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Huntington's disease: pathomechanism and therapeutic perspectives

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Summary. Huntington's disease is an autosomal dominantly inherited progressive neurodegenerative disorder. The mutant gene has been localised to chromosome 4p16.3. The gene product huntingtin is widely distributed in both neurones and extraneuronal tissues. The mutation in Huntington's disease involves the expansion of a trinucleotide (CAG) repeat encoding glutamine. The etiology of Huntington's disease is yet unknown but increasing evidence suggests important role of altered gene transcription, mitochondrial dysfunction and excitotoxicity. The expanded polyglutamine stretch leads to a conformational change and abnormal protein-protein interactions. Mutant huntingtin can bind to transcription factors, resulting in reduced levels of acetylated histones. One consequence of this appears to be a decreased expression of genes which may play critical roles in neuronal survival. To date, a number of palliative therapies have been demonstrated to be effective in reducing the motor features, and particularly the chorea, but no treatment is at hand for the other symptoms of Huntington's disease. However, these treatments produce very limited symptomatic benefit. In the absence of disease-modifying treatment, the other avenue is the neural transplantation.

However, recent advances in understanding have furnished new hope that a therapeutic strategy may one day be possible.

Keywords: Huntington's disease, CAG trinucleotide repeat expansion, altered gene expression, excitotoxicity, mitochondrial dysfunction, neural transplantation.

Introduction

Huntington's disease (HD) is an autosomal dominantly inherited progressive neurodegenerative disorder. The main symptoms are choreiform, involuntary movements, personality changes and dementia (Garron, 1973; Antal et al., 2003). The symptoms may appear in younger and older patients, but usually

in mid-life and the progression of the disease inevitably leads to death within 10–15 years.

The characteristic neuropathological features of HD are macroscopic atrophy of the caudate nucleus, neuronal loss and astrocytosis in the striatum. The neuronal loss is selective for medium-sized spiny neurones containing GABA/enkephalin and GABA/substance P. The large interneurones (containing NADPH diaphorase and somatostatin) and the large cholinergic neurones remain intact (McGeer et al., 1976; Ferrante et al., 1985; Reiner et al., 1998). The mechanism of selective neuronal loss is unknown. There is a loss of cortical volume too, particularly in advanced cases. Predominantly the large pyramidal neurones in layers III, V and VI are affected. There is also a loss of neurones in the thalamus, the substantia nigra pars reticulate and the subthalamic nucleus.

The gene for HD was identified in 1993 (Gusella et al., 1993). The mutant gene causing HD was localised to chromosome 4p16.3 and named IT 15 (''interesting transcript''). Its length is 210 kb, containing 67 exons and coding a 348 kD, 3144 aa protein, huntingtin, which is widely distributed in both neurones and extraneuronal tissues. The mutation in HD involves the expansion of a trinucleotide (CAG) repeat encoding glutamine at the 5′ end of the coding sequence. In healthy individuals, the CAG repeat number ranges from 9 to 39 (median: 19), while in patients with HD the range is 36–121 (median: 44) (Huntington's Disease Collab. Res. Group, 1993; Kremer et al., 1994). Expansion to >55 repeats causes the juvenile form of the disease. There is an inverse relationship between the CAG repeat number and the age at onset of the symptoms. The gene of HD displays marked instability, particularly when passed through the male germ line, where expansions tend to occur more frequently than contraction. This is the anticipation phenomenon, where the age at onset tends to decrease in successive generations.

One research aim is to determine the earliest molecular changes associated with HD. There is no possibility for this in humans, but various early changes have been identified in an animal model of HD. A major step was the creation of a transgenic mouse model that expressed exon 1 of the human HD gene, under the control of the human huntingtin promoter (Mangiarini et al., 1996; Bates et al., 1997).

The function of the mutant protein is still unknown as concerns its details, but the expanded polyglutamine stretch leads to a conformational change and abnormal protein-protein interactions. Mutant huntingtin alters numerous forms of the gene expression by altering the functions of the transcriptional factors and it reduces the level of acetylated histones (Walton et al., 2000; Wyttenbach et al., 2001). It has been demonstrated that this can be reversed by treatment with histone deacetylase (HDAC) inhibitors. A number of HDAC inhibitors reduce cell loss both *in vitro* and in *Drosophila* and mouse models of HD, suggesting that histone acetylation is the cause of cell death (McCampbell et al., 2001; Steffan et al., 2001). This kind of drug has been shown to be safe and efficacious for the long-term treatment of patients with other disorders (Chang et al., 2002).

