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Review

Therapeutic perspectives for the treatment of Huntington's disease: Treating the whole body

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Summary. Huntington's disease (HD) is a tremendously debilitating disorder that strikes relatively young individuals and progresses rapidly over the next ten to fifteen years inducing a loss of cognitive and motor skills and eventually death occurs. The primary locus of the disorder is a polyglutamine expansion of the protein product of the *huntingtin* (*htt*) gene. The htt protein appears to be a scaffolding protein that orchestrates the complex assembly of multiple intracellular proteins involved in multiple processes, including vesicular movement and cell metabolism. The htt protein is ubiquitously expressed in human tissues but the predominance of the interest in the pathology lies in its effects on the central nervous system (CNS). Most of the current therapeutics for HD thus have been targeted at preventing neuronal damage in the CNS, however, a considerable body of evidence has been accumulating to suggest that the maintenance of a healthy nervous system is tightly linked with peripheral physiological health. Therefore treatment of both the peripheral and central pathophysiologies of HD could form the basis of a more effective HD therapeutic strategy.

Key words: Huntingtin, Therapeutic, Aggregation, Polyglutamine, Expansion

Introduction

Huntington's disease (HD) is a genetically linked neurodegenerative disorder first described by George Huntington in 1872. It is primarily characterized as a hyperkinetic disorder marked by five specific features; a) heritability, specifically HD is autosomally dominant; b) chorea, or jerky dance-like movements; c) behavioral and physical disturbances, including personality changes and skewed balance; d) cognitive impairments, such as depression or dementia; e) and death 10-15 years after initial onset (Bates and Murphy, 2002; Li and Li, 2004). HD has a relatively similar frequency of occurrence in both men and women, and its incidence in the whole population is approximately 5-10 cases per 100,000 worldwide, making it the most common inherited neurodegenerative disorder (Landles and Bates, 2004). The primary cause of the disorder was identified as an expanded trinucleotide repeat in the gene encoding for the huntingtin protein. It is interesting to note however that in addition to the archetypical neurological phenotypic attributes, many HD patients develop a specific form of genetic diabetes and experience extreme weight loss.

The mutations that cause HD are found in exon 1 of chromosome four, which encodes for the protein huntingtin (htt). Typically, there are approximately 35 (or fewer) trinucleotide repeats (CAG) encoding for the amino acid glutamine in htt. However, in HD the number of CAG repeats increases past 40 causing a significantly expanded polyglutamine tract (Landles and Bates, 2004; Li and Li, 2004; Marx, 2005). The number of repeats is inversely correlated with the age of onset, with 70-100 repeats leading to juvenile onset (Landles and Bates, 2004). Furthermore, in the paternal line of inheritance a phenomenon known as "genetic anticipation" often occurs, in which the number of repeats increases as the disease is passed through the generations (Carpenter 1994).

HD is not the only disorder caused by an expansion of the polyglutamine tract. At least nine other disorders, including dentatorubral-pallidoluysian atrophy (DRPLA), spinal and muscular atrophy (SBMA), and spinocerebellar ataxias (SCA) are caused by glutamine expansion in specific individual genes and each manifest similar neurodegenerative symptoms (Zoghbi and Orr, 2000; Nakamura et al., 2001).

The deleterious effects of HD are primarily generated through the aberrant expression of a mutant htt protein (mhtt). Wild-type huntingtin is a large protein composed of 3144 amino acids. Although it is nearly ubiquitously expressed in all body tissues and is associated with many organelles, its specific molecular

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function(s) is still unknown (DiFiglia et al., 1995; Sharp et al., 1995; Gutekunst et al., 1998). Studies of associated proteins, for example ß-tubulin, suggest that it is involved in scaffolding multiple proteins for signaling processes and intracellular transport. It also plays an important role in mRNA transcription, as it associates with many transcription factors. A number of specific transcriptional pathways appear to be impaired in HD patients and in animal models of the disease (Harjes and Wanker, 2003). Htt also seems to be essential for development and tissue maintenance, as knockout htt murine models die at embryonic day 7.5, and loss of wild-type htt in adulthood causes tissue neurodegeneration throughout the brain (Bates and Murphy, 2002; Landles and Bates, 2004; Li and Li, 2004; Marx, 2005).

In a similar fashion, the exact mechanisms whereby mutant htt causes toxicity and cell death are still unclear; however, it is possible that polyglutamine expansions specifically disrupt the ability of the htt protein to complex other proteins with a correct stoichiometry. Deterioration of the spiny-projection GABAergic neurons of the striatum is prevalent early on in the onset of HD and is a major cause of the cognitive and physical symptoms associated with the disease. Additionally many other neuronal systems are grossly affected as well (Landles and Bates, 2004). Since wild-type htt is likely to be involved in a significant number of processes, the implications of its mutation are far reaching both in the CNS and in the peripheral organs and tissues. Furthermore, the lack or decrease of normally functioning wild-type htt may also have pathological consequences (Cattaneo et al., 2005). We shall briefly review some of mechanisms whereby mutant htt and the disruption of wild-type htt may lead to the HD disease pathology.

Pathological actions of htt

Proteolytic degradation of htt generates N-terminal fragments that are released into the extracellular matrix. These fragments are prone to aggregation, and, while their toxicity is debated, the aggregation of htt is probably an important factor in HD pathology. It has been shown that htt aggregates sequester transcription factors, such as CREB-binding protein, thereby disrupting transcription of essential genes by inhibiting the arrangement of downstream factors and counterparts and thus cellular signaling (Landles and Bates, 2004; Li and Li, 2004; Marx, 2005; Rubinsztein, 2006). Interestingly, several other polyQ disorders seem to also affect the CREB transcriptional pathway (Landles and Bates, 2004).

