Channelopathy

Channelopathy is caused by disturbed function of ion channel subunits or the proteins that regulate them.

These diseases may be either congenital (often resulting from a mutation or mutations in the encoding genes) or acquired (often resulting from autoimmune attack on an ion channel).

There are a large number of distinct dysfunctions known to be caused by ion channel mutations. The genes for the construction of ion channels are highly conserved amongst mammals and one condition, hyperkalemic periodic paralysis, was first identified in the descendants of Impressive, a registered Quarter Horse (see AQHA website).

The channelopathies of human skeletal muscle include hyper- and hypokalemic (high and low potassium blood concentrations) periodic paralysis, myotonia congenita and paramyotonia congenita.

Channelopathies affecting synaptic function are a type of synaptopathy.

Voltage-gated ion channels are critical for neuronal integration. Some of these channels, however, are misregulated in several neurological disorders, causing both gain- and loss-of-function channelopathies in neurons. Using several transgenic mouse models of Alzheimer's disease (AD), we find that sub-threshold voltage signals strongly influenced by hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels progressively deteriorate over chronological aging in hippocampal CA1 pyramidal neurons. The progressively degraded signaling via HCN channels in the transgenic mice is accompanied by an age-related global loss of their non-uniform dendritic expression. Both the aberrant signaling via HCN channels and their mislocalization could be restored using a variety of pharmacological agents that target the endoplasmic reticulum (ER). Our rescue of the HCN channelopathy helps provide molecular details into the favorable outcomes of ER-targeting drugs on the pathogenesis and synaptic/cognitive deficits in AD mouse models, and implies that they might have beneficial effects on neurological disorders linked to HCN channelopathies [1)].

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Musial TF, Molina-Campos E, Bean LA, Ybarra N, Borenstein R, Russo ML, Buss EW, Justus D, Neuman KM, Ayala GD, Mullen SA, Voskobiynyk Y, Tulisiak CT, Fels JA, Corbett NJ, Carballo G, Kennedy CD, Popovic J, Ramos-Franco J, Fill M, Pergande MR, Borgia JA, Corbett GT, Pahan K, Han Y, Chetkovich DM, Vassar RJ, Byrne RW, Matthew Oh M, Stoub TR, Remy S, Disterhoft JF, Nicholson DA. Store depletion-induced h-channel plasticity rescues a channelopathy linked to Alzheimer's disease. Neurobiol Learn Mem. 2018 Jun 12. pii: S1074-7427(18)30141-2. doi: 10.1016/j.nlm.2018.06.004. [Epub ahead of print] PubMed PMID: 29906573.