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Review

Molecular mediators, environmental modulators and experience-dependent synaptic dysfunction in Huntington's disease★✪

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Huntington's disease (HD) is an autosomal dominant disorder in which there is progressive neurodegeneration producing motor, cognitive and psychiatric symptoms. HD is caused by a trinucleotide (CAG) repeat mutation, encoding an expanded polyglutamine tract in the huntingtin protein. At least eight other neurodegenerative diseases are caused by CAG/glutamine repeat expansions in different genes. Recent evidence suggests that environmental factors can modify the onset and progression of Huntington's disease and possibly other neurodegenerative disorders. This review outlines possible molecular and cellular mechanisms mediating the polyglutamine-induced toxic 'gain of function' and associated gene–environment interactions in HD. Key aspects of pathogenesis shared with other neurodegenerative diseases may include abnormal protein–protein interactions, selective disruption of gene expression and 'pathological plasticity' of synapses in specific brain regions. Recent discoveries regarding molecular mechanisms of pathogenesis are guiding the development of new therapeutic approaches. Knowledge of gene–environment inter-

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Abbreviations: BDNF, brain-derived neurotrophic factor, DARPP-32, dopamine and cAMP-regulated phosphoprotein (32 kDa); DRPLA, dentatorubralpallidolusian atrophy; HD, Huntington's disease; LTP, long-term potentiation; LTD, long-term depression; mGluR, metabotropic glutamate receptor; PSD-95, postsynaptic density protein 95; SBMA, spinobulbar muscular atrophy.

actions, for example, could lead to development of 'enviromimetics' which mimic the beneficial effects of specific environmental stimuli. The effects of environmental enrichment on brain and behaviour will also be discussed, together with the general implications for neuroscience research involving animal models.

Polymorphic repeating elements of DNA in the coding and non-coding regions of a wide variety of genes are known as dynamic mutations (Richards & Sutherland, 1992). Many dynamic mutations consist of trinucleotide repeats, and have been identified through the deleterious effects of their expansion, which cause a large number of inherited diseases. The majority of trinucleotide-repeat expansion diseases involve neurological deficits, including fragile X syndrome, myotonic dystrophy, and a group of neurodegenerative diseases associated with expanded polyglutamine tracts, the most common of which is HD.

Huntington's disease (HD) and at least eight other neurodegenerative diseases are each caused by expansion of a CAG repeat in a different gene, encoding an extended tract of glutamines in the respective protein. The other diseases known to be caused by a CAG/glutamine repeat expansion are dentatorubralpallidolusian atrophy (DRPLA), spinobulbar muscular atrophy (SBMA or Kennedy's disease), and spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7 and 17 (Fig. 1). It is not clear from the generally ubiquitous expression patterns of the disease genes how a common mutation involving expanded polyglutamine could lead to differential neurodegenerative patterns and disease symptoms.

The onset of HD generally occurs in the fourth or fifth decade of life, although approximately 5% of cases have juvenile onset, followed by progressive neurological deterioration for 10–20 years (Huntington's Disease Collaborative Research Group, 1993; Bates *et al.*, 2002). This fatal disease is characterised by degeneration of the cerebral cortex and striatum, producing a movement disorder, including the eponymous Huntington's chorea, together with cognitive and affective impairment. HD patients have greater than 35 CAG repeats in exon 1 of the *huntingtin* gene (although there is incomplete penetrance in the range of 36–39 repeats), with an inverse correlation between repeat length and age of onset of symptoms (Huntington's Disease Collaborative Research Group, 1993; Duyao *et al.*, 1993). Thus, patients with a juvenile-onset of HD have substantially longer CAG repeats (approx. 70–250 repeats) compared to patients with an adult-onset of the disease.

Genetic modulators which influence the age of onset of HD are thought to include variations in the glutamate receptor 6 (GluR6) subunit of the kainate receptor (Rubinsztein *et al.*, 1997; Macdonald *et al.*, 1999). The influence of GluR6 expression on onset of the disease supports one possible hypothesis, discussed below, that excitotoxicity could be a significant aspect of HD pathogenesis. The search for other genetic polymorphisms which may modify HD onset and progression is ongoing (Li *et al.*, 2003a).

