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Review

Aging and neurodegeneration
Molecular mechanisms of neuronal loss in Huntington's disease

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Abstract

Huntington's disease (HD) is a fatal, genetically based late-onset neurodegenerative disorder in which a loss of neostriatal neurons is a main characteristic. The CAG trinucleotide repeat expansion encoding polyglutamine tract induces progressive deficits in intra- and inter-cellular signalling, and subsequent clinical signs developed with aging process. CAG-induced neurodegeneration and disease-onset shows aging-dependent pattern. Proposed mechanism of neurodegeneration includes intranuclear or intracellular protein aggregates, proteolytic cleavage of huntingtin (cf. caspase, calpain), altered transcription or other neurotransmitter signalling deficits. Recently, stem cell transplantation is of benefit to protect neurons against neurodegeneration and recover the functional deficit in the experimental HD model. This review focuses on current knowledge of molecular mechanisms in neurodegeneration and potential therapeutic targets in HD.

Keywords: Huntington's disease; Neurodegeneration; Caspase; Protein aggregation

Neurodegenerative disorder is one of most common neurological disorder characterized by progressive neurological deficits due to selective neuronal loss in the nervous system. Since the age of onset in neurodegenerative disease is late in their lifetime, prevalence is increasing with the aged population. Mechanism for the aging process improved the understanding of the neurodegeration, and information from neurodegenerative disorder is also of value in aging mechanism. This review focuses on current knowledge of molecular mechanisms of neurogeneration in Huntington's disease and the use of this information to identify potential therapeutic targets.

1. Clinical characteristics of Huntington's disease

Huntington's disease (HD), an autosomal dominant neurodegenerative disorder, is characterized clinically by progressive cognitive impairment, abnormalities of movement, and neuropsychiatric symptoms. Onset usually occurs during the fourth or fifth decade of life, and the disease symptoms and signs progress with aging, with a mean survival of 15–20 years. HD is fatal, and there is no effective treatment. Selective neuronal loss, predominantly in the striatum and other basal ganglia structures (HDCRG, 1993), accounts for most of the clinical features of HD. First description of HD was in 1872 by George Huntington, a medical practicioner of Pomeroy, Ohio, but the mechanisms involved in the premature degeneration of neurons in HD brain remain largely unknown over the 100 hundred years, which hamper effective therapeutic interventions.

2. CAG trinucleotide repeats determine the age of onset from neurodegeneration

The disease is caused by a mutation encoding an abnormal expansion of CAG-encoded polyglutamine repeats in a protein called huntingtin. At the gene locus implicated in HD, there are normally 10–29 (median, 18) consecutive repetitions of the CAG triplet that codes for glutamine. In contrast, HD patients have expanded CAG repeat that included from 36 to 121 repeats (median, 44). The length of the CAG/polyglutamine repeat is inversely correlated with the age of disease onset (Kremer et al., 1994). Therefore, more expanded CAG causes earlier onset, whereas, the less expansion shows first symptoms in their late lifetime. The disease progression is rapid in patients with more CAG expansion, suggesting the neurodegeneration by CAG is in an aging-dependent manner.

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In the transgenic mice expressing human huntingtin with an expanded CAG/polyglutamine also develop a progressive syndrome, which is characteristics of human HD (Ona et al., 1999).

3. Protein aggregation and toxicity

Protein deposition has been noted in aged cells and other degenerative disorders. In HD, expanded polyglutamine fragments, cleaved from their respective full-length proteins, form microscopically visible aggregates in affected individuals and in transgenic mice (Wellington et al., 1998). There is a correlation between the threshold for aggregation in vitro and the threshold for disease in humans, consistent with the idea that aggregation is related to pathogenesis (Scherzinger et al., 1999; Ross and Poirier, 2004).

Huntingtin intermediates seem to have the major role in aggregate formation and toxicity. Globular and protofibrillar intermediates form before mature huntingtin fibers might be crucial for toxicity (Chen et al., 2001; Sanchez et al., 2003a). The azo-dye Congo red, which binds preferentially to beta-sheets with amyloid fibrils, inhibit oligomerization, disrupt preformed oligomers and prevents ATP depletion or caspase activation. It preserves normal cellular protein synthesis and degradation functions, and promotes the clearance of expanded polyglutamine repeats in vivo and in vitro (Sanchez et al., 2003b).

