S 3-4

INVOLVEMENT OF HCN CHANNELS IN THE DRG AND THE SPINAL DORSAL HORN IN NEUROPATHIC PAIN

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Ion channels in the dorsal root ganglion (DRG) neurons play very important roles in neuropathic pain. Hyperpolarization-activated cyclic nucleotide-gated cation channels (HCNs) have been proven to contribute to neuronal excitability. In the present presentation, we aim to investigate the role of HCNs in the DRG and the spinal dorsal horn in neuropathic pain. Firstly, the characteristics of HCNs channels in different types of DRG neurons were examined. It was found that (1) large neurons had higher $V_{0.5}$ values and shorter time constants (τ) than small or medium-sized DRG neurons. Furthermore, large DRG neurons had higher I_h density (HCN current in neuron). (2) HCN-1 was found predominantly, but not exclusively, in large and medium-sized DRG neurons, HCN-2 was found in all DRG neurons, although HCN-4 was poorly visualized in all DRG neurons. HCN-1 and HCN-2 were co-localized in large and medium-sized neurons. In the dorsal horn of the spinal cord, HCN-1, HCN-2 and HCN-4 were all expressed in laminae I to IV, although HCN-1 was not detectable in lamina II. (3) Blockade of Ih current with ZD7288 in DRG neurons caused a significant decrease in $V_{0.5}$, resting membrane potential, repetitive firing numbers of action potential, and a significant increase in time of rising phase of action potential. Secondly, we observed the roles of HCN channels in ectopic discharges in neuropathic pain rats with SNL model. We found that (1) all three firing patterns (tonic, bursting and irregular) were inhibited with dose- and time-dependent manner by local application of ZD7288 to DRG. (2) While tonic firing pattern was gradually transformed to bursting type by application of 100 μM ZD7288, it could be transformed to integer multiples firing by 1,000 μM ZD7288. Thirdly, in SNL neuropathic pain rats, topical application of ZD7288 to DRG decreased mechanical allodynia and cold-induced pain in a concentration-dependent manner; intrathecal injection of ZD7288 also significantly decreased mechanical allodynia. **Conclusions:** (1) different HCN channels in the three types of DRG neurons might contribute to their differential electrophysiological properties; (2) HCN channels might participate in the ectopic discharge generation of the injured DRG neurons in neuropathic pain rats of spinal nerve ligation.

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Key Words: Neuropathic pain, Dorsal root ganglion, Spinal dorsal horn, HCN channel

S 4-1

INVOLVEMENT OF ICC IN NEURAL CONTROL OF GASTRIC SMOOTH MUSCLE

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The stomach generates a characteristic pattern of myogenic activity; rings of contraction originate in the corpus and migrate slowly down the stomach towards the gastro-duodenal junction. The rings of contraction are triggered by successive waves of depolarization, slow waves. The muscular wall of the stomach contains both smooth muscle cells and sets of Interstitial Cells of Cajal, ICC. In the upper stomach, fundus and corpus intramuscular ICC, ICC_{IM}, intermingle with the smooth muscle cells; in the lower stomach an additional network of ICC lies in the myenteric region, ICC_{MY}. Slow waves are generated by ICC, which are electrically coupled to nearby smooth muscle cells. Thus depolarizations initiated by ICC passively depolarize nearby smooth muscle cells, with the depolarization causing the opening of L-type calcium channels in smooth muscle cells and ensuring that a contraction ensues. The upper stomach, the fundus is electrically quiescent but it, like the rest of the stomach, is innervated by excitatory and inhibitory nerves. In the stomach the dominant excitatory transmitter is acetylcholine whereas inhibitory nerves appear to release two separate transmitters, ATP and nitric oxide, NO. In the fundus, excitatory nerve stimulation initiates an excitatory junction potential and a fundal contraction. Conversely inhibitory nerve stimulation initiates a bi-phasic inhibitory junction potential and fundal relaxation. In the lower stomach, unlike the heart, the major effects of nerve stimulation are to change the force of contraction generated by each slow wave rather than to change their rate of occurrence. Thus excitatory nerve stimulation simply increases the amplitude of antral rhythmic contractions and inhibitory nerve stimulation simply reduces the amplitude of antral contractions. In mutant animals, which lack ICC_{IM}, the responses to both inhibitory and excitatory nerve stimulation are absent. This indicates that neural control of gastric motility involves signal transduction at the membranes of ICC_{IM} rather than at those of smooth muscle cells.