OF MICE AND MEN: INSIGHTS INTO PATHOGENESIS FROM TRANSGENIC MODELS

The development of transgenic animal models has provided new insights into possible mechanisms of pathogenesis in HD as well as potential therapeutic avenues. Transgenic HD mice, in which the CAG repeat expansion in exon 1 of the *huntingtin* gene is expressed, provide one of the most accurate and powerful models of any neurological disease. The R6/1 and R6/2 lines of HD mice develop progressive behavioural symptoms and neurodegeneration, closely comparable to human HD (Mangiarini *et al.*, 1996; Murphy *et al.*, 2000; Van Dellen *et al.*, 2000a). Other transgenic models are also providing new insights into mechanisms of HD pathogenesis (Bates

et al., 2002). The absence of cell death in HD mice until late stages (Turmaine *et al.*, 2000) suggests that the early disease process, including onset of behavioural deficits, involves neuronal dysfunction rather than cell death. Similar themes are being revealed by transgenic mouse models of the other polyglutamine diseases (Burright *et al.*, 1995; Schilling *et al.*, 1999; Abel *et al.*, 2001; McManamny *et al.*, 2002; Garden *et al.*, 2002).

The normal huntingtin protein appears to play a role during embryogenesis as well as in regulation of gene expression and vesicle trafficking in mature cells (Zeitlin *et al.*, 1995; Zuccato *et al.*, 2001; 2003). Other accumulated evidence, such as the fact that mice with a CAG repeat expansion inserted into the coding region of HPRT, a 'housekeeping' enzyme not associated with any neurological disease, also develop a progressive neurodegenerative phenotype (Ordway *et al.*, 1997), suggests that expanded polyglutamine tracts have innate neurotoxicity. This has led to the hypothesis that the expanded polyglutamine confers a toxic 'gain of function' on the disease protein, which progressively and selectively disrupts the function of vulnerable populations of neurons.

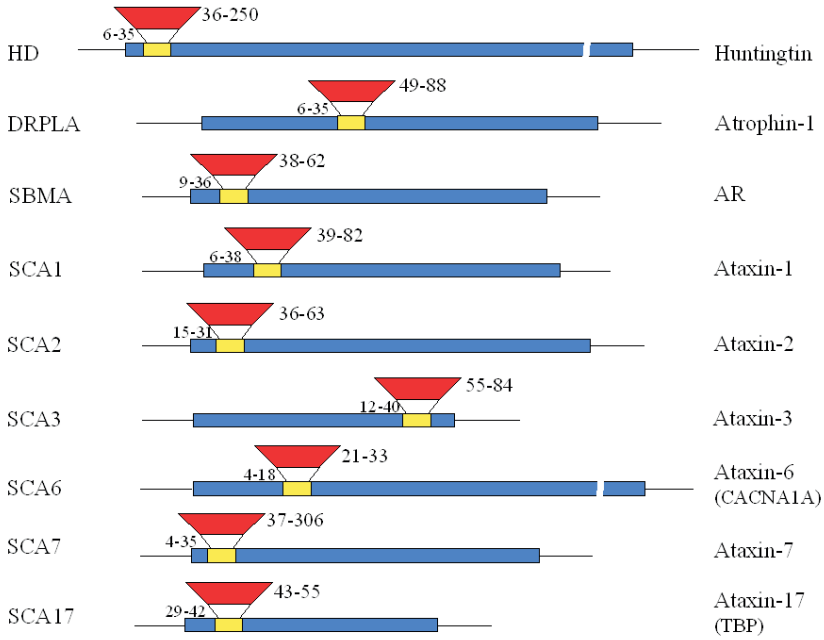

Figure 1. Huntington's disease (HD) is one of a group of neurodegenerative disorders, caused by trinucleotide (CAG) repeat expansions, encoding expanded polyglutamine tracts in different proteins.

In HD, the CAG repeat in exon 1 of the *huntingtin* gene is expanded to more than 35 repeats, resulting in an expanded polyglutamine tract in the huntingtin protein. Disease onset is inversely related to repeat length. The diseases are listed on the left and the coding regions (blue) of the disease genes are illustrated, with the CAG repeat shown in yellow. The range of CAG/glutamine repeat lengths found in each disease gene/protein is illustrated in red, above the normal range (with numbers referring to reported ranges of repeat numbers in the disease/normal populations). The names of the proteins encoded by the respective disease genes are listed on the right. Abbreviations: AR, androgen receptor; CACNA1A, voltage-dependent calcium channel α1A subunit; SCA, spinocerebellar ataxia; TBP, TATA-binding protein.

Although *huntingtin* is widely expressed in the embryo, adult nervous system and periphery, neurons of the cerebral cortex and medium spiny neurons in the striatum are preferentially damaged in HD (Bates *et al.*, 2002). Thus, spatiotemporal expression patterns of *huntingtin*, as well as the other CAG repeat disease genes, do not correspond to

the spatiotemporal vulnerability of specific neuronal populations in the diseases. Factors which influence cell specificity of neurodegeneration may include the protein context, differential proteolytic processing and intracellular localisation of the expanded polyglutamine, as well as subsequent specificity of abnormal protein–protein interactions. Selective vulnerability of neuronal populations could also be mediated by disrupted function of a subset of synapses, subsequent to aberrant gene expression and protein regulation.

