Neurophysiology, Vol. 47, No. 3, June, 2015

Biophysical Processes in a Urinary Bladder Detrusor Smooth Muscle Cell during Rehabilitation Electrostimulation: a Simulation Study

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Received March 18, 2014.

The work was aimed at the search for approaches to solving the problem of biophysically reasonable selection of the parameters of electrical stimulation of smooth muscle cells (SMCs) of the urinary bladder detrusor (UBD). Such stimulation is widely used in the rehabilitation of patients with surgical correction of congenital malformations accompanied by total or partial deficiency of the M2/M3 cholinergic receptors in the UBD. A computer model built on the basis of experimental data on ion channels and pumps of the sarcolemma and mechanisms of regulation of the intracellular calcium concentration ($[Ca^{2+}]_i$), providing both electrogenesis and the contractile function of the cell inherent to the biological prototype, was used. We studied changes in the membrane potential, partial transmembrane currents, and $[Ca^{2+}]_i$, caused by depolarizing current pulses applied with constant frequencies and combined in "packs" or "envelopes" typical of the protocols of rehabilitation stimulation; the stimuli had constant or trapezoid-modulated amplitudes. The examined UBD SMC responded to a single pulse by generation of the action potential (AP) close in its properties to the prototype. Stimulation by both packs and envelopes of identical pulses eventually led to the establishing of equal forced electrical and concentration oscillations with the parameters depending on the duration of interpulse intervals (IPIs). Such oscillations caused by stimulation with 5- and 50-msec-long IPIs, typical of the rehabilitation protocols and comparable with the durations of the absolute and relative refractoriness of the model SMC, significantly differed in the pattern of the regenerative responses (APs) and in the range and mean levels of depolarization shifts of the membrane potential and those of $[Ca^{2+}]_i$, which were greater at high-frequency stimulation. In the case of short IPIs, $[Ca^{2+}]_i$, having no time to return to the basal level, oscillated within a range of values which in other excitable cells are considered to exceed significantly the physiological norm. These data emphasize the necessity to estimate the exact kinetic characteristics of the mechanisms underlying the inflow and extrusion of Ca^{2+} in the UBD SMC necessary for a biophysically justified choice of the parameters of rehabilitation stimulation that would prevent possible cytotoxic side effects associated with excessively long-lasting high levels of $[Ca^{2+}]_i$. Essential for the observed processes and, therefore, requiring targeted studies, was such a parameter of UBD SMCs as the reversal potential for Ca^{2+}-dependent chloride current (E_{Cl}); this current is activated, in particular, by parasympathetic action on the M2/M3 receptors. When high-frequency oscillations of the membrane potential periodically exceeded the E_{Cl} level, the mentioned current changed its main (depolarizing) direction to the opposite (hyperpolarizing) one.

Keywords: mathematical model, smooth muscle cell (SMC), urinary bladder detrusor (UBD), electrostimulation, ion channels, intracellular calcium.

INTRODUCTION

Trans-tissue electrical stimulation of the pelvic floor and urinary bladder detrusor (UBD) is an important component of medical rehabilitation procedures demonstrating rather high efficacy in patients with surgical correction of severe congenital malformations of the pelvic organs (rectal atresia, RA, and bladder exstrophy–total epispadias, BETE) [1–3]. The occurrence and severity of the mentioned pathologies necessitate in-depth studies of the physiological and biophysical mechanisms

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