

Huntington's disease

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Abstract

The most recent findings in the elucidation of the molecular pathology of Huntington's disease are reviewed. Particular interest has been paid to the role of huntingtin and its associated proteins in excitotoxicity mediated via NMDA and kainate receptors.

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Keywords: Huntington's disease; neurodegenerative disorder; Huntingtin; NMDA receptors; kainate receptors

This short review sets out to consider the most recent findings in the search to elucidate the pathological mechanisms underlying the fatal, neurodegenerative disorder known as Huntington's disease (HD), first described by George Huntington in 1872. HD involves the extrapyramidal motor system and is characterised by chorea, a dementia which is progressive, and other psychiatric symptoms. In terms of brain pathology, GABAergic medium spiny striatal neurones are most affected, resulting in atrophy of the caudate nucleus, putamen, and globus pallidus; there is also pronounced atrophy of the cerebral cortex.^{1,2} The neuronal loss in the striatum is accompanied by pronounced gliosis. The vulnerable striatal neurones contain enkephalin, dynorphin, and substance P, and primarily innervate the substantia nigra and globus pallidus. Medium sized spiny neurones containing somatostatin, neuropeptide Y, and NADPH diaphorase, in addition to cholinergic interneurons and parvalbumin containing GABAergic neurones, are relatively spared.³ In the cerebral cortex, large neurones in layer VI are the most affected, with smaller amounts of degeneration seen in layers III and V.^{2,4} Neurones may also be lost in the thalamus, zona reticulata of the substantia nigra, superior olive, lateral tuberal nucleus of the hypothalamus, and deep cerebellar nuclei.^{3,5} In exploring the sequence of neurodegeneration, Glass *et al* looked at receptor changes in the basal ganglia in the various stages of HD (summarised in

table 1). Their data indicate an overlapping pattern of neurodegeneration of GABAergic efferent projection neurones with the progress of the disease, accompanied by the loss of cannabinoid receptors throughout the basal ganglia.⁶

The importance of CAG repeats

One of the important early triumphs of modern molecular biology has been the demonstration that the underlying cause of HD is the expansion of a CAG repeat sequence in the first exon of a gene on chromosome 4p16.3, which encodes the protein huntingtin.^{6–8} CAG is the codon for glutamine (Q in the single letter code for amino acids). The normal range for the number of Qs in the polyglutamine tract (polyQ) is between six and 34, with disease being found when polyQ is greater than 40. Interestingly, within the HD disease genome, expansion of trinucleotide repeats appears not to be limited solely to the huntingtin gene. Keckarevic *et al* reported that allelic frequency distributions for two other genes containing such repeat sequences (SCA1 and FRDA) were shifted towards larger alleles compared with healthy controls, and suggested that a common mechanism caused expansion in all three genes.⁹ The expanded CAG repeat is transmitted predominantly through the male germ line in humans and transgenic mice. Using the transgenic mouse model to explore transmission, Kovtun *et al* found that the size of the CAG repeat was influenced by the sex of the offspring from identical fathers. Thus, male offspring had expanded repeats, whereas the opposite was seen in females. This finding led them to propose that X and Y chromosomal encoded factors influenced embryonic DNA repair and replication.¹⁰ Furthermore, within striatal cells, expansion biased changes were shown to increase with age, suggesting that non-replication based mechanisms may also contribute to CAG repeat instability.¹¹

The pathology of HD

The first substantive step towards understanding the pathological mechanisms underlying the disease process was the demonstration that intrastriatal injections of kainic acid produced lesions similar to those seen in HD; the model was further refined by the use of quinolinic acid injections. This led to the suggestion that glutaminergic overactivity (excitotoxicity) plays a central role in the pathogenesis of HD. Subsequently, the excitotoxicity hypothesis has proved to be the dominant concept influencing thinking on the pathology of HD. Nevertheless, other pathways—oxidative stress, impaired energy metabolism, apoptosis, and abnormal protein–protein interactions—which in turn may cause transcriptional dysregulation and altered gene expression,^{4,12} have also attracted

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Table 1 Receptor changes in Huntington's disease⁶

Decreased		Increased	
Receptor	Regions	Receptor	Region
Early clinical phase			
Cannabinoid CB (1)	CN, P, GPE	GABA (A)	GPE
Dopamine D2	CN, P, GPE		
Adenosine A (2a)	CN, P, GPE		
Intermediate clinical phases			
Cannabinoid CB (1)	CN, P, SN		
Dopamine D1	CN, P, SN		
Final clinical phase			
Cannabinoid CB (1)	CN, P, GPI	GABA (A)	GPI
Dopamine D1	CN, P, GPI		

CN, caudate nucleus; GPE, globus pallidus externum; GPI, globus pallidus internum; P, putamen; SN, substantia nigra.

much interest. Central to all these have been attempts to understand the role of huntingtin in normal physiology and in HD.

