and Cs^+ symbols of FIGURE 1 and Equation 6. Since the best a scientific theory can do is to enable us to make precise predictions, the association-induction hypothesis has demonstrated its usefulness in relation to the membrane theory.

Another argument against the diffusion-potential concept can be derived from the fact that the final value of the RP is reached two minutes after addition (or subtraction) of K^+ to (or from) a given extracellular K^+ concentration. The steady state between extra- and intracellular K^+ occurs very much later^{2,3!} Similarly, the steady state of Rb^+ or Cs^+ occurs much later than 25 minutes or 60 minutes after addition of these ions. Why are the final values of the RP reached two minutes, 25 minutes, or 60 minutes after addition of K^+ , Rb^+ , or Cs^+ to a given extracellular K^+ concentration? The problem may be attributable to the migration rates of the different ions to the adsorption sites of the cell surface. Further potential measurements on cells of the perfused guinea-pig heart should reveal if this assumption is correct.

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