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A COMPUTATIONAL MODEL OF ACTION POTENTIAL IN THE MOUSE DETRUSOR SMOOTH MUSCLE CELL

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ABSTRACT

Urinary incontinence is associated with enhanced spontaneous phasic contractions of the detrusor smooth muscle (DSM). It is suggested that the spontaneously evoked action potentials (sAPs) in DSM cells initiate and modulate the contractions. In order to further our understanding of the underlying ionic mechanisms in sAP generation, we present here a biophysically detailed computational model of a single DSM cell. We constructed mathematical models for nine ion channels found in DSM cells based on published experimental data. After incorporating all ion channels, our DSM model is capable of reproducing experimentally recorded spike-type sAPs of varying configurations. Our model, constrained heavily by physiological data, provides a powerful tool to investigate the ionic mechanisms underlying the genesis of DSM electrical activity, which can further shed light on urinary bladder function and dysfunction.

1 INTRODUCTION

Urinary incontinence (UI) is defined as the involuntary loss of urine that can be demonstrated objectively and which constitutes a social or hygienic problem (Abrams et al., 1990). Overactive Bladder is a type of UI, which is an associated with a strong premature desire to urinate and correlates with an overactive detrusor smooth muscle (DSM) cell. Spontaneous contractile activity is recorded in DSM strips of mouse, rat, pig, guinea pig and humans. Membrane electrical activity in the form of action potentials (AP) play an important role in initiating the DSM contraction by mediating influx of Ca^{2+} through voltage-gated Ca^{2+} channels. Computational models can quantitatively analysis the interactions among various ion channels and allow the user to investigate the contribution of each ion channel to the overall observed cellular electrical behavior. To date, a biophysically detailed computational model does not exist for DSM cells. Here, our primary goal was to develop a robust biophysical model of the AP as feasible from available experimental data, and from this, to gain insights into experimental observations made on DSM cells as well as to make predictions regarding the behavior of these cells under conditions of abnormal ion channel function.

2 METHODS

Cylindrical single cell morphology was considered as a DSM cell model. The cylinder length, diameter, membrane capacitance (C_m), membrane resistance (R_m) and axial resistance values are taken from experimental value (Fry et al.1999). The individual membrane current components that were modelled were (i) three inward currents: L-type and T-type Ca^{2+} currents, a hyperpolarization-activated current; (ii) six outward K^+ currents: two voltage-gated K^+ currents, an ATP-dependent K^+ current and three Ca^{2+}-activated K^+ currents; and (iii) an outward back-ground leak current. Here the mathematical model for individual ionic current is based on the classical Hodgkin-Huxley approach. The membrane potential is function of both time and ionic currents across the membrane. It is governed by the following equation.

$$\frac{dV_m(t)}{dt} = -\frac{I_{ion\,(t)}}{C_m} \quad (1)$$

In equation (1), V_m (in mV) and I_{ion} (in pA) are known as transmembrane potential and the sum of ionic currents crossing the cell membrane respectively. The ion channel conductance value determines the ion channel current and it is calculated after putting different time and voltage dependent parameters in differential equations. The parameters are extracted from the experiments.

3 RESULTS

The resting membrane potential V_m is tuned to ─ 50 mV in the output simulation by adjusting the respective ion channels' conductance value, within their respective physiological ranges. Then, APs were simulated by injecting an external stimulus, either as a brief rectangular pulse of current duration (0.5-50ms) or as bi-exponential function with rising and falling time constants that mimic synaptic conductance. Fig 1 illustrates the AP and associated ionic currents elicited by injecting 0.2 nA brief rectangular pulse for 5ms. The voltage threshold is ≈ ─ 30 mV.

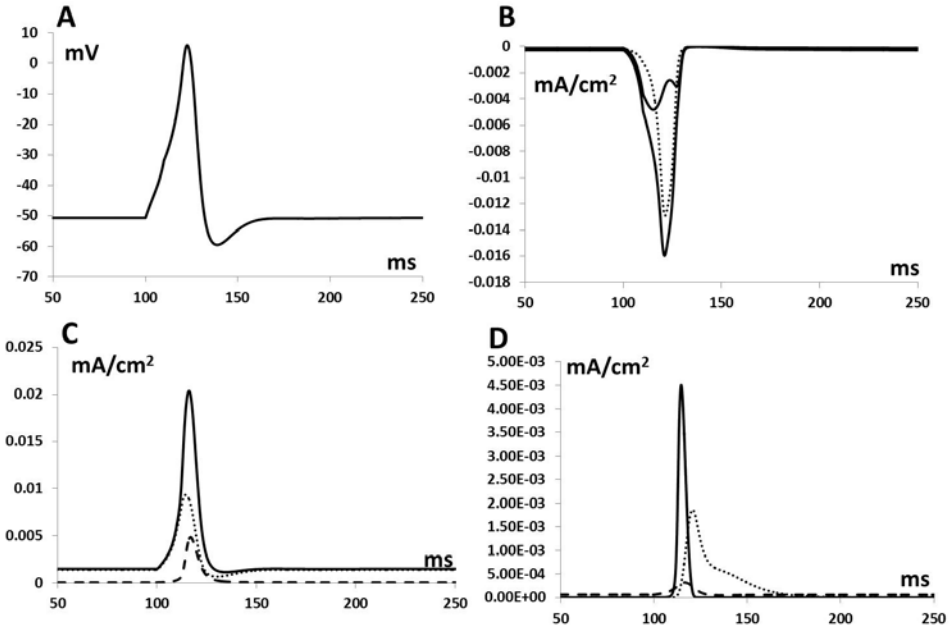

Fig 1. Current induced Simulated AP and ionic currents. (A) Simulated AP. (B) Total inward current (thick solid line), L- type Ca^{2+} channel current (dotted line) and T- type Ca^{2+} channel current (dashed line). (C) Total outward current (thick solid line), BK channel current (dotted line) and KCNQ channel current (dashed line) (D) Outward current Kv2 channel current (thick solid line), SK channel current (dotted line) and IK channel current (dashed line).

The precise cause of unstable detrusor still remains elusive and little has changed in the last 40 years. Further development of the DSM cell model may help in the testing or validation of contending hypotheses. This may help in the identification of the underlying causes of unstable DSM and allow better drugs to be developed for its treatment.

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