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Computational assessment of drug-induced effects on the mouse ureter smooth muscle cells: from ionic current to action potentials.

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Background: Ureter smooth muscle (USM) cell generates spontaneous myogenic contraction. Although the mechanisms underlying these spontaneous myogenic contractions are unclear, it is suggested that intracellular ionic mechanisms plays a dominant role in generating spontaneous electrical activities in term of action potential (AP) for spontaneous contraction. Computational models can succinctly describe 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. Our work presents the first biophysically based model of USM AP to simulate the effect of drugs action on the electrical activity of the USM cells, at the level of the ion-channels and APs.

Methods: The cylindrical single cell morphology is based on experimental data. We have developed the mathematical models for seven ionic currents in USM cells, where the magnitudes and kinetics of each ionic current are described by differential equations, in terms of maximal conductances, electro chemical gradients, and voltage-dependent activation/inactivation gating variables. A drug model is introduced using an ion channel conductance block for the 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. We have simulated mouse USM APs (spike type and pace maker type) and compared the effects under different drug actions with experimental validation.

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. Introducing a 50% L – type Ca^{2+} channel current block results elimination of APs. The blocking of 50% T – type Ca^{2+} channel current results 10% decrease in RMP, resulting in increased threshold for AP initiation. The 50% voltage gated potassium channel current block results 15% increase in AP's peak amplitude, 30% increase in AP width,14% decrease in RMP and no change in after hyperpolarization (AHP) amplitude. The 50% large conductance (BK) calcium gated potassium channel current block results 30% increase in AP's peak amplitude, 50% increase in AP width,10% decrease in RMP and no change in AHP amplitude. Introducing 50% small conductance (SK) calcium gated potassium channel current block prolongs the AHP period, whereas other parameters of APs are not affected.

Conclusion: The T – type Ca^{2+} channel current block modulates RMP, but the underlying mechanisms also depend upon potassium channels. The L – type Ca^{2+} channel is essential for AP generation. The SK channel

regulates the AHP period, hence the AP frequency in DSM cells. As BK channel block regulates the peak and duration of APs, it is a dominant channel in USM contraction. This study shows the applicability of in silico models for the investigation of drug effects on the USM cells, from ion channels to AP.

Keywords: Ion channel , Biophysical model , Spontaneous contractions