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T-type Ca^{2+} channels make your brain smarter

Commentary on: Chung, et al. Behavior training reverses asymmetry in hippocampal transcriptome of the $Ca_v3.2$ knockout mice. PLOS One 2015; 24:987-93.

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One of the most remarkable features of T-type Ca^{2+} channels originates from their low-threshold of activation that makes these channels perfectly suited for regulating neuronal excitability and oscillatory behavior near the resting membrane potential of the cells. They generate a low-threshold burst discharge that occur during diverse forms of neuronal rhythmogenesis, and in some neurons also generate a "window current" that provides a unique opportunity for Ca^{2+} entry at rest.[1] In addition, T-type channels also contribute to a low-threshold form of neurotransmitter release provided by the biochemical coupling of the channel with the vesicle release machinery.[2,3] All of these features of T-type channels are of essential importance for regulating the excitability and electrical responsiveness of nerve cells under physiological conditions near resting states. The implication of T-type channels in the central nervous system is best exemplified by the occurrence of neurological disorders caused by disruption of channel function and includes sleep disorders, absence epilepsy, Parkinson disease, neuropathic pain, and possibly neuropsychiatric disorders such as depression and autism spectrum disorders.[4] In addition, and consistent with the abundant expression of T-type channels in brain regions involved in cognitive functions,[5] a role for T-type channels in learning and memory processing has been proposed. Indeed, $Ca_v3.2$ T-type channel deficient mice showed altered long-term potentiation in the hippocampal CA1 region and impaired memory.[6,7] However, the cellular and molecular mechanisms by which T-type channels possibly contribute to memory formation remain largely unknown. In a recent study reported in *PLos One*, Chung and colleagues[8] have examined the possibility that T-type channels may affect gene expression in cognitive brain areas, which could provide a molecular support for memory formation and long-term consolidation.

Memory formation and maintenance is accompanied by a profound remodeling of gene and protein expression in cognitive brain structures including the hippocampus which supports contextual, temporal and spatial learning and memory.[9,10] In order to test if T-type channels affect gene expression in memory formation, Chung and colleagues performed a transcriptome analysis on the hippocampus of $Ca_v3.2$ knockout mice ($Ca_v3.2^{-/-}$) and their wild-type (WT) littermates. Interestingly, these authors found that while the gene expression pattern in the right hippocampus was largely unchanged, a profound remodeling occurred in the left hippocampus of $Ca_v3.2^{-/-}$ mice, with 1302 genes and 2220 genes up-regulated and down-regulated, respectively. These genes essentially encode for proteins involved in the MAP kinase signaling pathway and long-term potentiation pathway that are of direct relevance for memory processing.[11] In contrast, the transcriptome of the left and right hippocampus of WT animals was undistinguishable, supporting a specific role of T-type channels in the brain asymmetry produced by disruption of $Ca_v3.2$ channels. In order to gain further insights on the role of T-type channels in learning and memory formation, Chung and colleagues also investigated the effect of behavioral training. To perform this analysis, these authors used trace fear-conditioning (TFC) protocols aimed at investigating associative learning task in which mice are presented with a neutral conditioned stimulus (CS) that is paired with an aversive unconditioned stimulus (US), where CS and US are separated by a stimulus-free "trace interval" which engages the hippocampus and prefrontal cortex. Interestingly, while TFC had minor effects on hippocampal gene expression of WT mice, the asymmetry in hippocampal transcriptome of $Ca_v3.2^{-/-}$ animals was found largely reversed by behavior training. Indeed, after TFC training, only 6 genes were remained differentially expressed in the left hippocampus of $Ca_v3.2^{-/-}$ mice compared to WT mice, while 3522 genes were concerned before TFC.

Collectively, the results by Chung and colleagues support the hypothesis that $Ca_v3.2$ T-type channels may contribute to memory processing by modulating gene expression. The finding that genetic disruption of $Ca_v3.2$ channels selectively affects the left hippocampus raises intriguing questions about the functional importance of T-type channels in brain lateralization. Considering that there is every reason to believe that $Ca_v3.2$ channels are functionally expressed in both hippocampi, the selective transcriptome alteration observed in the left hippocampus of $Ca_v3.2$ deficient mice suggest that T-type channels may control signaling pathways specifically present in the left hippocampus. Consistent with this idea, a comparative proteomic analysis performed on the hippocampus has revealed a lateral asymmetry in the expression profile of numerous proteins that may contribute to the selective effect of $Ca_v3.2$ knockout.[12] Chung and colleagues have also reported that the transcriptome profile of the left hippocampus of $Ca_v3.2^{-/-}$ mice can be restored after behavioral training. Interestingly, it was recently shown that down-regulation of $Ca_v3.2$ channels produced by genetic knockout of the neuronal actin-binding protein kelch-like 1 is accompanied by an up-regulation of the closely related $Ca_v3.1$ channel, supporting a compensatory mechanism.[13] Hence, it is possible that activation of $Ca_v3.1$ channels during TFC may compensate the deficit of $Ca_v3.2$.

In conclusion, regardless the underlying mechanism by which T-type channels differentially modulate hippocampal gene expression, the study of Chung and colleagues is of direct relevance to a previous report showing that T-type channels are the primary target of the cognitive enhancer ST101.[14] Considering that a

decreased expression of T-type channels was reported in the aging brain with possible implication in Alzheimer disease,[15,16] targeting signaling pathways and downstream effectors of T-type channel activation may represent a potential strategy for cognitive symptoms associated with neurodegenerative disorders, possibly in combination with modulators directed against other relevant ion channel-dependent signaling pathways.[17-19]

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