Altered axonal ER calcium dynamics: Role in aberrant cortico-striatal glutamate signaling in Huntington disease mouse model

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Synaptic dysfunction is one of the earliest changes driving neuronal degeneration in a variety of brain disorders, including Alzheimer and Huntington disease (HD). As a monogenic inherited disorder, HD is a model for identifying therapeutic targets to modify the course of neurodegeneration. GABAergic spiny projection neurons (SPN)s of the striatum and cortical pyramidal neurons show the most severe degeneration in HD, and dysfunction at synapses between these two neuronal types precedes neuron loss. Aberrant calcium release from endoplasmic reticulum (ER) stores, a result of mutant huntingtin-induced sensitization of Inositol-1,4,5-Phosphate receptors and leaky Ryanodine receptors (RyR)s, contributes to SPN spine loss. Here, we uncover a role for dysfunctional ER calcium homeostasis in altering patterns of glutamate release from cortical terminals in cultures from YAC128 HD mice. Miniature excitatory postsynaptic currents recorded from striatal or cortical neurons show increased frequency in YAC128 cultures by day in vitro (DIV) 14 and remain elevated through DIV 18. The increase correlates with enhanced presynaptic vesicular release and is mimicked by stimulation of RyR-mediated ER calcium release in wild-type neurons. In contrast, action potential (AP)-dependent vesicular glutamate release is reduced at this stage in YAC128 cortical culture. These findings are mirrored by optogenetic measures of cortical terminal calcium transients, showing markedly elevated sparks in YAC128 cortical terminals/axons in the presence of TTX, whereas action potential-dependent (no TTX) calcium transients were more frequent and of larger amplitude and duration in wild-type cultures. In acute cortico-striatal brain slice, the glutamate sensor iGluSnFR revealed ryanodine-dependent modulation of cortical glutamate release in wild-type but not YAC128 mice. Together, our results indicate a shift in balance favoring increased AP-independent (miniature) vs. AP-dependent glutamate release in YAC128 cortical pyramidal neurons and support a key role for ER calcium dysregulation in aberrant cortical signaling in HD.

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