Mechanisms of Nociceptive Signal Coding: Role of Slow Sodium Channels

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DOI: 10.1134/S1990747809030325

Using whole-cell patch-clamp method, the rat DRG nociceptive neuron membrane was investigated. Extracellular ouabain applications lead to a decrease of the effective charge transfer in the activation gating system of the slow sodium channels (TTX_r, Na_v1.8). Ouabain concentration–effective charge transfer (dose–response) dependence has U-like shape after extracellular ouabain application. Left branch of this dependence is monotonous in the range from 100 pM to 1 μM ($K_d = 3$ nM). Quantum-chemical calculations have shown that the ouabain molecule could effectively form the chelate complex with free calcium ion. As a result, the equilibrium geometry of this complex changes and the probable consequence of this binding is the fact that

this complex better fits the transducer site of the Na⁺,K⁺-ATPase. Besides, the chelate complex should specifically activate this transducer site due to the ionic binding. Less specific free (without calcium) ouabain higher concentration binding takes place at the different Na⁺,K⁺-ATPase site that probably controls its pumping function. Heterogeneity of the ouabain binding sites could explain the U-like shape of the dose–response function under investigation. The inflammatory pain test shows that injections of ouabain at low concentration (i.p., 0.3 mg/kg) lead to pain relief. We hypothesize that physiological role of the endogenous ouabain results in the decrease of nociceptive signals.