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Part 6/6

Track 5. Student Activities & Paper Competition
Track 12. Artificial Intelligence & Information
Track 13. Computers in Medicine
Track 14. Neural Networks

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Track 5: Student Paper Competition

THE DYNAMIC BREAKDOWN OF HEART CELL MEMBRANES EXPOSED TO RAMP INCREASES IN TRANSMEMBRANE POTENTIAL

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ABSTRACT

Membrane patches of single frog ventricular cells drawn into glass micropipettes were exposed to relatively large transmembrane potentials using a custom-built whole cell patch clamp unit. The current through the pipette was measured during the application of voltage ramps which enabled the observation of rapid changes in membrane impedance due to electrical breakdown. Our results show that the dynamic electrical breakdown of heart cell membrane involves threshold levels of transmembrane potential above which there exist, 1) a period of reversible membrane instability, and 2) a rapid, irreversible increase in membrane permeability.

The data suggest that the threshold voltages for the onset of these events are independent of the polarity of the applied voltage ramp. The data support the theory that membrane breakdown is a function of transmembrane potential, i.e. a process of electroporation. The advantage of using ramp waveforms for membrane breakdown studies is discussed.

INTRODUCTION

Electroporation of the cell membrane by high intensity, pulsed electric fields appears to be a universal phenomenon and is critically dependent on the magnitude of the induced transmembrane potential [1,2]. A transmembrane potential around 1 volt appears to be the threshold level for electroporation to occur [3]. Direct studies have not, however, been performed in cardiac muscle, despite the common clinical situation in which heart muscle is subjected to intense electric fields during defibrillation. Electrophysiological studies in intact heart [4] and heart cell aggregates [5] provide indirect evidence for an increase in the permeability of the cell membrane as a function of field intensity. Our laboratory has recently used cell contractility as a biological assay of cell permeability and shown it to be a hyperbolic function of field intensity and duration [6]. One difficulty with this approach is that the relation of transmembrane potential to the applied electric field is not known exactly. We have therefore adopted a variation of the whole cell voltage clamp technique, using a suction pipette with a "loose seal" around a membrane patch. In this way we can control the membrane potential across a portion of the cell membrane and observe the dynamic change in membrane resistance as the threshold for breakdown is exceeded. The aim of our study is to obtain information relevant to the understanding of the possible role of electroporation in high energy shock of cardiac muscle.

METHODS

Single ventricular heart cells (5 -10 μm diameter, 200 - 400 μm long) isolated from adult frogs (*Rana pipiens*) were drawn into a glass micropipette using suction until a seal resistance of 10 - 50 MΩ was attained (see Figure 1 inset diagram) [7]. Seal resistances <10 MΩ allowed too much shunting of current to permit the changes in the cell membrane impedance to be sensed. Cell size and pipette lumen diameter determined how much of the cell entered the pipette; the range was approximately 5 - 15 μm.

The experimental set-up included an inverted microscope, a custom-built whole cell patch clamp unit, and a ramp generator circuit. The experimental protocol was to 1) apply suction to the pipette while imposing 10 mV, 2.0 msec rectangular pulses to monitor the seal resistance; 2) apply ± 100 mV, 7.0 msec ramps to assess the linearity of the total pipette impedance; and 3) deliver a single ± 2.0 V, 7.0 msec ramp shock. A transmembrane potential of 1 volt corresponds to a peak field intensity on the order of 10^6 V/cm across the cell membrane. The total pipette impedance consists of three major parallel pathways (see Figure 1 below): 1) the distributed capacitance across the glass pipette, 2) the cell-to-glass seal resistance, and 3) the cell membrane impedance. Changes in 3) would then be reflected in changes in pipette impedance.

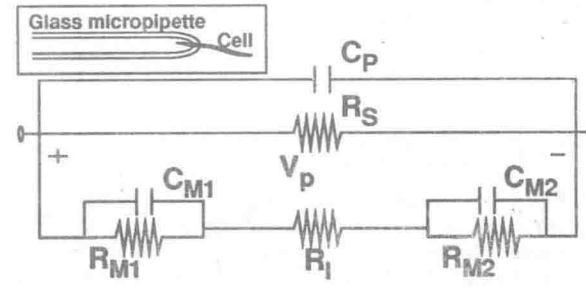

FIGURE 1 - Equivalent electrical circuit for the total pipette impedance: C_P is the distributed pipette capacitance, R_S is the cell-to-pipette seal resistance, $R_{M(i)}$,$C_{M(i)}$ are the membrane resistance and capacitance (subscript 1 denotes membrane patch within pipette and 2 denotes the membrane within the bath), R_I is the intracellular resistance and V_p is the pipette voltage. The inset diagram depicts the cell inserted into the pipette.

EXPERIMENTAL RESULTS

Following the formation of the seal the cell was exposed to the low level voltage ramps shown in Figure 2 A. For the case of a cell depolarized by using a bath solution which mimicked the intracellular environment (high potassium, low sodium, zero calcium), the pipette current responded linearly and symmetrically (Figure 2 B). This current most likely flows through the seal resistance pathway (Figure 1). Depolarization of the cell was used to inhibit ionic action currents which would interfere with the measurement of membrane impedance.

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