N-terminal htt fragment aggregates are recognized by the body as misfolded proteins. Normally, molecular chaperones work to refold the proteins and if this is unsuccessful, then the aggregates are cleared by the ubiquitin-protease system (UPS). However, in HD the rate of misfolding and aggregation seem to overwhelm the cells' UPS. It has been proposed that the failure of the UPS is necessary for the pathogenesis of HD (Sakahira et al., 2002). The inability of the UPS to degrade the large stretches of glutamine may result in the release and aggregation of N-terminal fragments. Furthermore, the sequestration of molecular chaperones into the N-terminal aggregates reduces their availability to other physiological systems (Hay et al., 2004). Thus vital methods of cellular waste management are disrupted (Landles and Bates, 2004; Li and Li, 2004; Rubinsztein, 2006).

As previously mentioned, the absence of wild-type htt also plays a role in the disease pathogenesis and the production of brain-derived neurotrophic factor (BDNF), a potent neurotrophic factor, is a prime example of its importance. The production of BDNF is controlled by the transcription factors REST/NRSF, which halt the production of this growth factor (Zuccato et al., 2003). Normally, wild-type htt binds to the REST/NSRF complex and prevents them from antagonizing the transcription of BDNF. The mutant polyQ expanded form of htt is unable to properly bind the REST/NSRF complex resulting in a profound reduction of BDNF transcription and translation. This reduction of the neurotrophic factor BDNF may in part underlie the death of the spiny-projection neurons of the striatum, as they are especially reliant on this factor (Landles and Bates, 2004; Li and Li, 2004; Cattaneo et al., 2005; Marx, 2005).

Animal models of Huntington's disease

A comprehensive animal model is essential in the effort to successfully design drug therapies that selectively reverse or prevent the patterns of pathogenesis in HD. Since the discovery of the Huntingtin gene in 1993 several animal models were formulated to mimic the characteristic pathologies and behavioral anomalies associated with human HD. Each different model offers a unique perspective from which to study the pathways underlying htt-mediated pathogenesis. However, there are limits to this approach as there are often phenotypic differences observed between mhtt knock-in mice and human HD patients. There are many different ways to induce HD-like symptoms and paralleling pathology *in vivo* and *in vitro*. The closest modeling of the disease is done through genetic alteration of animals with little other physiological variability. Introduction of certain neuro- and excito-toxins offer localized induction of HD-like pathologies in mice and non-human primates. One of the primary limitations of non-primate HD models is their significantly shorter lifespan which may curtail manifestation of the full gamut of pathologies associated with HD.

Regardless of their limitations, animal models provide a large body of data from which research can develop eventual therapeutic strategies for treating this devastating disease. A note of interest though should be

made in that often much more salient information can be gleaned from these models, i.e. from multiple tissue sites and not just from the CNS. Knock-in mice provide the most theoretically sound model for HD. These mice carry a murine polyglutamine-expanded mutant htt under an endogenous transcriptional promoter called Hdh (Wheeler et al., 2000). Other genetic models use exogenous forms of the gene and express it at aberrant chromosomal locations. This undoubtedly introduces additional experimental variables. The Hdh knock-in mouse model has been shown to mimic many of the molecular abnormalities and cellular dysfunction of HD patients. Such mouse models were initially dismissed, however, because there were little or no phenotypic behavioral or motor abnormalities (Wheeler et al., 2000). However, subsequently derived animals managed to address these limitations by elongating the N-terminal glutamine expansions. Such mice showed early signs of subtle behavioral anomalies before any neuropathology was detected (Lin et al., 2001). The length of the polyglutamine expanded htt protein was sufficient to cause neuropathology and behavioral defects when about 90 or more CAG repeats were used. Lin et al. (2001) have demonstrated a range of severe physiological and behavioral anomalies in a 150 polyglutamine expanded knock-in mouse model.

The common appearance of nuclear staining and microaggregates of htt in the brains of 2-6 month old knock-in mice suggests that they are an early indication of pathogenesis. Neuronal intranuclear inclusions (NIIs) in the mouse brain are however seen later in the course of the disease (10-18 months of age). The functional role of these nuclear inclusions is still unclear however; they have been shown to have a neuroprotective activity against htt toxicity (Schilling et al., 1999). Certain human pathological characteristics have not been described in these mice. For example there is little gliosis and no overt neuronal loss (Shelbourne et al., 1999). Cellular dysfunction has however been demonstrated in the 94 CAG repeat homozygous knock-in mice, as a down regulation of striatal proteins and increased sensitivity to N-methyl-D-Aspartate (NMDA: Perez-Navarro et al., 2006). Unfortunately, there was a slower progression in phenotype and pathology in this mouse model than that seen in HD patients. However, this actually allows a more detailed analysis of the disease's progression (Menalled et al., 2002). Temporal variability aside, the patterns of disease progression in these mice closely resembles that of human HD.

Knock-out models

Murine knock-out models provide an angle of studying htt and its associated proteins under a loss of function mutation. The phenotypic contributions of wild-type htt can also be better understood from the knock-out model. Unfortunately the most common phenotype observed in homozygous htt knockouts was high embryonic lethality. Mutant htt was however found to rescue this phenotype in mice which showed that the effect of the mutation is not solely due to loss of function (Duyao et al., 1995). Human patients with homozygous polyglutamine expansions do not, however, present with developmental impairments. Other homozygous mouse knock-out models have been targeted to investigate the nature of the polyglutamine stretches found on mhtt.

Clabough and Zeitlin (2006) demonstrated that the removal of all N-terminal glutamine expansions on htt in homozygous (DQ/DQ) mice had no gross phenotypic consequences. This mouse model applies the deletion of polyglutamine expansions on endogenous wildtype htt. These mice are born with normal mendelian frequency and share a remarkable phenotypic resemblance to their control littermates. This suggested that the glutamine expansions are not necessary for proper embryonic development. Therefore the polyglutamines may simply modify htt's function throughout life (Clabough and Zeitlin, 2006).

