Models and mechanisms in neurodegeneration: Towards neuroprotective therapy in Huntington disease

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Neurological and psychiatric diseases are the leading cause of disability in Canada, and the prevalence of age–related neurodegenerative diseases is rapidly increasing with the aging population. Alzheimer disease (AD), Parkinson disease (PD), and Huntington disease (HD) share some common clinical and pathogenic features. All can impact cognition, movement, and mood at some stage of disease. Common mechanisms include insoluble protein deposits with impaired protein degradation, oxidative stress with mitochondrial dysfunction, and synaptic changes that occur before clinical manifestations. Although more rare than AD and PD, studying HD has advantages for leading the effort to develop neuroprotective therapies. Since HD is an inherited, monogenic disorder, the cohort of affected patients is well–defined. Predictive genetic testing identifies people destined to manifest HD, affording the possibility of intervention to delay disease onset and extend high–quality life. Moreover, genetically accurate mouse models of HD that exhibit phenotypes similar to human HD are invaluable for investigating pathogenic mechanisms.

Huntington disease

HD is inherited in an autosomal dominant fashion caused by expansion of a polymorphic CAG repeat in exon1 of the gene HTT, encoding the protein huntingtin with an expanded polyglutamine tract (mutant huntingtin; mHTT). Recent estimates of prevalence in populations of European descent have increased to 17.2 per 100,000, largely as a result of two factors—availability of the genetic test and increased life–span; however, certain populations in Asia and Africa have a much lower prevalence. Age of onset is inversely correlated with CAG repeat length. The disease manifests with a clinical triad of movement disorder, psychiatric disturbance, and cognitive decline, progressing to death 15-20 years following the motor diagnosis (for review, see 16). The movement disorder typically includes involuntary dance–like, or jerky, movement called chorea, deficits in voluntary motor coordination, and impairments of speech, swallowing, and balance. Depression and anxiety are the most common psychiatric manifestations and cognitive impairment involves frontal executive dysfunction, impaired recall, and deficits in skilled learning. Currently, no disease–modifying agents are available and treatment is symptomatic.

Striatal medium–sized spiny projection neurons, which receive glutamatergic afferents from the cortex and thalamus and project to other basal ganglia nuclei, are affected earliest and most severely by degeneration. As well, certain layers of cortex are also vulnerable. Recent reports using human autopsy brain tissue indicate that predominance of mood versus movement disorders correlate with more severe neuronal loss in striatal striosomes/anterior cirgulate cortex versus primary motor cortex. Since predictive testing can identify healthy individuals carrying the mutation associated with HD, two world–wide observational studies have elucidated changes that occur prior to clinical diagnosis of HD. These include significant atrophy of the striatum—up to 40% loss at the time of diagnosis—as well as prominent loss of cortical white matter. Magnetic resonance spectroscopy (MRS) has shown chemical changes that distinguish controls from prodromal versus early stages of HD. Notably, advances in detection of femtomolar quantities of protein in cerebrospinal fluid (CSF) samples have revealed increasing levels of mHTT through the prodromal and early–to mid–stages of HD. Use of such biomarkers will enable interventional trials to delay onset of a clinical diagnosis.

Synaptic dysfunction: An early pathogenic feature of Huntington disease

Accumulating data implicate synaptic dysfunction as among the earliest changes in a variety of neurodegenerative disorders. Synaptic transmission changes occurring in the pre–manifest stages of several HD mouse models include: increased cortical excitability; altered balance of synaptic/extrasynaptic NMDA–glutamate receptor distribution on striatal spiny projection neurons, leading to downstream changes in survival/death pathways; altered plasticity at cortical–striatal synapses; and increased inhibitory synaptic activity. As the phenotype progresses, there is a profound loss of potassium conductances in astrocytes and striatal neurons, which increases neuronal excitability. Evidence suggests there are enhanced levels of dopamine in the early stages and reduced dopamine input in late stages of HD. These changes have been targeted by several drugs in recent clinical trials. Pramipexole, reportedly a “dopamine stabilizer” as a partial agonist at dopamine receptors, has completed two phase III studies with promising results in improving the movement disorder. Tetabenazine, which inhibits vesicular dopamine transporter type 2 thereby depleting vesicular stores and reducing dopamine release, is highly effective in controlling chorea, but has significant side effects. Memantine, which selectively blocks extrasynaptic NMDA receptors while preserving activity of synaptic receptors, improves motor performance and skilled motor learning and protects against striatal degeneration in HD mice. Memantine has also been studied in a small phase II study of early HD with MRS/MRI and clinical endpoints (NCT01458170), but the results are not yet reported. Finally, deep brain stimulation of the globus pallidus, to re–balance opposing output pathways of the striatum, is in the early stages of investigation; a small number of patients found benefit on error/performance monitoring.

