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SIMULATION OF PATHOPHYSIOLOGICAL MECHANISMS OF CARDIAC MYOCYTES

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Pathophysiology offers a challenge to mathematical models of cell function, and provides opportunity to polish the model. The cardiac cell model, Kyoto model has successfully reconstructed electrical and mechanical responses of the cardiac myocyte to various interventions observed in usual physiological experimental conditions, such as varying the external ion concentrations, the stimulus frequency, applying pharmacological agents and modulating energy metabolism (Matsuoka et al., 2003, 2004). Recently we used Kyoto model to analyze mechanisms underlying the survival of the NCX knockout mice and also the cell swelling during the failure of the Na/K pump activity. Surprisingly, both simulation studies strongly suggested the involvement of PMCA (the Ca^{2+} pump on the cell membrane). Although the detail of the PMCA kinetics was not implemented in the model, the magnitude of PMCA reported in experimental studies was large enough to keep $[Ca^{2+}]_i$ in the physiological range in the NCX knockout condition in the guinea pig cell model, where the rhythmic contraction was achieved (Sarai et al., in press). The model suggested, however, the system depending on PMCA is much less stable than the physiological NCX dominant system. The cell volume is maintained by the active transport of the Na/K pump. However, the cell volume of the guinea-pig ventricular myocyte remains almost constant during 1~2 hrs exposure of guinea-pig ventricular myocytes to ouabain (Drewnowska and Baumgarten, 1991). Simulation using the cardiac cell model, incorporated with Cl^- and water fluxes, predicted roles of PMCA and Na^+/Ca^{2+} exchanger in maintaining the cell volume in addition to the reported low membrane permeabilities for Na^+ and Cl^-. Namely, PMCA might keep the $[Ca^{2+}]$ gradient across the membrane though compromised, and thereby promote the reversed Na^+/Ca^{2+} exchange supplemented with the increased $[Na^+]i$ as well as the membrane depolarization during the Na^+/K^+ pump block.

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SIMULATION OF PACEMAKER ACTIVITY IN MOUSE SMALL INTESTINE

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The pacemaker activity of interstitial cells of Cajal (ICCs) has been known to initiate the propagation of slow waves along the whole gastrointestinal tract through spontaneous and repetitive generation of action potentials. We studied the mechanism of the pacemaker activity of ICCs in the mouse small intestine and tested it using a mathematical model. The model includes ion channels, exchanger, pumps, and intracellular machinery for Ca^{2+} regulation. The model also incorporates inositol 1,4,5-triphosphate (IP3) production and IP3-mediated Ca^{2+} release activities. We also introduced the quantal nature of IP3-mediated Ca^{2+} release into the model. Most of the parameters were obtained from the literature and were modified to fit the experimental results of ICCs from mouse small intestine. We were then able to compose a mathematical model that simulates the pacemaker activity of ICCs. The model generates pacemaker potentials regularly and repetitively as long as the simulation continues. The frequency was set at 20 min-1 and the duration at 50% repolarization was 639 ms. The resting and overshoot potentials were -78 and +1.2 mV, respectively. The reconstructed pacemaker potentials closely matched those obtained from animal experiments. We also found that the quantal nature of IP_3-mediated Ca^{2+} release adds complexity to the duration and frequency of pacemaker activity. The model supports the idea that cyclic changes in $[Ca^{2+}]_i$ and $[IP_3]$ play a key role in the generation of ICC pacemaker activity in the mouse small intestine.

Key Words: Cajal Cell, Pacemaker, Small Intestine