There is currently no cure or even effective therapy for HD. However, recent advances in understanding have furnished new hope that a therapeutic strategy may one day be possible.

Excitotoxicity

The process of glutamate-mediated neuronal death (called excitotoxicity) was discovered about three decades ago (Olney, 1969). There is evidence that excitotoxicity may play a role in the pathogenesis of HD (Coyle et al., 1976; McGeer et al., 1976; DiFiglia, 1990). It has been demonstrated that the injection of quinolinic acid produces a lesion which is a reliable model of HD (Schwarcz et al., 1983; Beal et al., 1986; Vécsei et al., 1991, 1996, 1998). There is an increased vulnerability to NMDA receptor agonists in cultured striatal neurones from a different mouse model of HD (Cepade et al., 2001). An impairment of the mitochondrial energy metabolism can result in decreased ATP production, with an accompanying reduction of the Na^+–K^+ ATP-ase activity. Partial cell depolarization may occur, leading to alleviation of the voltage-dependent Mg^{2+} blockade of NMDA receptor-associated channels. Accordingly, endogenous levels of glutamate activate NMDA receptors. The concomitant increase in Ca^{2+} influx into the neurones may trigger further free radical production (Beal, 1992; Csillik et al., 2002). Medium spiny neurones are especially affected in HD. These ''spines'' are rich in excitatory N-methyl-D-aspartate (NMDA) receptors. The state of phosphorylation of the NMDA receptor subunits enhances their synaptic efficacy so as to favour the appearance of choreiform movements. Mutant huntingtin enhances excitotoxic death in cultured cells via an enhanced NMDA receptor sensitization (Table 1).

A clinical trial on the glutamate release inhibitor lamotrigine revealed that it reduced the chorea in HD patients, but had no effect on the disease progression (Kremer et al., 1999). Riluzole, another glutamate release inhibitor, stimulates a G-protein-dependent signal transduction pathway and inactivates voltage-dependent Na^+ channels. These effects together diminish glutamatergic neurotransmission. Riluzole has been found to reduce the chorea and improve the UHDRS total motor score, but to have no effect on the functional capacity and other clinical features (Rosas et al., 1999; Seppi et al., 2001). The Huntington Study Group does not recommend the routine use of riluzole (Huntington Study Group, 2003). A European study with riluzole is under way. Remacemide,

Table 1. Evidence for excitotoxicity in HD pathogenesis

Create the term ''excitotoxin''.	Olney (1969)
Intrastriatal injection of kainic acid leads to the degeneration of the striatal neurones.	Coyle et al. (1976); McGeer et al. (1976)
Quinolinic acid results in selective neuronal damage similar to that of HD.	Schwarcz et al. (1983); Beal et al. (1986); Vécsei et al. (1991, 1996)
There is increased vulnerability to NMDA receptor agonists in cultured striatal neurones.	Cepade et al. (2001)
Mutant huntingtin enhances excitotoxic cell death.	Zeron et al. (2001)

another blocker of this receptor-mediated excitatory pathway, tends to alleviate the chorea too but Remacemide failed to produce significant slowing in functional decline (Kieburtz et al., 1996; Huntington Study Group, 2001). Chorea is the typical motor disorder in HD. This is the source of the functional impairment and an eventual contributor to social isolation. The pharmacologic actions of amantadine include antagonistic effects at the NMDA receptors and the enhancement of dopamine release or the reduction of dopamine reuptake. Dopaminergic effects are unlikely because the chorea would then be expected to be exacerbated (Verbagen et al., 2001).

