Isoform-selective blockade of HCN channels in dorsal root ganglion neurons as a potential pharmacological strategy against pain

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Background and purpose

A prominent role of hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels has been suggested based on their expression and (dys)function in dorsal root ganglion (DRG) neurons, being likely involved in peripheral nociception. Using HCN blockers as antinociceptive drugs is prevented by the widespread distribution of these channels. However, tissue-specific expression of HCN isoforms varies significantly, HCN1 and HCN2 being considered as major players in DRG excitability. We characterized the pharmacological effect of a novel compound, MEL55A, able to block selectively HCN1/HCN2 isoforms, on DRG neuron excitability and underlyng hyperpolarization-activated current, Ih.

Experimental approach

HEK293 cells expressing HCN1, HCN2 and HCN4 isoforms were used to verify channel blockade and drug selectivity. The pharmacological profile of MEL55A was tested on mouse DRG neurons by patch-clamp recordings and compared to the non-isoform-selective drug, Ivabradine.

Key results

MEL55A showed a marked selectivity toward HCN1 and HCN2 isoforms expressed in HEK293, with respect to HCN4. In cultured DRG, MEL55A reduced Ih amplitude, both in basic conditions and after stimulation by forskolin, and cell exitability; it's effect being quantitatively similar to that observed with Ivabradine.

Conclusions and implications

This is the first demonstration that selective blockade of HCN1/HCN2 channels, over HCN4 isoform, was able to modulate electrophysiological properties of DRG neurons similarly to that reported for classical Ih blockers, ZD7288 and Ivabradine. The availability of small molecules with selectivity toward HCN channel isoforms involved in nociception might represent a safe and effective strategy against chronic pain.