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Impact of the Ratio of Metabotropic and Ionotropic Components of Parasympathetic Action on the Excitability of a Urinary Bladder Smooth Muscle Cell: a Simulation Study

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On a computer model of a smooth muscle cell (SMC) of the urinary bladder detrusor (UBD) having a corresponding set of ion channels and intracellular signaling mechanisms, we investigated the influence of ionotropic (purine, P) and metabotropic (muscarinic, M) components of the parasympathetic stimulus on the membrane potential of the cell and Ca^{2+} concentration inside it ($[Ca^{2+}]_i$). The P and M components of the stimulus were simulated, respectively, by the increasing conductivity of P2X receptor channels of the SMC membrane (G_{P2X}) and the permeability of calcium channels of the sarcoplasmic reticulum activated by inositol triphosphate (P_{IP3}), considering that IP3 is the end product of the metabotropic chain starting from the M3 cholinergic receptors. The G_{P2X} and P_{IP3} values, latent periods (LPs) of their activation, and relations of the above parameters were chosen in such a mode that application of a single stimulus evoked the SMC response with the P and M components close to those of the prototype. The normal magnitude and LP of the M component of the concentration response (calcium transient) were significantly greater than the respective parameters of the P component; the M component was accompanied by generation of an action potential (AP) with after-processes analogous to those of the prototype. A decrease in the P_{IP3} simulating a deficiency of M3 receptors observed under a few pathological conditions led to a decrease in the electric and concentration SMC responses, down to full elimination of AP generation and changes in $[Ca^{2+}]_i$. Under such conditions, a significant increase in the G_{P2X} could provide a $[Ca^{2+}]_i$ increase to a nearly normal level. Using paired parasympathetic stimulation with different interstimulus intervals, ΔT, allowed us to obtain a situation where the M response to the first stimulus (M1) was preceded by the P response to the second stimulus (P2) with a short adjustable interval. The use of such stimulation with certain values of the ΔT and conductivity of purinergic channels G_{P2X} can compensate for the attenuation of the M component, due to interaction of the latter with the P component caused by the second stimulus. Thus, pathological attenuation of the M component of the parasympathetic stimulation effect can be compensated in clinical practice (at least partly) by applying purinomimetics and/or paired stimulation.

Keywords: mathematical model, smooth muscle cell, urinary bladder detrusor, parasympathetic stimulation, purinoreceptors, muscarinic cholinoreceptors, intracellular calcium.

INTRODUCTION

Emptying of the urinary bladder is provided by contraction of smooth muscle cells (SMCs) of its detrusor (UBD) resulting from arrival of impulsation via parasympathetic nerve fibers. Excitation and contraction of UBD SMCs is associated with an increase in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) provided by co-activation of membrane ionotropic P2X purinoreceptors and metabotropic muscarinic M2/M3 cholinoreceptors under the influence of, respectively, ATP and acetylcholine released from parasympathetic efferents [1]. According to the existing concepts, the purine (P) pathway includes opening of the P2X receptor channels passing a depolarizing current, generation of the excitatory junction potential, and activation of the L-type calcium current transferring Ca^{2+} from the extracellular space [2, 3]. The muscarinic path (M path) is based on a chain of biochemical reactions, whose final product is inositol-3-phosphate (IP3).

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