Transgenic mouse models

Transgenic mice have been developed that contain a mutant gene or a fragment of it inserted into the genome. Introduction of a mutant htt gene leads to a resultant expression of both mutant and endogenous htt proteins. Much of the pathophysiology documented in these mice may result from over-expressed mhtt proteins, in contrast though in humans there appears to be a poor correlation of htt-encoding IT15 (important transcript 15 gene) mRNA expression and susceptibility to degeneration in HD (Landwehrmeyer et al., 1995). The main element of variability in these murine models is the length of mhtt polyglutamine tract that is expressed. Some transgenic models possess N-terminal fragments of mhtt encoding several polyglutamine stretches while others incorporate the entire gene. The general phenotypic theme in these mice is that longer polyQ expansions with higher expression levels and shorter transgenes cause the most severe forms of disease.

The R6 mouse model expresses exon 1 of the human htt gene with variable polyQ stretches. There are several lines of the R6 mouse, each expressing a different CAG repeat length, e.g. *R6/1 $(CAG)_{115}$; R6/2 $(CAG)_{145}$; R6/5 $(CAG)_{135\text{-}156}$; and R6/0 $(CAG)_{142}$*. In all but one of these lines (R6/0) the transgene was ubiquitously expressed in all tissues, as is the case in humans. The age of HD symptomology onset in these mice is correlated with the length of CAG repeat insertions; hence in R6/2 onset takes 2 months and in R6/1 onset takes about 4-5 months. However, progressive weight loss was documented in these transgenic mice that persisted until death at about 12 weeks.

The R6/2 line is the most extensively studied and used in research due to the fact that it is readily commercially available (Wang and Qin, 2006). The course of HD disease progression is relatively fast in these mice although they have a characteristically

progressive phenotype with moderate inter-animal variability. Therefore smaller sized test groups may be sufficient for analytical purposes. These mice exhibit motor behavioral impairments that can be seen as early as 5-6 weeks of age. However, overt behavioral anomalies are often not seen until about 8 weeks of age. In addition no overt neuronal cell death is typically observed. These mice also have a drastically attenuated lifespan of about 13 weeks, which imposes time limitations upon researchers. These mice show extensive htt aggregate formation which is more pronounced than that seen in human HD patients (Davies et al., 1997).

N-171-82Q mice have a longer N-terminal fragment of htt (exon 1 and 2), than R6/2 mice, which includes 82 glutamine repeats (Wang and Qin, 2006), these mice express the first 171 amino acids of htt with 82 polyQ stretches under a prion promoter (Schilling et al., 1999). N-171-82Q mice exhibit a less well-defined neurobehavioral phenotype than the R6/2 mice. They share similar neurodegenerative patterns with human HD patients. As opposed to R6/2 mice, the observed phenotypic features are quite variable and thus require larger experimental groups for clear statistical analyses. These mice also exhibit minimal neuronal death, in contrast to the significant neuronal loss seen in human HD pathophysiology.

Another transgenic mouse model incorporates the full-length human htt. The human htt gene was initially identified as 'important transcript 15 (IT15)' by the Huntington's Disease Collaborative Research Group (1993). These mice carry the human IT15 gene as a transgene under a human promoter. As in other models, the strains carrying IT15 develop more severe phenotypes with increasing CAG repeats. However, many of these strains were unsuccessful because they failed to show clear symptomatic and pathological phenotypes. These mice do not normally show NIIs and have much smaller aggregates of nuclear htt.

A similar phenotype is observed in Yeast Artificial Chromosome (YAC) mice (Hodgson et al., 1999). These YAC mice express the IT15 gene with variable polyQ repeats. The disease progression of a YAC model carrying 72 repeats was slow, however this was found to be correlated to smaller repeat lengths and much looser transgene expression rates (Hodgson et al., 1999). Neuronal cell loss is limited to the striatum which recapitulates the selectivity of pathogenesis in human HD. Graham et al. (2006) developed caspase -3 and -6 resistant lines of YAC mice to demonstrate the effect of proteolytic processing on htt toxicity. The caspase-6 resistant YAC mice exhibited ameliorated pathophysiology. This is consistent with the observation that smaller htt aggregates, which are composed of caspase/calpain-mediated proteolytic products of htt, cause a more severe pathology than larger aggregates.

Excitotoxic lesion models

Various treatments with toxins have been shown to selectively induce HD-like symptoms in mice and higher primates. One of the earliest lesion models was generated by direct intrastriatal injections of kainic acid (Coyle and Schwarz, 1976). The effects of kainic acid were shown to mimic the axon-sparing striatal lesions associated with human HD. These models are however limited in that both projection neurons and NADPH-positive interneurons are killed whereas in HD a relative sparing of striatal interneurons has been described.

Intrastriatal injections of the NMDA-selective glutamate agonist quinolinate have also been employed to induce HD. Quinolinate injections have been shown to induce preferentially degenerate GABAergic neurons (Ferrante et al., 1993). Various mitochondrial toxin administrations also can induce the generation of HD-like neuronal degeneration by metabolic disruption and excitotoxicity. 3-Nitropropionic acid (3-NP) has been shown to inhibit the destruction of succinate dehydrogenase (Brouillet et al., 2005). This excitotoxic model shared histochemical and pathological similarities with human HD. About 30-40% of treated animals exhibited motor abnormalities as well as striatal lesions. Administration of 3-NP to non-human primates reproduced human HD more closely with respect to a more progressive pattern of pathogenesis. While these models show some similar patterns of disease between humans and animals, they do not entirely reflect human pathogenesis. As a result, human disease progression may occur through distinct, as of yet, unrecognized pathways.

