Chansik Hong, J Neurol Disord 2018, Volume 6
DOI: 10.4172/2329-6895-C5-038

Increased TRPC5 glutathionylation contributes to striatal neuron loss in Huntington's disease

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Aberrant glutathione or Ca^{2+} homeostasis due to oxidative stress is associated with the pathogenesis of neurodegenerative disorders. The Ca^{2+}-permeable TRPC channel is predominantly expressed in the brain which is sensitive to oxidative stress. However, the role of the TRPC channel in neurodegeneration is not known. Here, we report a mechanism of TRPC5 activation by oxidants and the effect of glutathionylated TRPC5 on striatal neurons in Huntington's disease. Intracellular oxidized glutathione leads to TRPC5 activation via TRPC5 S-glutathionylation at cysteine-176/cysteine-178 residues. The oxidized glutathione-activated TRPC5-like current, results in a sustained increase in cytosolic Ca^{2+}, activated calmodulin-dependent protein kinase and the calpain-caspase pathway, ultimately inducing striatal neuronal cell death. We observed an abnormal glutathione pool indicative of an oxidized state in the striatum of Huntington's disease transgenic (YAC128) mice. Increased levels of endogenous TRPC5 S-glutathionylation were observed in the striatum in both transgenic mice and patients with Huntington's disease. Both knockdown and inhibition of TRPC5 significantly attenuated oxidation-induced striatal neuronal cell death. Moreover, a TRPC5 blocker improved rearing behaviour in Huntington's disease transgenic mice and motor behavioural symptoms in littermate control mice by increasing striatal neuron survival. Notably, low levels of TRPC1 increased the formation of TRPC5 homotetramer, a highly Ca^{2+}-permeable channel, and stimulated Ca^{2+}-dependent apoptosis in Huntington's disease cells ($STHdh^{Q111/111}$). Taken together, these novel findings indicate that increased TRPC5 S-glutathionylation by oxidative stress and decreased TRPC1 expression contribute to neuronal damage in the striatum and may underlie neurodegeneration in Huntington's disease.

Biography

Chansik Hong completed his PhD from Seoul National University and Post-doctorate from Seoul National University, College of Medicine. He is an Associate Professor in the Physiology Department at Chosun University, College of Medicine. He has published more than 25 papers on ion channels in reputed journals.

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