The role of huntingtin in HD

Huntingtin has no great structural homology with other human proteins, so determination of its normal function has proved difficult. Changes seen in embryonic stem cells of huntingtin knockout mice indicate that it is essential for normal nuclear and perinuclear organelles and that one factor regulating its synthesis is iron.¹³ The protein (~ 349 kDa) is composed of approximately 3150 amino acids (depending on the size of the polyQ tract).¹⁴ As with many other large proteins, huntingtin is made up of repeated structures. The polyQ tract starts at residue 18. In addition, there are 10 Huntingtin elongation factor 3 (a subunit of protein phosphatase 2A-TOR1 (HEAT)) repeats, each of which is a loosely conserved repeating segment of approximately 40 amino acids, forming two hydrophobic α helices and a polymorphic polyproline region.¹⁵ The protein is widely distributed throughout the central nervous system (CNS), and this has posed the question of how its altered functioning gives rise to selective neuronal loss in HD. Initially, the most likely explanation was thought to be that the huntingtin gene mutations confer a “deleterious gain of function”, with the concept of loss of function gaining ground more recently,¹⁶ although how the variant huntingtins go on to cause neurodegeneration has remained a mystery.

HUNTINGTIN AND THE FORMATION OF NUCLEAR AGGREGATES

Both normal and variant huntingtins are localised chiefly in the cytoplasm of neurones.¹⁷ The wild-type protein is associated with cytoplasmic granules, organelles involved in retrograde transport and protein degradation, in some cortical and striatal neurones.¹⁸ In HD, ubiquitinated, polyQ containing, proteolytic N-terminal fragments of huntingtin form insoluble deposits both in the cytoplasm and nucleus. Both transgenic animals and genetically modified cell lines have been used to investigate the effects of expanded polyQ repeats on the localisation and processing of huntingtin. In knockin mice, increasing polyQ size was shown to increase nuclear localisation of full length huntingtin, in addition to the formation of N-terminal inclusions and aggregates in medium spiny neurones,¹⁹ and, in striatal embryonic cell lines, localisation in nuclear and perinuclear organelles.²⁰ The formation of N-terminal nuclear aggregates causes a shift in the core catalytic component of the proteasome to the nucleus. Thus, the formation of nuclear aggregates reduces the availability of the proteasome for digestion of other intracellular proteins that need to be removed, such as the apoptosis promoting protein p53. Nevertheless, despite the increased attraction of the proteasome to the aggregates, the rate of proteolysis of the N-terminal fragments was inversely related to polyQ length.²¹ Thus, disturbed proteolysis is an important feature of

HD. However, it is unclear whether the formation of aggregates per se is the essential cytotoxic step or a consequence of cellular dysfunction. Inhibition of aggregate formation by molecular chaperones that localise with the aggregates, such as heat shock protein 70, reduced cell death, suggesting a direct causal relation between aggregate formation and cell death,^{22, 23} although other data indicate that the formation of nuclear inclusions and apoptosis are not closely related, with huntingtin acting via other routes.²⁴ Huntingtin has several protease susceptible domains. Within the human CNS, different patterns of proteolysis were seen in different regions. In the cortex, cleavage at two N-terminal sites (termed A and B) predominated, whereas in the striatum the dominant cleavages occurred at one N-terminal (A) and a C-terminal site.²⁵ Huntingtin is a caspase substrate. Inhibition of digestion of huntingtin by caspases 3 and 6 reduced apoptotic rates in cell models, suggesting that caspase inhibitors might provide a potential new therapeutic approach to the treatment of the disease.^{26, 27}

HUNTINGTIN, EXCITOTOXICITY, AND APOPTOSIS

Although the above evidence supports the concept that aggregate formation is a causal agent in neuronal death, it is unclear whether this is the sole mechanism and how variant huntingtins relate to other features of the pathology, such as excitotoxicity. Much has been written about excitotoxicity via the NMDA and kainate receptors in HD (recent, extensive reviews on the structures and functions of these are by Chittajullu *et al*,²⁸ Lerma *et al*,²⁹ Cull-Candy *et al*,³⁰ and Ravenscroft and Brotchie³¹). Over the past two years, much of the intracellular signalling cascade underlying excitotoxicity in HD has been pieced together. Key players in this are the NMDA and kainate receptors, a protein with the formidable name of “post-synaptic density protein 95” (also known as synapse associated protein 90), abbreviated here to PSDP-95, mixed lineage kinase (MLK), and c-Jun-N-terminal kinase (JNK). Glutamate receptor stimulation was shown previously to be involved in MLK-1 activation,³² and in a separate study JNK activation was linked to apoptosis.³³ Now the connection between these processes and the roles of huntingtin and PSDP-95 in excitotoxicity are becoming more clearly understood. PSDP-95 is a scaffold protein, which binds to several intracellular proteins and possesses guanylate cyclase activity. PSDP-95 binds via repeat units in its structure, termed PDZ domains, to the NMDA receptor. PSDP-95 plays a pivotal role in regulating synaptic plasticity and synaptogenesis.³⁴ Specifically, PSDP-95 binds to the NR2 NMDA receptor and kainate receptor, GluR6, subunits. Variant huntingtins with expanded polyQ tracts interfere with the binding of PSD-95 to NMDA and kainate glutamate receptors, causing both receptors to become hypersensitive,^{35, 36} thereby allowing increased Ca²⁺ influx via specific uptake pathways.³⁷ In turn, the MLK isoform, MLK-2,³⁸ is activated, causing activation of MAP kinase kinases 4 and

