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ELECTROPHYSIOLOGICAL MODELING OF ELECTRICAL ACTIVITIES IN DETRUSOR SMOOTH MUSCLE CELLS: ROLE OF PURINERGIC SYNAPTIC INPUT IN SHAPING ACTION POTENTIAL

Hypothesis / aims of study

Detrusor smooth muscle (DSM) instability is a major cause of urinary bladder overactivity. According to various experimental results, DSM cells from several families of species invoke spontaneous contractile activity at different frequency [1]. Excitation of the DSM cell is achieved through the parasympathetic activation of both purinergic (ATP) and cholinergic (ACh) neurotransmission [3]. Spontaneous Purinergic Neurotransmission (SPN) was characterized in the DSM cells in terms of spontaneous excitatory junction potential (sEJP) that triggers the opening of L-type Ca^{2+} channels to initiate spontaneous action potentials (sAP). Information on how these sEJPs modulate the shape and time course of sAPs in DSM cell is sparse. A computational model can concisely summarize the experimental measurements and provides a common framework for interpreting future hypothesis. Here, we have aimed to establish a computational platform to advance our understanding of the electrophysiological basis of sAP modulation due to SPN in DSM cell.

Study design, materials and methods

The DSM cell membrane is described as an equivalent electrical circuit consisting of a membrane capacitance connected in parallel with a number of variable conductances representing the ion channels. We have considered a cylindrical single cell morphology 200 µm in length and 6µm in diameter. Membrane capacitance (Cm) is taken as 1µF/cm^2. The membrane resistance (Rm) is 138MΩ– cm^2 and axial resistance is 181Ω-cm. This model has incorporated voltage gated Ca^{2+} (T - type and L- type) channels, three voltage gated potassium (Kdrs, Kdrf and Ka) channels and two calcium dependent potassium (BK and SK) channels. These channel models are borrowed from our previous model [2]. The purinergic synaptic conductance profile is consisting of a sum of two exponentials defined in following equation.

$$g_{syn}(t) = \bar{g}_{syn} f\left(e^{\frac{-(t-t_0)}{\tau_{decay}}} - e^{\frac{-(t-t_0)}{\tau_{rise}}}\right)$$

Where $g_{syn}(t)$ is synaptic conductance, $\bar{g}_{syn}$ is maximum synaptic conductance, τ_{rise} is time constant for rising exponential and τ_{decay} is time constant for the decay phase exponential. The purinergic synaptic input is injected when time is 300ms.

Results

The resting membrane potential (RMP) is determined (–50mV) mostly by the balance between depolarizing currents through T - type Ca^{2+} channel and repolarizing currents through various Potassium channels. The rising time constant τ_{rise} and decaying time constant τ_{decay} are 5ms and 60ms respectively. In figure 1(A), black solid line represents the membrane depolarization (EJP) due to purinergic neurotransmission and red solid line represents evoked AP due to EJP. The synaptic conductance $\bar{g}_{syn}$ of 0.0001µs depolarizes the membrane to –30mV, which subsequently opens L- type Ca^{2+} channel for AP generation. The AP is characterized by rising (depolarizing) phase, falling (repolarizing) phase, and presence of an after- hyperpolarization (AHP) or after-depolarization (ADP) phase. L – type Ca^{2+} channel with zero conductance results elimination of AP. In Figure 1(B), two APs are presented with different value of $\bar{g}_{syn}$. The AP in blue solid line has $\bar{g}_{syn}$ of 0.0002 µs, whereas AP in red solid line has $\bar{g}_{syn}$ of 0.0016 µs. The AP with lower synaptic conductance (blue solid line) shows –10mV of after hyperpolarization and slow rise in depolarization phase. However, the AP with higher synaptic conductance (red solid line) shows 5mV of after depolarization and fast rise in depolarization-phase.

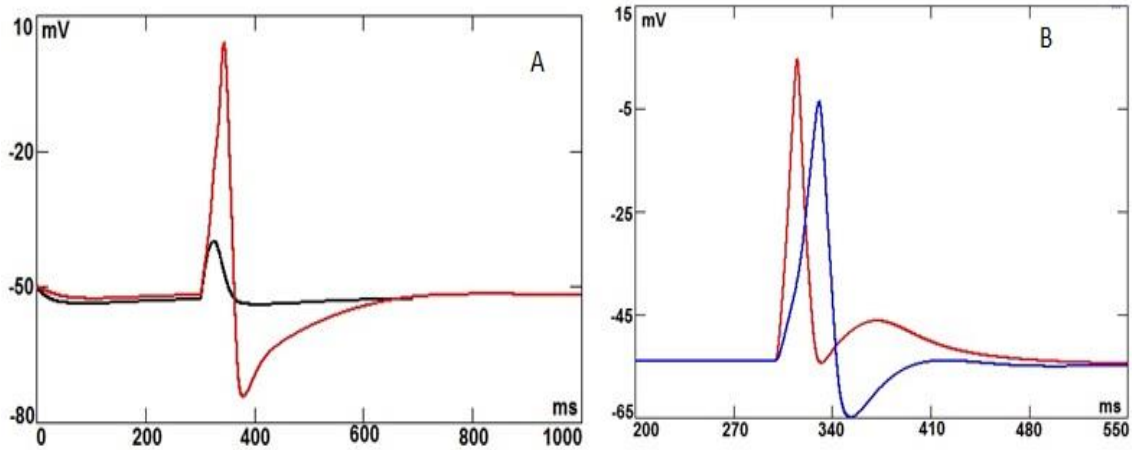

Figure 1: (A) Spontaneous sEJP (black solid line) and evoked sAP (red solid line), (B) AP with $\bar{g}_{syn}$ of 0.0002 µs (blue solid line) and 0.0016 µs (red solid line).

Interpretation of results

The presence of T – type Ca^{2+} channel depolarizes the resting membrane potential. It is also observed that L – type Ca^{2+} channel is essential for AP generation. As the $\bar{g}_{syn}$ is directly proportional to amount of purinergic neurotransmission, an important implication of our simulation result is that the shape and time course of sAPs are purely neurogenic.

Concluding message

To the best of our knowledge, this is the first biophysical model of purinergic neurotransmission in DSM cell. Our simulated sEJPs and sAPs show good agreement with experimental documented data. This present model demonstrates that sAPs occur when the amplitude of sEJPs are sufficient to trigger L-type Ca^{2+} channel opening. The time course and depolarization amplitude of sEJPs modulate the timing and amplitude of sAPs. We are looking forward to integrate this model in a smooth muscle syncytium to investigate the influence of gap junction in detrusor overactivity.

References

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