Mitochondrial dysfunction, altered calcium regulation, and metabolic changes in HD

Mitochondrial dysfunction, energy metabolism, oxidative stress, and calcium homeostasis have all been implicated in HD, as well as other neurodegenerative diseases. Huntington associates with mitochondria and mitochondrial respiration is impaired in cells expressing mHTT. Consistent with this, lower ratios of ATP to ADP have been identified

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in lymphoblasts from HD patients.\textsuperscript{36} Mutant Htt–induced reduction in PGC1-alpha, a master regulator of energy metabolism, has been implicated in mitochondrial dysfunction\textsuperscript{17} and drugs to counter this mechanism are under investigation in preclinical studies.\textsuperscript{36,39} Calcium–induced calcium release via IP3 receptors has been shown to be enhanced in HD mouse models,\textsuperscript{40} leading to depletion of endoplasmic reticulum calcium stores and a compensatory increase in calcium influx through plasma membrane store–operated channels, which may contribute to spine loss in striatal neurons.\textsuperscript{41} Three large clinical trials targeted some of these mechanisms. Creatine is thought to boost ATP levels, but a large phase III study, CREST-E, was recently halted for futility. Co-enzyme Q10, a component of complex I in mitochondria with anti–oxidant properties, showed promise in an initial study,\textsuperscript{42} however, a follow–up 5–year trial (2-CARE) was also halted for futility. Dimebon, which exerts neuroprotection, in part through a mitochondrial mechanism,\textsuperscript{43} showed no effect in a phase II study.\textsuperscript{44}

**Transcriptional dysregulation as a pathogenic mechanism in HD**

Transcriptional dysregulation is another central mechanism in HD pathogenesis. Huntingtonin has a role in shuttling between nucleus and cytoplasm and likely has important physiological roles in both compartments.\textsuperscript{45} However, with the CAG repeat expansion, mHtt has the capacity to interact with a variety of transcription factors in the nucleus and alter transcriptional regulation, which may be especially important at times of stress.\textsuperscript{46} Trafficking of mHtt can be modulated by post–translational modifications, including phosphorylation, sumoylation, and protease cleavage, which may play a major role in regulating its access to the nucleus.\textsuperscript{47} A downstream consequence of these changes is altered histone acetylation levels; histone deacetylase inhibitors have been tested in mouse models and a dose–finding study in humans.\textsuperscript{48} Further work is required in this area.

**Role of inflammation and altered protein homeostasis in HD pathogenesis**

Inflammation and clearance of misfolded proteins are also important areas of investigation in HD, as in other neurodegenerative disorders. Microglia (central nervous system) and macrophages (peripheral nervous system) show enhanced activation.\textsuperscript{49} To target this mechanism, there is an ongoing clinical trial of Laquinimod (NCT02215616), which has already shown neuroprotective effects in progressive multiple sclerosis.\textsuperscript{50} Reduction of mHtt levels is a primary goal of therapeutic development. To this end, HD mouse models have shown that upregulation of autophagy and/or manipulation of post–translational modifications of mHtt can enhance its clearance with beneficial effects.\textsuperscript{51} An exciting recent development is genetic therapy used to lower levels of HTT in the brain. This has been shown to improve phenotype in HD mouse models\textsuperscript{52} and is now in human clinical trials where antisense oligonucleotides are injected intrahemically in a phase I study (NCT02519036).

**Conclusions**

In the early stages of disease, protecting synapses and re–balancing circuits, as well as mitigating the damaging effects of oxidative stress/ mitochondrial dysfunction, calcium dysregulation, and inflammation, provide promising avenues for further therapeutic development in a variety of neurodegenerative disorders. As well, enhanced clearance of misfolded proteins by using antibodies or upregulating endogenous cellular pathways (e.g. autophagy) represents a common target for AD, PD, and HD. With HD trials leading the way, therapies that use genetic tools to directly lower levels of damaged, misfolded proteins are becoming a real possibility and can be generalized to a number of heritable neurological disorders, including familial AD and PD.

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**Conflict of interest**

None to declare.

**References**


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