PROTEIN AGGREGATION IN HD AND OTHER NEURODEGENERATIVE DISEASES

Aggregation of protein fragments containing expanded polyglutamine, together with a range of other proteins including transcription factors and proteasome components, occurs early in the disease process, prior to the onset of symptoms (Davies *et al.*, 1997; DiFiglia *et al.*, 1997; Chen *et al.*, 2002; Yang *et al.*, 2002; Bates, 2003), although it is not yet clear whether the insoluble aggregates are cytotoxic *per se*. Polyglutamine expansion within huntingtin and other disease proteins leads to the progressive formation of these abnormal intracellular protein aggregates, also known as neuronal inclusions (Davies *et al.*, 1997). It is possible that protein fragments containing expanded polyglutamine induce neuronal dysfunction through abnormal protein–protein interactions prior to their sequestration into large aggregates (Fig. 2). Some of the cytoplasmic and nuclear proteins which can bind to expanded polyglutamine in HD have been identified and include proteasome components and transcription factors (Sugars & Rubinsztein, 2003). The prevention of abnormal protein–protein interactions, including pathological aggregation, is nevertheless one promising avenue for the development of therapeutics.

DISRUPTED GENE EXPRESSION AND NEURONAL CELL DYSFUNCTION

It appears that cell death is a relatively late phenomenon in R6 lines of HD mice (Mangiarini *et al.*, 1996; Turmaine *et al.*, 2000; Spires, van Dellen & Hannan, unpublished observations) as well as other transgenic mouse models (Bates *et al.*, 2002), occurring long after onset of symptoms. While apoptosis has been observed at a late stage in the disease process in clinical HD and some mouse models (Butterworth *et al.*, 1998; Hickey & Chesselet, 2003), non-apoptotic dark cell degeneration has been described in R6 lines of HD mice (Turmaine *et al.*, 2000). Thus neuronal cell dysfunction seems to be more important than neuronal cell death. One implication of this is that therapeutic approaches will need to prevent or ameliorate neuronal dysfunction, rather than cell death alone.

Gene expression profiling data from transgenic models of HD and other polyglutamine diseases has revealed a number of interesting genes for further investigation. Amongst the mRNAs that were found to be decreased in the striatum of symptomatic R6/2 HD mice were mRNAs encoding proteins related to inter-neuronal (synaptic) and intra-neuronal signal transduction (including calcium and retinoid signaling pathways) and transcriptional regulation (Luthi-Carter *et al.*, 2000). There were also increased levels of mRNAs associated with cellular stress and inflammation. While transcriptional dysregulation appears to be a fundamental component of HD, analysis of different brain regions, stages of disease and transgenes reveal overlapping subsets of affected genes (Luthi-Carter *et al.*, 2000; 2002a; 2002b; Chan *et al.*, 2002; Sipione *et al.*, 2002), providing new insights into molecular mechanisms of polyglutamine-induced pathogenesis. Of interest is the accumulating direct and indirect evidence for a primary role of disrupted gene transcrip-

tion, consistent with other data implicating histone acetylation as a potentially important process, and therapeutic target, in HD (Steffan *et al.*, 2001; Hockly *et al.*, 2003).

the cortex and striatum, and decreased striatal dopamine and adenosine receptor binding (Cha *et al.*, 1998; 1999; Cha, 2000). In subsequent studies, the expression of many

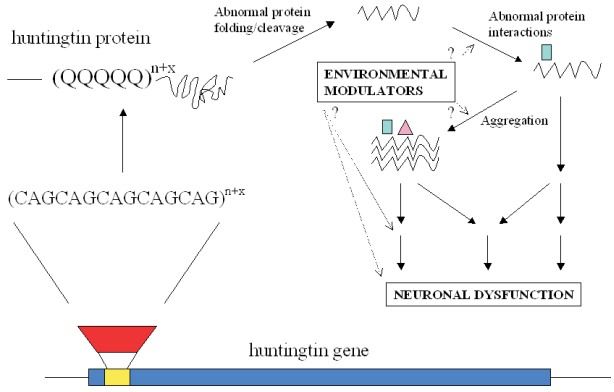

Figure 2. An outline of early steps by which the trinucleotide (CAG) repeat expansion, translated into an expanded polyglutamine tract in the huntingtin protein, leads to neuronal cell dysfunction and death in HD.

A more detailed outline of postulated molecular mechanisms is presented in Fig. 3. Possible points at which environmental factors may exert modulatory effects on the polyglutamine-induced pathogenesis are indicated with dotted arrows.

