Faulty Brain Development and Synaptic Transmission in Huntington's Disease Model Mice

Carlos CEPEDA

Semel Institute for Neuroscience & Human Behavior, University of California Los Angeles, USA

Email: ccepeda@mednet.ucla.edu

In this talk, I will review recent advances in the understanding of mechanisms underlying Huntington's disease (HD), a progressive, fatal neurological disease caused by a mutation (CAG/glutamine repeat expansion) in the *Huntingtin* gene. Although widely considered a neurodegenerative disease starting in midlife, recent studies indicate a neurodevelopmental component that sets the stage for striatal and cortical projection neurons degeneration. Indeed, mutant huntingtin (Htt) protein affects corticogenesis, cell migration, and differentiation. Morphological, electrophysiological, and behavioral studies demonstrate early signs of brain maldevelopment. Cerebral cortex morphology is aberrant and resembles human focal cortical dysplasia, a malformation of cortical development that leads to hyperexcitability, epileptic activity, and cognitive deficits. In HD autopsy brains, a high percentage of heterotopias has been demonstrated. Abnormal cortical architecture also has been revealed using NeuN staining. Importantly, this specific neuronal marker was identified as RBFOX3, an RNA binding protein that regulates alternative splicing and interacts with Htt. Reduced expression of RBFOX3 has been demonstrated in HD animal models and human striatal tissue. In our studies in developing HD R6/2 mouse brains, a deficit of RBFOX3 was observed starting at about postnatal (P) day 15. This could have deleterious consequences in terms of alternative splicing as well as cortical excitability. In our studies, we examined wildtype (WT) and R6/2 mice at postnatal (P) days 7, 14, and 21. *ex vivo* electrophysiological recordings of cortical pyramidal neurons (CPNs) demonstrated significant age- and genotype-dependent changes of intrinsic membrane and synaptic properties. In general, CPNs had reduced cell membrane capacitance and increased input resistance, along with reduced frequency of excitatory and inhibitory synaptic events during very early development (P7 and P14), suggesting delayed cortical maturation. This was confirmed by increased occurrence of $GABA_A$ receptor-mediated giant depolarizing potentials in R6/2 CPNs at P7. Altered membrane and synaptic properties recovered progressively, and by P21 they were similar to WT CPNs. In the R6/2 model of HD, we also found significant alterations of striatal development. However, In striatal medium-sized spiny neurons (MSNs), a different picture emerged. Intrinsic membrane properties were relatively normal throughout development. The first alterations in MSNs synaptic activity were observed at P14 and consisted of significant deficits in GABAergic inputs, however, these also were normalized by P21. In contrast, excitatory inputs began to decrease with age. We conclude that the HD brain development is altered, but it is capable of compensating for early abnormalities and that cortical alterations are probably the primary driver of striatal changes. Discovering and promoting intrinsic compensatory mechanisms, in conjunction with early intervention, will aid in finding the best therapeutic approaches for HD.