Pharmacological treatment of Huntington's disease

HD is primarily considered a neurological disorder, however due to the ubiquitous expression of the htt protein it is likely that truly effective future therapeutics will need to address the central and peripheral pathophysiologies of this disease. As with all disorders pharmacotherapies fall into two broad categories, prophylactic and therapeutic. Unfortunately there is a great skewing in the distribution of current or future HD-ameliorating agents to the therapeutic and not the prophylactic. It appears likely that prophylactic remedies may require a gene-therapeutic approach which will be considered in another section.

The therapeutic chemical agents that are currently employed consist of both existing anti-neuro-degenerative agents and also of mechanistically unrelated compounds that perhaps hint to novel potential HD therapeutics. The majority of these therapeutics are designed to ameliorate the primary symptomology of the HD condition itself, i.e. psychiatric agents for the control of behavioral symptoms, motor sedatives, cognitive enhancers and neuroprotective agents. In addition to the classical anti-HD therapeutic groups there are novel agents that can fall into the neuroprotective category but they possess specific anti-htt-directed actions such as inhibition of polyglutamine protein aggregation. We shall discuss the currently used HD therapeutics and

their limitations with respect to their ability to treat the whole-body aspects of this disease.

Psychoactive agents

The psychological symptoms that often present themselves with HD include depression, irritability and apathy (Thompson et al., 2002). Typically these negative symptoms are treated with standard anti-psychotics, anti-depressants and mood stabilizers such as carbamazepine, risperidone, olanzapine, clozapine and quietapine (Barker and Rosser, 2001; Blass et al., 2001). The primary antidepressants that have shown the greatest promise include the selective serotonin uptake inhibitors (SSRIs) such as paroxetine or fluoxetine (Rosenblatt and Leroi, 2000). Other psychoactive compounds such as anti-convulsants like the sodium channel antagonist lamotrigine have also been employed to alleviate HD symptomology (Kremer et al., 1999).

Several other psychoactive compounds have also been employed to treat the central motor dysfunctions induced by mutant htt aggregation in the brain. Essentially these compounds tend to act by attenuating excessive or aberrant dopaminergic neurotransmission.

Dopamine receptor signaling and Huntington's disease

'Neuroleptic' dopamine receptor antagonists such as the conventional 'typical' anti-psychotics, haloperidol (Gimenez-Roldan and Mateo, 1989), fluphenazine (Korenyi and Whittier, 1967) and sulpiride (Quinn and Marsden, 1984) have been extensively used in HD therapeutic trials. In these studies an effective reduction of the chorea symptoms was demonstrated.

The more modern 'atypical' anti-psychotic agents, which generally possess a wider range of G protein coupled receptor activity outside of dopamine receptor antagonism, such as olanzapine (Bonelli et al., 2002), risperidone (Dallochio et al., 1999) and clozapine (Vallette et al., 2001) have all been shown to exert positive therapeutic effects upon chorea and orolingual dysfunction.

While the majority of the dopaminergic therapeutic attention has centered on controlling the hyperkinetic aspects of the disease with dopamine receptor antagonists, recently dopamine receptor agonists have been employed to treat some terminal aspects of the disorder. For example, cabergoline, a dopamine D2 and dopamine D3 receptor agonist, that was previously used to attenuate motor rigidity in Parkinsonian patients, has recently demonstrated promise to treat similar problems such as muscular rigidity in HD patients (Magnet et al., 2006).

Several agents, working often through distinct mechanisms can achieve the effective reduction in dopaminergic neurotransmission that controls fine motor function. Tetrabenazine acts by causing a pre-synaptic depletion of the dopaminergic nerve terminals thereby attenuating excessive outflow of the neurotransmitter that is responsible for HD hyperkinesias. Clinical trials of tetrabenazine have shown its efficacy with respect to attenuating the chorea of HD patients (Soutar, 1970; Toglia et al., 1978; Jankovic and Beach, 1997). Apomorphine, which can cause effective reductions in the levels of dopamine release from neurons has also shown some efficacy in HD symptomology control (Caraceni et al., 1980).

Neuroprotective mechanisms and Huntington's disease

As with many other neurodegenerative disorders, the excitoxicity paradigm has been invoked for HD. Hence the excessive pathological excitatory actions of synaptic glutamate transmission may underlie the early generation of neuronal dysfunction (DiFiglia, 1990). In the central nervous system glutamate can activate either ionotropic (NMDA, AMPA or kainic acid) or metabotropic (mGluR) glutamate receptors.

Several NMDA receptor ion channel-blocking antagonists have been clinically tested for their neuroprotective effects. Amantadine was demonstrated to effectively lower chorea symptoms (Verhagen-Metman et al., 2002). However this compound has negative effects upon other neuronal conditions, *i.e.* increasing irritability and aggressiveness in HD patients (Stewart, 1987). Remacemide, like amantadine, also reduced chorea symptoms (Bodner et al., 2001) but failed to demonstrate any significant neuroprotective action (Bonelli and Niederwieser, 2002). Another promising glutamate receptor agent for HD is the NMDA receptor functional antagonist Memantine (Lipton, 2004). This compound has also been used to treat other forms of neurodegenerative disorders such as Alzheimer's disease. Perhaps the most efficacious glutamate receptor antagonist for HD appears to be Riluzole as this was better tolerated during trials than the two previous compounds (Wu et al., 2006).

