In silico pharmacological assessment of Nifedipine and Mibefradil in mouse detrusor smooth muscle cells towards detrusor instability

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BACKGROUND

Detrusor smooth muscle (DSM) instability is a major cause of urinary bladder overactivity. Due to adverse side effects of conventional anticholinergic drugs, researchers are focusing on novel drug compounds with high specificity. Understanding the drug effects with respect to various ion channels offers additional possibilities for safety pharmacological assessment. Here our overarching objective is to utilise the computational model to simulate the effects of nifedipine and mibefradil on DSM cell action potential (AP).

METHODS

The DSM cell is described as an equivalent electrical circuit consisting of a membrane capacitance connected in parallel with a number of variable conductances representing two voltage gated Ca^{2+} (T and L type) channels, two voltage gated potassium (Kv , KCNQ) channels, three calcium dependent potassium (BK , IK and SK) channels, an ATP dependent potassium channel and an inward rectifying cation channel. A drug model for nifedipine and mibefradil were simulated by multiplying the maximal conductance of L and T type channel with a scaling factor between 0 and 1 to mimic the drug concentration.

RESULTS

The resting membrane potential (RMP) is set at negative 50mV by balancing the ion channel conductances. A current pulse of 2 nA for 10 ms is injected to evoke the AP. The peak amplitude of AP and total inward current are substantially reduced after adding nifedipine by half fold and two fold to its control value. Adding mibefradil by half fold of its control value reduced the peak amplitude of AP and inward current. However, the addition of mibefradil by two fold results no AP and zero inward currents. The results show that both L and T types Ca^{2+} channel play important roles in generating APs, although L type Ca^{2+} channel is the major contributor to the total inward current.

CONCLUSIONS

This in silico assessment showed that while inhibition of L type Ca^{2+} channel suppresses or eliminates APs, the RMP is left unaffected. Complete inhibition of T type Ca^{2+} channel hyperpolarized the RMP, eliminated the AP and reduced DSM cell excitability. A compound of nifedipine and mibefradil may form a part of new pharmacological maneuver towards detrusor instability.