# Inositol Trisphosphate Receptor Type 1 Hyperactivity in Cardiac Arrhythmia and Neuronal Disorder

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Inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) is an intracellular calcium release channel that plays important roles in numerous cellular processes, including fertilization, muscle contraction, rhythm generation, motor coordination, learning and memory in a variety of cells. Although the physiology of ITPR1 has been studied for decades, the pathological significance of ITPR1 dysfunction remains poorly understood. Despite its widespread expression and ubiquitous physiological contributions, ITPR1 has thus far been linked to only a few disorders, primarily movement disorders. Interestingly, most disease-associated ITPR1 mutations generate a loss of function. This leaves our understanding of ITPR1-associated pathology oddly one sided, as little is known about the pathological ramifications of ITPR1 hyperactivity. We functionally characterized a large number of human ITPR1 mutations, and found many of which enhance the sensitivity of IP3-induced calcium release in HEK293 cells. We generated knock-in mouse models expressing some of these hyperactive ITPR1 mutants and determined their pathological ramifications. Interestingly, ITPR1 hyperactivity markedly increased the occurrence of spontaneous calcium release in cardiac Purkinje fibers and the propensity for stress-induced cardiac arrhythmias. Furthermore, these ITPR1 mice also displayed motor deficits and reduced muscle strength. However, ITPR1 hyperactivity did not significantly alter spatial learning and memory capacity and did not change the learning and memory impairment when crossed with 5xFAD Alzheimer's disease mice. Therefore, this study reveals novel pathological phenotypes associated with ITPR1 hyperactivity and extends the known spectrum of ITPR1-linked disorders.