Replenishment of energy metabolism due to oxidative stress

The disruption of the mitochondrial function and the glucose metabolism contributes to neuronal cell death (Beal, 1997) (Table 2). A mitochondrial dysfunction has been implicated in the pathogenesis of HD, but it could be secondary (Manfredi et al., 2000). In HD patients, the glucose metabolism is decreased in the affected striatal and cerebral cortex. Defects in the glucose metabolism lead to the generation of free radicals and oxidative damage. In the event of an impaired oxidative phosphorylation, creatine and co-enzyme Q10 exert a neuroprotective effect in transgenic mouse models of HD (Koroshetz et al., 1997; Ferrante et al., 2000). Hence, restoration of ATP levels could offset the impaired energy metabolism and the toxicity of mutant huntingtin. One way to achieve this could be a creatine diet in R6/2 transgenic mice, creatine improved the survival and delayed the striatal atrophy and the formation of neuronal inclusions (Klivenyi et al., 1998; Ferrante et al., 2000, Andreassen et al., 2001). Nevertheless, such efficacy was not observed in a human clinical trial (The Huntington Study Group, 2001). Studies have been planned for other free-radical scavengers (co-enzyme Q10, OPC-14117).

Table 2. Evidence for dysfunction of mitochondria in HD pathogenesis

Ultrastructural studies of cortical biopsies from HD patients reveal abnormal mitochondria.	Goebel et al. (1978)
Reduced glucose metabolism.	Podolsky et al. (1977); Kuhl et al. (1982)
Mitochondrial toxins (e.g.: 3-NP) cause selective cell death in the striatum, resembling the pathology of HD.	Coyle et al. (1976); McGeer et al. (1976); Brouillet et al. (1995)
Elevated lactate levels in the cerebral cortex and basal ganglia.	Jenkins et al. (1993)
Reduced ratio of phosphocreatine to inorganic phosphate in resting muscle.	Koroshetz et al. (1997); Lodi et al. (2000)
Abnormal mitochondrial membrane potential depolarization in lymphoblasts from HD patients.	Sawa et al. (1999)
Biochemical studies demonstrate impaired complex II–III activity in basal ganglia of HD patients.	Gu et al. (1996); Browne et al. (1997); Tabrizi et al. (1999)

Apoptosis – caspase inhibitors

Huntingtin-mediated aggregation might induce the initiation of programmed cell death (apoptosis) via activation of the initiator caspase-8, -9 and -10. During the cascade events, caspase-3 is activated, which cleaves mutant huntingtin. The small, N-terminal peptide containing the expanded polyQ fragment seems to be toxic. The progression of the disease could be reduced by using caspase inhibitors, which protect against the formation of truncated huntingtin.

The tetracyclines are broad-spectrum antibiotics, inhibitors of caspase-1 and -3 and matrix metalloproteases, and of the aggregation of amyloids. Although tetracycline itself does not cross the blood-brain barrier, the related compounds minocycline and doxycycline do, and their levels in the CSF have been estimated to be 14–30% of the blood levels. Tetracycline, doxycycline and minocycline reduce the aggregation of huntingtin in the organotypic slice culture assay and inhibit caspase-1 and -3. Treatment with minocycline, like that with creatine, can delay the disease progression in animals, but not cure HD. The results of *in vivo* trials by different groups are controversial (Chen et al., 2000; Smith et al., 2003).

Protein aggregation

The full details of the function of normal huntingtin are not known. It is clear that it has an essential role during development and throughout life; via its anti-apoptotic function, it blocks the activation of procaspase-9. Mutant huntingtin is known to form high molecular weight complexes and inclusion bodies in nuclei and in neuronal processes. It is also generally accepted that aggregation is a causative factor (Davies, 1997). The reduction of polyglutamine inclusion formation through the overexpression of heat shock proteins and bacterial and yeast chaperones is associated with a decreased extent of cell death *in vitro*. The modulation of aggregates seems to be a viable approach to the treatment of HD (Carmichael et al., 2000).

A new avenue for therapy involves the identification of cytoplasmic and nuclear protein–protein interactions. Cytoplasmic targets include microtubules, the vesicular trafficking system and ubiquiting-conjugating enzymes. Nuclear targets include p53, the cAMP response element-binding protein (CBP) and Sp1 (see below).