7 and stress signalling kinase, SEK-1, and consequently JNK-2³⁹ (dominant negative SEK-1 blocks JNK-2 activation³⁹). Activated JNK2 phosphorylates the N-terminal region of c-Jun, which is one half of the transcription factor AP-1, thus modulating gene transcription. Activated JNK also phosphorylates the C-terminal region of MLK-2. This step appears to be crucial in the triggering of apoptotic cell death. Cotransfection of a dominant negative MLK-2 blocks apoptotic cell death induced by variant huntingtins.⁴⁰

Interestingly, full length variant huntingtins, rather than N-terminal fragments, were found to be potent triggers of apoptosis in model cells expressing the NMDA receptor subtype prevalent in human striatal medium spiny neurones. Therefore, both full length variant huntingtins and nuclear N-terminal fragment aggregates cause cell death by different mechanisms. The actions of the full length variants may account for the observation that cellular dysfunction can be seen before aggregate formation in the nucleus.⁴¹

MULTIPLE PATHWAYS LEADING TO CELL DEATH

There is continuing evidence that variant huntingtins affect multiple pathways, which potentially lead to cell death. One such pathway is the deprivation of neurotrophic support. Brain derived neurotrophic factor (BDNF) expression is reduced in the caudate and putamen of patients with HD.⁴² That enhanced expression of neurotrophic factors may mitigate the effects of neurotoxins and thus be a potential therapeutic strategy was explored in animal and cell models. Both BDNF, nerve growth factor 3 (NGF-3), and NGF4/5 support proved effective treatments against quinolinic acid treatment in the various models, with BDNF being the most effective, opening the possibility of treatment by implantation of neurotrophic factor releasing systems.^{42 43}

One potential cause of cell death that has received much interest in several neurodegenerative diseases, including HD, is oxidative stress. However, a detailed investigation of oxidative stress indices in the caudate nucleus, putamen, and frontal cortex of HD brains revealed no alterations in concentrations of thiobarbituric acid-malondialdehyde adducts and lipid peroxides (measures of lipid peroxidation), or of oxidative DNA and protein damage. These data strongly suggest that oxidative stress is not a major contributor to neurodegeneration in HD.⁴⁴ However, evidence indicates that an alternative marker of oxidation— isoprostane concentration—is increased. This has been reviewed by Greco *et al.*⁴⁵

Reduced energy production as a consequence of defective mitochondrial complex II function is a well established feature of the late stages of HD. Garseth *et al* presented evidence of reduced lactate and citrate in the cerebrospinal fluid (CSF) of patients with HD, and this led them to suggest that the decreased citrate values were indicative of astrocytic and neuronal dysfunction.⁴⁶ Whether the energy deficit is a cause or consequence of the disease

is uncertain. Using a ³¹P nuclear magnetic resonance assay, Lodi *et al* found that the phosphocreatine to inorganic phosphate ratio was reduced in muscle tissue of both symptomatic and presymptomatic gene positive individuals, indicating that impaired energy production is an early feature of the disease.⁴⁷ In contrast, Guidetti *et al* found no evidence of change in the functioning of mitochondrial complexes I to IV in the neostriatum and cortex of presymptomatic individuals and patients with mild symptoms.⁴¹ Guidetti *et al* also found no change in the activities of complexes I to IV in the striatum and cortex of transgenic mice expressing full length polyQ expanded huntingtin before changes in the morphology of striatal and cortical neurones. They concluded that the changes in energy metabolism were a consequence rather than a cause of the disease.⁴¹ However, another group using a different animal model—3-nitropropionic acid treatments—came to conclusions suggesting that energy impairment was at the root of the disease. Calabresi *et al* found that treatment with 3-nitropropionic acid, which is a specific inhibitor of complex II, produced long term NMDA mediated excitation in striatal medium spiny neurones.⁴⁸ This effect was dopamine dependent, with dopamine acting via D2 receptors, whereas it was negatively regulated via D1 receptors, all of which mirrors the human disease.²¹ In a quinolinic acid treated rat model, energy metabolism, as measured by 2-deoxy-(¹⁸F)fluoro-D-glucose uptake was impaired within one week of lesioning, and this impairment deepened with time. However, D2 receptor expression did not simply follow the changes in glucose analogue uptake. One week after lesioning D2 receptor levels increased, after which there was a progressive decline.⁴⁹ These last two sets of findings raise the question of the relation of animal models to the human condition. They clearly demonstrate changes that parallel pathological changes seen in humans but leave the question of the ultimate cause of HD unanswered.