Corroborating the role of excitotoxicity in HD etiology it has been demonstrated that there is a reduction of gamma amino butyric acid (GABA) in both brain tissue and cerebrospinal fluid of HD patients (CSF: Perry et al., 1973; Glaeser et al., 1975). The inhibitory GABA acts as a functional brake upon excessive stimulatory glutamate receptor activation. Therefore a diminution of GABAergic neurotransmission may lead to the generation of widespread excitotoxicity. To redress this neurotransmitter imbalance, GABA receptor agonists such as baclofen could have therapeutic value. Baclofen has been shown to reduce the choretic activity in HD patients (Anden et al., 1973). In addition chemical precursors of GABA (L-glutamate and pyridoxine), which increase the levels of GABA in nerve terminals, have been shown to alleviate HD motor dysfunction (Barr et al., 1978). Agents capable of inhibiting the breakdown of GABA (Isoniazid) have also been tested for their efficacy in HD. Isoniazid can effectively elevate

the CSF levels of GABA but unfortunately it failed to adequately control HD symptomology (Manyam et al., 1987).

Caspase inhibition

Evidence implicating the typical cellular apoptotic cascades as a possible cause for the neurodegeneration in HD has directed researchers towards investigating therapeutic treatments targeting the proteolytic caspase family and other proapoptotic factors (Pattison et al., 2006). Caspases are ubiquitously expressed cysteine proteases that are crucially involved not only in apoptotic mechanisms but also in the maintenance of synaptic plasticity (Jellinger, 2006).

Animal models of HD have recently presented evidence that caspase-mediated cleavage of htt could be the cause for the neurodegeneration seen in HD. Caspase-mediated cleavage of htt was shown to occur in the presence of expanded polyglutamine repeats (Wellington et al., 2002). This evidence led to the proposal that caspase-mediated cleavage of htt could be the cause of neurodegeneration, although this is not to suggest that apoptotic cascades are the single cause of degeneration seen in HD. Several types of caspase inhibitors have shown efficacy in HD models, e.g. cystamine (Dedeoglu et al., 2002), cystagon (Dubinsky and Gray, 2006) and the antibiotic minocycline. Among these, the most progressed with respect to therapeutic application is minocycline. Minocycline is a tetracycline-derivative that exhibits a significant neuroprotective capacity in HD. In addition, this compound demonstrates an anti-microbial action (similar to all tetracyclines) and more importantly for HD, it has an anti-inflammatory capacity via inhibition of microglial activation, known to be a prime mediator of cellular apoptosis (Tikka et al., 2001; Bye et al., 2006). In addition, minocyline has also been shown to even extend the lifespan of transgenic R6/2 HD mice (Berger, 2000; Chen et al., 2000). Not only has this antibiotic proven effective with respect to longevity and motor function in animal models but recent evidence from experimental human clinical groups have demonstrated that it can improve neuropsychological performance and motor function (Bonelli et al., 2003; Thomas et al., 2004).

Recently, multifunctional caspase inhibitors have been created. The lead compound among these is Miraxion (formerly known as LAX-101). Miraxion possesses not only a caspase inhibiting capacity but can also antagonize the activity of phospholipase A2 (Scatena et al., 2007). This compound's ability to additionally inhibit phospholipase A2 appears to allow it to promote plasma membrane stabilization and retain mitochondrial integrity. Using high throughput screening, another set of neuroprotective compounds (R1-R4 compounds) have been generated by Varma et al. (2007) that also appear to act through a selective caspase inhibitory mechanism.

Disruption of Huntingtin aggregation

Upon the generation of mutant htt fragments, potentially through caspase-mediated proteolysis, htt misfolds and accumulates into large aggregates. Therefore, in addition to attempting to prevent the generation of fragments with caspase inhibitors another therapeutic avenue that has been explored is the use of agents that prevent the aggregation of mutant htt or compounds that promote the proteolytic clearance of these pathological aggregates.

Proteins which become aberrantly folded typically are recognized by chaperone proteins such as members of the heat shock protein (Hsp) family (Hsp40, 70, 90). These heat shock proteins attempt to refold the proteins back into their native, benign form. Agents such as geldenamycin elevate the expression of Hsps and therefore may limit the accumulation of large htt aggregates in HD (Hay et al., 2004). Interestingly another compound that has been demonstrated to reduce the generation of toxic protein aggregates in vitro and in vivo is, rather surprisingly, the disaccharide trehalose (Tanaka et al., 2004, 2005). This carbohydrate molecule appears to possess a proclivity to disrupt polymerization of glutamine-containing proteins.

Rather than attempting to refold or prevent htt aggregation an additional mechanism to attenuate the levels of aggregated htt is to stimulate the cells' capacity to proteolyse excessive levels of intracellular protein. Hence, activation of the proteasomal and autophagy pathways has been another route therapeutically exploited for the treatment of HD. Several chemically unrelated compounds have been shown to possess some degree of efficacy in treating HD symptoms, via alteration of the protein degradation machinery of the cell. The mood stabilizing compound lithium, amongst many other actions, appears to elevate the beneficial autophagic capacity of cells (Wood and Morton, 2003). The antibiotic rapamycin also appears to alleviate some HD symptomology through a similar autophagy-stimulating mechanism (Berger et al., 2006; Yamamoto et al., 2006).

Finally, the Akt-1-mediated phosphorylation of htt at serine 421 appears to prevent excessive toxic aggregation (Pardo et al., 2006). Neurotrophic factors such as nerve growth factor (NGF) or BDNF potently stimulate the intracellular activation of Akt-1 and thus can reduce htt toxicity. In cells, the serine 421 phosphorylation of htt is rapidly removed by the action of serine/threonine phosphatases. It has therefore been shown that chemical inhibition of the serine/threonine phosphatase calcineurin by FK506 (Tacrolimus) protects neuronal cells from htt-mediated toxicity (Pardo et al., 2006). Whether this therapeutic strategy will eventually be of benefit to humans however may be in doubt as a subsequent study has shown that FK506 and another calcineurin inhibitor (cyclosporin A) actually accelerated the course of HD progression in the R6/2 HD animals (Hernandez-Espinoza and Morton, 2006).