Early changes in gene expression

The acetylation and deacetylation of histones in nucleosomes are important in the regulation of gene expression. The nucleosome, the basic unit of chromatine, is composed of highly conserved core histones (H2A, H2B, H3 and H4) and DNA. The degree of acetylation and deacetylation of histones is controlled by the activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Post-translational acetylation of these proteins by HATs is thought to neutralize the positive charge and generate a more open DNA conformation. The deacetylation of histones by HDACs restores the positive charges on the histones and leads to condensation of the nucleosome. Hyperacetylated histones

are linked to transcriptionally active domains, whereas hypoacetylated histones are associated with transcriptionally silent domains. The roles of individual HDACs in regulating gene expression patterns and cellular functions are not totally clear (Luthi-Carter et al., 2000; Marks et al., 2001; Krämer et al., 2001; Chang et al., 2002; Hoshimo, 2003).

The cell function and lifespan are modulated by alterations in gene expression in response to extracellular stimuli. The precise cause of neuronal death has not been fully elucidated, but recent work suggests that the interactions of pathologic huntingtin with transcription factors may play important roles in cell survival. The level of mutant huntingtin level is increased intranuclearly. This results from an impaired clearance of the mutant protein as a consequence of the impaired proteosome function. The nuclear transport and accumulation of huntingtin may disrupt the transcriptional machinery by its binding to other polyglutamine-containing proteins. Numerous of these are transcriptional factors. Mutant polyglutamine can alter the distribution of nuclear factors, including CBP, p53, $TAF_{II}130$ and Sp1. Many of these nuclear factors directly regulate histone acetylation. CBP is particularly important, because the CBP level influences a variety of different transcription factors. Mutant huntingtin sequesters CBP and other coactivators, and thereby alters the protein acetylation and gene expression (Walton et al., 2000; Wyttenbach et al., 2001).

The cell loss can be reversed by the overexpression of CBP or the use of HDAC inhibitors (McCampbell et al., 2001; Steffan et al., 2001). HDAC inhibitors have received attention as potential therapeutic drugs for several other diseases, including tumors, sickle cell anaemia, adrenoleukodystrophy and cystic fibrosis. There are 6 classes of HDAC inhibitors. The specificity of each inhibitor for different HDACs has not been demonstrated (Chang et al., 2002). In a *Drosophila* model of polyglutamine-dependent neurodegeneration, the HDAC inhibitors suberoylanilide hydroxamic acid (SAHA) and sodium butyrate arrest ongoing progressive neuronal degeneration (Steffan et al., 2001). These two inhibitors have also been reported to increase acetylated histone levels and to improve the motor performance in transgenic HD mice (Hockly et al., 2003; Ferrante et al., 2003). This raises the possibility that HDAC inhibitors may prove to be useful in the treatment of HD.

Transplantation

A number of groups have been investigating alternative approaches to the treatment of HD, including cell and tissue transplantation. The history of trials of cell transplantation in Parkinson's disease has provided relevant experience for the design of trials in HD. The aim of transplantation is to restore the neuronal circuitry and provide a substrate for functional restoration. To date, cells from the developing CNS (foetal brain, brainstem and spinal cord) are the only appropriate sources for transplantation. Such cells must be harvested at approximately 8–12 weeks post-conception. Translation of a potential novel therapy from the experimental laboratory to the clinic requires good experimental evidence. Excitotoxins induce the most reliable and stable lesion for evaluating striatal graft efficacy in rodent and primate models of HD (Sanberg

et al., 1984). In animal models, transplanted striatal cells have been demonstrated to survive, grow and establish afferent and efferent connections. It is anticipated that transplanted foetal allogenic striatal cells lacking the HD mutation would not be affected by the host disease, because the mutation causes neuronal death through an intracellular process. The available evidence suggests that human foetal striatal grafts may survive transplantation and induce clinical benefit in patients with HD. The success of grafting is sensitive to the age of the donor and to the degree of neuronal loss in the patient. The collection and use of human foetal tissue raises a number of ethical concerns relating both to the collection itself and to the safeguarding of the recipient. It is important to note that such clinical trials are still in their early stages of development and many technical issues remain to be fully resolved (Boer, 1994; Peschanski et al., 1995; Bachoud-Levi et al., 2000; Hauser et al., 2002). The aims of these pilot studies are to evaluate the feasibility and safety of the procedure and to provide information regarding the efficacy of this novel therapy.

Although no means of curative therapy is known as yet, advances in the understanding of the mechanism of the disease are leading to ever more therapeutic strategies and possibilities.

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