In addition, polyglutamine aggregates recruit other transcriptional regulators containing short polyglutaime stretches, such as CREB binding protein (CBP) (Ross and Poirier, 2004). Expanded polyglutamine repeats specifically interfere with CBP-activated gene transcription, and overexpression of CBP rescued polyglutamine-induced neuronal toxicity (Nucifora et al., 2001). Mutant huntingtin can also inhibit the proteasome. Transient expression of a huntingtin fragment with polyglutamine repeat causes inhibition of the ubiquitin–proteasome system (Bence et al., 2001).

Protein aggregates or inclusion with huntingtin are present in regions of the brain that degenerate, but the neurons with inclusions do not correspond exactly to the neurons that degenerate. Inclusions are more enriched in populations of large interneurons than in medium spiny projection neurons, which are more susceptible to degenerate (Kuemmerle et al., 1999). In addition, inclusion body formation improved survival and leads to decreased levels of mutant huntingtin elsewhere in a neuron. Thus, it is possible that inclusion body formation may function as a coping response to toxic mutant huntingtin (Arrasate et al., 2004).

4. Caspase activation and neurotransmitter dysfunction

One of the earliest events in the presymptomatic and early symptomatic stages of the disease is transcriptional up-regulation of the caspase 1 gene (Ona et al., 1999). Nuclear translocation of N-terminal fragments of mutant huntingtin increases the expression of caspase-1, which may in turn activate caspase-3 and trigger the apoptosis (Li et al., 2000). Activation of caspase 8, caspase 9 and release of cytochrome *c* have also been demonstrated in HD (Kiechle et al., 2002; Sanchez et al., 1999). Caspase-1 and -3 (but not caspase-7 or caspase-8) cleave huntingtin Wellington et al., 1998. As the disease progresses, caspase-mediated cleavage of huntingtin increases the generation of huntingtin fragments and depletes wild-type huntingtin, suggesting both toxic effect of fragments and depletion of huntingtin might be responsible for the HD pathogenesis (Ona et al., 1999).

Loss of neurotransmitter receptors, especially glutamate and dopamine receptors, is another hallmarks of Huntington disease (HD). Altered expression of neurotransmitter receptors precedes clinical symptoms in transgenic mice and contribute to subsequent pathology (Cha et al., 1998). Inhibition of caspase activation prevents receptor down regulation, suggesting caspases are mediators not only for the cell death but also for the cell dysfunction (Ona et al., 1999).

Although these pathogenic processes can occur in all central nervous system, HD patients show region-specific neuronal loss mainly involving striatum (Vonsattel et al., 1985). But to date, the mechanism of this selective cell death remains unknown. Strong evidence from studies in humans and animal models suggests the involvement of energy metabolism defects, which may contribute to excitotoxic processes, oxidative damage, and altered gene regulation (Browne and Beal, 2004).

5. Therapeutic approach

Currently, there is no effective therapeutic option for HD and only symptomatic treatment is possible. However, novel therapeutic approach to using neuroprotective agents and cell transplantation have been tried.

Among neuroprotective agents, neuroprotection by minocycline has also been observed in mouse models of HD (Chen et al., 2000). Recent clinical study shows that minocycline treatment exhibited stabilization in general motor and neuropsychological function and a significant amelioration of psychiatric symptoms in HD (Bonelli et al., 2004). Riluzole (Seppi et al., 2001), creatine (Verbessem et al., 2003), tauroursodeoxycholic acid (Keene et al., 2002), or the combination of these drug have been considered as a new therapeutic candidates and further controlled studies appear highly warranted (Seppi et al., 2001).

Neuro-transplantation has been proposed over recent years as a potential treatment for neurodegenerative disorders. To modify disease progression, fetal tissue transplantation to the striatum has been tried in humans, and has been found to show a favorable effect (Bachoud-Levi et al., 2000; Gaura et al., 2004; Hauser et al., 2002). The transplantation of neural tissue has been shown to improve functional outcome (Hantraye et al., 1992; Hurelbrink et al., 2000), to restore electrophysiological sensitivity to dopamine (Chen et al., 2002), neuronal differentiation, and fiber outgrowth from grafts in an animal model of HD (Armstrong et al., 2000). Recent progress shows that neurons suitable for transplantation can be generated from stem cells in culture, and that the adult brain produces new neurons from its own stem cells in response to injury. These