Genetic amelioration of Huntington's disease

The polyglutamine expansion that occurs in HD has been shown to induce widespread repression of gene transcription and a potent reduction in histone acetylation (Steffan et al., 2001). To compensate for this lack of histone acetylation, which maintains transcriptional integrity, inhibitors of deacetylation have received interest as potential HD therapeutics. Histone deacetylase (HDAC) inhibitors such as suberoylanilide hydrozyamic acid and phenyl butyrates have been shown to improve motor function, maintain body weight and delay the onset of neurological pathology in animal models (Hockly et al., 2003; Gardian et al., 2005). Resveratrol can also act as a specific HDAC inhibitor (of the sirtuin class of HDACs) and as well as a potent anti-oxidant agent thus potentially controlling both neurotoxic oxidation and pathological disruption of transcription, both of which are present in HD (Parker et al., 2005). However this efficacy of resveratrol has primarily been demonstrated only in primitive nematode models of HD at very high concentrations.

Non-pharmacological treatment of Huntington's disease

Along with the pharmacotherapeutic approaches to treat the symptomology of HD many new non-drug approaches have been taken in recent years. We will now summarize and discuss the most promising agents that have been employed so far.

Neuroprotective agents

During the neurodegenerative processes of many diseases there are common physiological pathways that can be treated or exploited to improve the patient's outcome. Non-drug neuroprotective agents have been developed to target molecular pathways of pathology rather than focusing on the reversal of motor and cognitive impairments associated with HD progression. The molecular aspects of pathogenesis that are targeted in these treatments include metabolic dysfunction, apoptosis, oxidative DNA damage, protein fragment aggregation, impaired neuronal cell trafficking, and gain of function toxicity of mhtt. Hence the majority of neuroprotective agents either modulate excitatory glutamate signaling, enhance mitochondrial energy production or reduce the generation of toxic chemical metabolites, e.g. reactive oxygen species.

Creatine can support energy production in ailing neurons in HD by acting as a source of adenosine trisphosphate generation. In clinical trials creatine supplementation has been shown to retard the rate of progression of HD (Tabrizi et al., 2003). Bender et al. (2005) found a change in brain metabolite levels in response to creatine administration in HD patients. However, there was little or no motor recovery documented after treatment. Still, creatine was effective in delaying deterioration in the Unified Huntington's Disease Rating Scale (UHDRS). This treatment was considered to be well tolerated and safe for administration to HD patients. Serum 8-hydroxy-2'-deoxyguanosine levels, a biomarker for oxidative DNA damage, were lower in HD patients treated with creatine as opposed to the group receiving a placebo. Despite this early promise from these studies, subsequent trials have often not yielded positive results (Verbessem et al., 2003). Further investigation is required before the true efficacy of creatine can be accurately assessed.

Highly unsaturated fatty acids (HUFAs) constitute a high percentage of the major plasma membrane phospholipids of most neuronal tissue. The functional status of the plasma membrane controls both the activity of transmembrane receptors and ion channels, and also the functional capacity of phospholipases that generate soluble second messengers. Loss of HUFAs during the neurodegenerative process may be reversed by exogenous supplementation. Examples include gamma linoleic acids and eicosapentaenoic acids which, when given in clinical trials to HD patients, improved their dyskinesias and prevented their weight loss (Vaddadi et al., 2002).

Considerable evidence exists to suggest that a bioenergetic deficit exists in HD. The locus of this deficit is considered to be at the level of the mitochondria. Results from HD patients have shown that plasma levels of coenzyme Q10 (CoQ10) are significantly lower compared to non-HD subjects (Andrich et al., 2004). Remedial supplementation of the mitochondrial co-factor CoQ10 has been shown to significantly extend the survival time of R6/2 mice, and it resulted in a marked improvement in grip strength, a reduction of their progressive weight loss and a reduction of htt neuronal inclusions (Smith et al., 2006).

Reactive oxygen species scavengers may alleviate neuronal damage observed in many neurodegenerative disorders. Recent data concerning the use of novel therapeutic anti-oxidant agents has suggested a potential place for such therapeutics in the HD pharmacopeia. Klivenyi et al. (2003) employed a novel anti-oxidant agent, BN82451, in trials using the R6/2 HD model. Oral administration of the agent improved both motor performance and survival of the transgenic animals. These gross improvements were accompanied by a reduction in brain atrophy and intranuclear inclusions.

Along with the neuronal damage seen in many HD models, it seems that cerebral blood flow is often highly abnormal in the early stages of HD progression (Deckel et al., 2001). It has also been demonstrated that dietary L-arginine supplementation can inhibit disease progression (Deckel et al., 2000). These data suggest a potential role for the nitric oxide synthase (NOS) system in the progression of HD. Both enzymatic activity and expression of neuronal NOS (nNOS) are decreased in HD models (Deckel et al., 2001). To ameliorate this deficit in the cerebral vasculature, L-arginine was added to the diet of HD model animals (R6/2), and it was found

to alleviate the motor and cognitive deficits induced by the disease progression (Deckel et al., 2000). Biomarkers in these mice for the neurotoxin peroxynitrite were also reduced in a dose dependent manner. These mice also exhibited reduced expression of calmodulin kinases II and IV.

