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Biophysical Mechanism of Parasympathetic Excitation of Urinary Bladder Smooth Muscle Cells: a Simulation Study

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Using the Hodgkin-Huxley formalism, we developed a computer model of a smooth muscle cell (SMC) of the urinary bladder detrusor; the model included the main types of ion channels and pumps, as well as intracellular calcium regulatory mechanisms inherent in the prototype cell. The biophysical mechanisms of generation of action potentials (APs) necessary for initiation of muscle contraction and those of calcium transients in response to parasympathetic activation of metabotropic M2/M3-cholinoreceptors and co-activation of P2X-purinoreceptors were investigated. The simulated SMC in response to a depolarizing current pulse generated an AP that was, by a number of indices, similar to real APs and was also accompanied by a transient elevation of the intracellular calcium concentration. We demonstrated a possibility of generation of such APs in response to a transient increase in the conductivity of channels of calcium-dependent chloride current accompanied by increase in the conductivity of channels associated with P2X-receptors (the conductivity ratio was 95 to 5 % and similar to that in the prototype). For the AP generation, temporal relations of the processes of increases in the mentioned conductances simulating the final effect of activation of M2/M3- and P2X-receptors were significant. These results obtained on the rather simplified model allow researchers to use the latter as an appropriate starting point for the development of more detailed models (in particular, those representing cascades of metabolic reactions triggered by a parasympathetic action).

Keywords: smooth muscle cell (SMC), urinary bladder detrusor (UBD), metabotropic activation, mathematical model.

INTRODUCTION

Disclosing the biophysical mechanisms that provide nervous regulation of smooth muscle cells (SMCs) of the urinary bladder detrusor (UBD) is a topical fundamental task of cellular physiology and biophysics; successful solution of this task is of essential theoretical and practical significance. The significance of this problem for medicine is determined by the fact that functional disorders of the lower urinary tract, including neurogenic ones (e. g., UBD hyper- [1] or hypoactivity [2]), are widespread [3–5], and the diagnostics and treatment of them are rather difficult largely because of incomplete understanding of the mechanisms of innervation of SMCs of this tract in health and disease [3, 6, 7]. Many biophysical and physiological aspects of SMC excitation and contraction are still poorly understood because of methodological limitations of this object characterized by natural movability (changes of dimensions) that impedes stable recording of the electrical and concentration processes. Excitation and contraction of UBD SMCs are associated with activation of metabotropic muscarinic receptors by acetylcholine (ACh) released from terminals of the parasympathetic efferents [4, 8–10], namely axons of post-ganglionic neurons situated in the pelvic plexus and the bladder wall. A small contribution (normally 3–5 % and somewhat greater under some types of pathology [11, 12]) is provided also by ATP released from parasympathetic post-ganglionic nerve endings and acting on purinergic ionotropic receptors [9, 12]. In the above-described picture, many principal details are lacking. It is not entirely clear how functioning of the channels of inward current (in particular calcium current providing generation of depolarization action potentials, APs) depends on activation of metabotropic muscarinic receptors. Other matters of debate are the roles that different receptors (cholinergic and purinergic

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