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

BACKGROUND AND PURPOSE: Detrusor smooth muscle (DSM) instability is a major cause of urinary bladder overactivity. Due to unpleasant side effects of conventional drugs, researchers are trying for novel targets to modulate over active bladder. Different ion channels within urinary bladder DSM cell play role in generating electrical activities such as action potentials (APs) and synaptic depolarizations. Understanding the drug effects with respect to various ion channels on DSM cells is the key to safety pharmacology assessment. Computational models can succinctly describe the drug interactions among various ion channels and allow the user to investigate the contribution of each ion channel to the observed cellular electrical behavior. Here our goal is to demonstrate the ability of computational models to simulate the effect of drugs action on the electrical activity of the DSM cells, at the level of the ion-channels and APs.

METHODS: The 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. The cylindrical single cell morphology is based on experimental data. We have developed the mathematical models for seven ionic currents in DSM 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 DSM APs (spike type and pace maker type) and compared the effects under different drug actions with experimental validation.

KEY RESULTS: The resting membrane potential (RMP) is determined (–55mV) 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.

CONCLUSIONS AND IMPLICATIONS: 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 detrusor instability. This study shows the applicability of in silico models for the investigation of drug effects on the DSM cells, from ion channels to action potentials.