Several different interventions that have been effective in slowing down the disease process do not specifically target the CNS; instead, they can be considered 'holistic treatments'. As described above, some HD patients and many lines of HD mice exhibit impaired glucose regulation and a diabetes-like metabolic phenotype. When HD mice were placed on an intermittent fasting dietary energy restriction regimen that improves glucose metabolism, the neuropathological processes in the brain were inhibited, the onset of motor deficits was delayed, and their life-span was significantly increased (Duan et al., 2003). The latter study showed that in a mouse model of HD, dietary energy restriction can protect striatal and cortical neurons against damage by mutant huntingtin, and can also preserve levels of BDNF in these brain regions. Exercise, another intervention that is also known to improve glucose regulation, has also demonstrated a therapeutic benefit in a mouse model of HD. HD mice that were provided access to a running wheel for voluntary exercise were found to exhibit a delay in the onset of motor and cognitive deficits (Pang et al., 2006). Both dietary energy restriction and exercise are known to improve insulin sensitivity in skeletal muscle, which could contribute to the benefits of these interventions in HD mice. Indeed, the skeletal muscle of both presymptomatic and symptomatic HD patients has been shown to exhibit impaired energy metabolism and an impaired ability to recover from exercise (Saft et al., 2005). Additionally, keeping the mind active may be another holistic approach to counteracting the pathogenic effects of mutant HD. For example, when HD mice were maintained in enriched environments, their neurological deficits and the loss of body weight (that typically occurs in HD) were prevented to some extent (Schilling et al., 2004; Spires et al., 2004).

Transplantation repair

Several clinical studies in HD patients have employed transplantation techniques for replacing damaged or dead striatal neurons with healthy wildtype neuroblasts. This method had sound results in the first two years after treatment with declined cognitive and motor deficits according to the UHDRS and significant delay in disease progression. Bachoud-Levi et al. (2006) conducted a study where grafted striatal areas were examined in HD patients for up to 6 years post operation. The effectiveness of this procedure appeared to diminish after the first two years after the procedure was performed. This method therefore is not a definitive cure for HD, in fact after about 4-6 years, most patients displayed consistently deteriorating dystonia, although the onset and intensity of chorea seemed to be attenuated. Chorea was in fact quite manageable in treated patients and remained at a stably improving state. Still, the diminished effectiveness of this method over the years following the transplantation has significantly decreased the appeal of the treatment due to its invasive nature.

Gene-targeting therapies

Targeting the pathogenesis of HD upstream at the genetic level has many promising applications for Huntington's research. There are multiple genetic components to HD and thus many potential target areas for therapeutic intervention.

Viral delivery of neurotrophic factors has also demonstrated significant disease ameliorating results in various mouse models. A study by McBride et al. (2006) showed improvements in behavioral and motor deficits as well as a slower progression of disease. N171-82Q transgenic mice were injected with a recombinant adenoassociated viral vector (rAAV) carrying glial cell line-derived neurotrophic factor (GDNF), and were compared to a control viral injection carrying enhanced-green fluorescent protein (eGFP). GDNF seemed to preserve neuronal function and delay (or to some extent prevent) neuronal atrophy. The virally infected striata showed to have decreased levels of inclusion bodies through a mechanism which is presently still unclear.

RNA interference (RNAi) was employed to ameliorate neuropathology in HD mice by Machida et al. (2006). Small hairpin siRNA (shRNA) targeting htt were delivered via an rAAV viral vector into HD190QG transgenic mice that possess a truncated N-terminal htt containing 190 CAG repeats fused with eGFP. Introduction of the htt-shRNA caused a significant reduction in the amount of striatal nuclear aggregates. The animals themselves also demonstrated a delayed onset, less behavioral deficits, and neuronal sparing in the spinal cord. Another study conducted by Skogen et al. (2006) showed similar aggregate inhibition using short 20-mer guanine (G)-rich oligonucleotides. This group demonstrated an ability of the G-rich oligonucleotides to prevent the nuclear aggregation of mutant glutamine-expanded htt. These oligonucleotides appear to form stable structures with the htt monomeric forms and actively inhibit the creation of intraneuronal htt aggregates.

Biophysical therapies

Studies have suggested that the hyperactivity of the globus pallidus externus (GPe) correlates with cognitive and motor decline in HD. It has been hypothesized that GPe inhibition by means of deep brain stimulation could improve cognitive and motor deficits. Indeed the cognitive and behavioral dysfunction in a new rat transgenic model of HD was diminished after treatment with deep brain stimulation (DBS: Temel et al., 2006).

Therefore experimental globus pallidus-DBS may eventually provide a viable therapeutic for alleviation of the cognitive and motor defects present during HD progression.

Huntington's disease – beyond the brain

The primary mediator of Huntington's pathology is undoubtedly the mutated htt protein. However, htt is ubiquitously expressed throughout the whole body but yet there seem to be only limited accounts of cellular pathology, localized to very specific regions such as the CNS (for review, see Perez-Navarro et al., 2006). A clearer picture of the pattern of pathology may be created with our increasing appreciation of the precise molecular mechanism whereby HD pathology is generated. One explanation of the specificity of htt functional pathology could be due to the metabolic requirements of cells that harbor the mutant htt. Energetic dysfunction, specifically at the mitochondrial level, appears to be one of the hallmarks of neuronal pathology (Brennan et al., 1985; Browne et al., 1997). Attenuated mitochondrial function has been reported in both animal models and human subjects (Sanchez-Pernaute et al., 1999; Jenkins et al., 2005). This reduced energy creation capacity may in part be responsible for the observed progressive weight loss in humans (Trejo et al., 2004) and animals (Stack et al., 2005) suffering from HD. As we have discussed previously, therapeutics that will support mitochondrial energy generation (such as CoQ10) could have beneficial actions in HD, and thus further reinforce such a concept. A current hypothesis that may explain how there is localized pathology despite ubiquitous htt expression is linked to the metabolic demands and differentiation state of the tissue. Hence highly differentiated (terminally differentiated in the case of central neurons) tissues with a high energy demand seem to be specifically sensitive to HD pathology. For example skeletal muscle which like neurons is excitable and requires a high energy generation capacity can exhibit the same energy dysfunctions as striatal neurons in HD patients (Arenas et al., 1998; Lodi et al., 2000; Perez-Navarro et al., 2006). Along with skeletal muscle it seems that cardiac tissue as well is another critical htt pathology locus outside of the CNS. Interestingly, as with the general healthy population, advanced cardiovascular disease is one of the prime causes of mortality in Huntington's disease patients (Chiu and Alexander, 1982; Lanska et al., 1988; Sorensen and Fenger, 1992). Energy generation imbalances, causing oxidative damage and metabolic injury, are commonly observed in failing