Another potential cause of cell dysfunction in HD is disruption of gene transcription by binding of variant huntingtins to transcription factors and intracellular signalling proteins. Of particular interest have been the interactions with the cAMP response element (CRE) binding protein and p53. N-terminal huntingtin fragments were shown to colocalise with both of these proteins in nuclear aggregates in cell culture and transgenic mouse models.^{50 51} This colocalisation within nuclear aggregates occurs because of interaction between the polyQ repeats in huntingtin and a similar short repeat in the CRE binding protein.⁵¹

Protein kinase C (PKC) is thought to be important in long term potentiation affecting brain plasticity and learning. In symptomatic transgenic mice expressing polyQ, expanded huntingtin steady state levels of PKC beta II mRNA were decreased in brain compared with control animals. This parallels the reduction of this mRNA in the caudate-putamen of human HD brain. It was postulated that the reduction

in PKC may play a part in the reduced ability to store information in HD.⁵²

The multiplicity of other pathways potentially affected in HD is illustrated by the number of proteins recognised to interact with huntingtin. These are known either as huntingtin associated proteins (HAPs), huntingtin interaction proteins (HIPs), and huntingtin–yeast partners (HYPs). Examples are HAP-1, HYP-J (*a* adaptin C), and HIP-3, which are associated with vesicular trafficking. HYP-A and HYP-I have nuclear functions, HIP-2 is a ubiquitin conjugating enzyme, and HYP-F is part of the 26S proteasome. New members of these categories are still being discovered and the physiological functions of recognised ones elucidated. Most recently, the functions of HIP-1 have been clarified. This molecule is encoded by a large gene of 32 exons, scanning 215 kb, which gives rise to two transcripts.⁵³ The translation product is involved in D1 receptor trafficking, linking huntingtin and the endocytic protein, clathrin.⁵⁴ In an immortalised striatal neuronal cell line, dopamine altered the subcellular localisation of huntingtin, resulting in an increase in membrane fractions containing HIP-1 and clathrin. Another recently described member of the HIP family (the gene located on 12q24),⁵⁵ HIP-1R was also shown to be involved in endocytosis. The C-terminal, talin-like domain of this protein binds to F-actin, thus linking the endocytic machinery with the actin cytoskeleton of cells.⁵⁶ HIP-1 is also a pro-apoptotic protein, the over-expression of which results in rapid caspase 3 dependent cell death via the intrinsic pathway of apoptosis.⁵⁷ The association of huntingtin with HIP-1 attenuated the pro-apoptotic actions of HIP-1. Interestingly, wild-type huntingtin binds more strongly with HIP-1 than do the polyQ expanded forms, which thus represents another potential neurodegenerative mechanism in HD.

The latest HAPs and HIPs to be identified are HAP40 and HIP-12. HAP40 is a 40 kDa protein encoded within intron 22 of the factor VIII gene. In the presence of normal huntingtin, HAP 40 is located in the cytosol, and in its absence it is actively transferred to the nucleus, although the consequences of this are not known.⁵⁸ HIP-12 was discovered while elucidating the gene structure of HIP-1. HIP-12 has no detectable pro-apoptotic properties, does not bind to huntingtin, but does bind to HIP-1.⁵⁹

A model of cell death in neurodegenerative disease

Finally, in this brief review, mention should be made of an advance in the understanding of the rate of cell death in neurodegenerative diseases. Clarke *et al* studied photoreceptor decay in model systems and, with reference to HD, the uptake of 18F-glucose into the caudate nucleus of patients with HD, this being regarded as a measure of surviving neurones.⁶⁰ The mathematical description that best fitted the data was that of a constant risk of cell death, with the qualification that an exponential decrease in the risk of cell death may also be a valid

model. The constant risk model means that cell death would be random and that the death of a neurone would be independent of the fate of other neurones, whereas the exponential decrease model proposes that the chance of cell death decreases as the number of surviving neurones decreases. They propose that the features of a neurodegenerative disease such as HD—genotype dependence, the random nature of cell death within a specific population, the constant risk or exponentially decreasing risk of cell death, and the late onset of the clinical signs and symptoms, which clearly means that most neurones survive for a considerable period of time—imply that the organism exists in a steady state. This condition, which they term the mutant steady state, is different from the normal healthy state, and is achieved by adaptive changes in metabolism to cope with the effects of the mutant gene product.

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