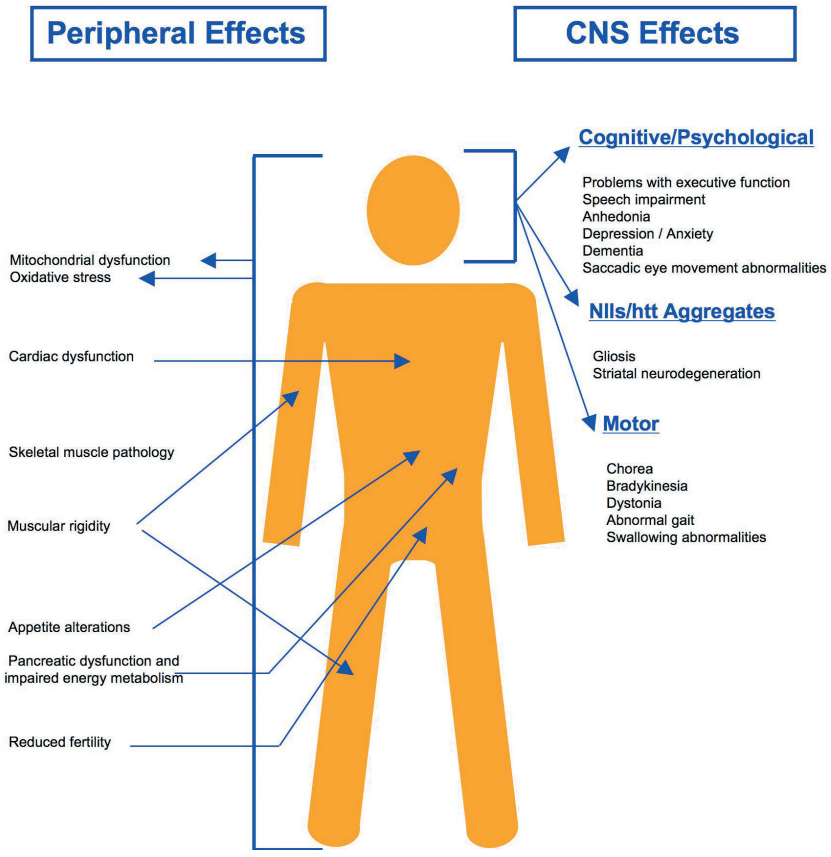

Fig. 1. Brief schematic overview of the some of the potential peripheral (mostly shown in murine HD models) and central nervous system (CNS) deficits in Huntington's disease. The CNS effects include cognitive and psychological problems, neuronal intranuclear inclusions (NIIs) and mutant huntingtin protein (htt) aggregates in the cortex and striatum, and motor dysfunction. The peripheral effecs include mitochondrial dysfunction and oxidative stress, muscular rigidity, alteration in appetite, pancreatic dysfunction and imparied energy metabolism.

cardiac myocytes (Katz, 1998; Vogt and Kubler, 1999). A recent study in R6/2 mice has comprehensively demonstrated that htt exerts a strong cardiotoxic action associated with alterations in mitochondrial ultrastructure, increased lysine acetylation and elevated general protein nitration (Mihm et al., 2007). Several other vital peripheral functions have also been seen to be especially vulnerable to htt-mediated pathology, such as the reproductive endocrine system and also the regulation of glycemic control. High levels of mutant htt have been documented in the ovaries and testes (Strong et al., 1993; Sathasivam et al., 1999) and in the pancreatic islet cells (Bjorkqvist et al., 2005). In the R6/2 mouse HD model a decrease in both ß-cell mass and also exocytic insulin release capacity was observed (Bjorkqvist et al., 2005). It has been estimated that approximately 10-25% of HD patients possess significantly impaired glucose homeostasis (Podolsky et al., 1972). HD patients can also present with significantly reduced testosterone and luteinizing hormone (LH) levels (Markianos et al., 2005). This appears to be due to htt-mediated degradation of hypothalamic gonadotrophin-releasing hormone neurons (the pulse generator for secretion of LH and Follicle Stimulating Hormone (FSH)) (Papalexi et al., 2005), although direct pathology of the testes themselves is also a strong possibility.

Conclusions

Since its discovery in 1872, Huntington's disease has primarily been considered and treated as a neurological disorder. However our understanding of neurodegenerative disorders has evolved to a point in which we no longer should isolate central neuronal health from whole somatic health. Hence the phrase *'mens sana in corpore sano'* stated by the Roman satirist Juvenal (A.D. 120) has never been more appropriate than today. The contribution of both cardiovascular and glycemic health seems critical to the maintenance of healthy functioning central nervous tissue (Martin et al., 2006). In the paradigm of HD, we have a predisposition to consider only the detrimental neural effects of aberrant htt processing while largely overlooking the fact that htt is ubiquitously expressed. Therefore are there other functional arms of the pathology induced by htt glutamine expansion that also form important therapeutic targets? (Fig. 1)

One such effect of the htt mutation that could be a tractable therapeutic target is the modulation of peripheral blood glucose control, as both HD patients (Podolsky et al., 1972; Farrer, 1985) and murine HD models (R6/2; Hurlbert et al., 1999) present a diabetic-like condition characterized by small pancreatic islet populations. Disruption of glucose uptake and the resultant diabetes have long been considered as strong risk factors for the development of neurodegenerative disorders (Martin et al., 2006). Therefore novel compounds that could attenuate both the htt-induced neuronal loss and also alleviate the metabolic stress, induced by disruption of euglycemia, may prove to be superior therapeutics for the treatment of HD, than therapeutics that merely treat the central nervous system.

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