SYNAPTIC DYSFUNCTION AND PATHOLOGICAL PLASTICITY OF SYNAPSES IN HD

The disrupted neuronal gene expression observed in HD mice includes numerous neurotransmitter receptors and synaptic signal transduction pathways (Cha *et al.*, 1998; 1999; Cha, 2000; Luthi-Carter *et al.*, 2000; 2002a; 2002b; Bibb *et al.*, 2000; van Dellen *et al.*, 2000b; Chan *et al.*, 2002; Sugars & Rubinsztein, 2003). Decreases in expression of specific receptors occur before neuronal loss and precede the onset of clinical symptoms in HD. There is extensive evidence for downregulation of the cannabinoid CB_1 receptors in the basal ganglia of both HD patients and mouse models (Glass *et al.*, 1993; 2000; 2004; Denovan-Wright & Robertson, 2000; Lastres-Becker *et al.*, 2002). HD mice show decreases in both ionotropic and metabotropic glutamate receptor binding in molecules that mediate synaptic and intraneuronal signaling has been found to be altered in the striatum, cortex and other brain areas of HD mice (Luthi-Carter *et al.*, 2000; 2002a; 2002b; Bibb *et al.*, 2000; van Dellen *et al.*, 2000b), suggesting that both pre- and post-synaptic function could be disrupted. Thus there is increasing evidence for extensive inter- and intra-neuronal signaling deficits in HD.

There is also extensive data demonstrating altered synaptic densities and associated pathological changes in neuronal morphology in the brains of HD patients at post-mortem and various lines of transgenic HD mice (Graveland *et al.*, 1985; Ferrante *et al.*, 1991; Guidetti *et al.*, 2001; Klapstein *et al.*, 2001; Spires *et al.*, 2004a). Other approaches have provided more direct evidence for synaptic dysfunction in neuronal networks of the HD brain (Li *et al.*, 2003b). For example, medium spiny neurons from the striatum of R6/2 HD

mice were found to be more depolarised than those of wild-type striatum (Levine *et al.*, 1999). This change in the basic biophysical properties of the neuron may be linked to polyglutamine-induced changes in its selective neurotransmitters and signaling mechanisms. One contributing factor may be a decrease in pre-synaptic group II metabotropic glutamate receptors (mGluR2/3) (Cha *et al.*, 1998) at cortico-striatal synapses, which would reduce pre-synaptic 'damping' of neurotransmission, thus increasing glutamate release. This would lead to increased activation of post-synaptic NMDA receptors and increased calcium influx into striatal neurons, causing chronic excitotoxic neurodegeneration. NMDA also evoked increased caspase activity in HD transgenic mice, as well as potentiating excitotoxicity, possibly mediated through the NR2B-subtype NMDA receptor (Zeron *et al.*, 2002). Medium spiny neurons, the cell population in the striatum which is most affected in HD, receives extensive input from the cortex, supporting the notion that the cumulative effects of receptor changes and synaptic dysfunction could mediate chronic excitotoxicity. In keeping with this, the smaller number of cell populations in the striatum not receiving direct input from the cortex are spared in HD.

Deficits in long-term potentiation (LTP), a form of synaptic plasticity, have been described in hippocampal slices from R6/2 HD mice (Murphy *et al.*, 2000) as well as knock-in (Usdin *et al.*, 1999) and YAC transgenic HD mice (Hodgson *et al.*, 1999). HD mice display deficits in LTP, increased depotentiation, and an ability to undergo long-term depression (LTD) in response to microelectrode stimulation frequencies which do not induce LTD in wild-type slices (Murphy *et al.*, 2000). In addition to these findings in the hippocampus *in vitro*, there is recent evidence that disruption of neocortical plasticity *in vivo* occurs prior to the onset of motor deficits in HD mice (Mazarakis *et al.*, 2003). Dysfunction of cortical neurons could drive dysfunction of medium spiny neurons *via* cortico-striatal synapses (van Dellen *et al.*, 2001; Laforet *et al.*, 2001; Cepeda *et al.*, 2003). Synaptic plasticity is believed to be one of the key cellular mechanisms contributing to learning and memory. Thus the 'pathological plasticity' of synapses could explain some of the early symptoms that occur in HD, particularly cognitive deficits, and provide targets for the development of novel therapeutics.

Brain derived neurotrophic factor (BDNF) is a key protein manufactured in the cortex and transported down the cortico-striatal tract to the striatum. BDNF is known to regulate postsynaptic NMDA receptors, thus having a direct effect on synaptic signaling and postsynaptic influx of calcium ions (Suen *et al.*, 1997). The fact that BDNF was found to be reduced in the striatum but not in the cortex of humans with HD (Ferrer *et al.*, 2000) as well as R6/1 HD mice (Spires *et al.*, 2004b) could be explained by disruption of cortico-striatal protein trafficking, and may contribute to excitotoxicity at cortico-striatal synapses. Furthermore, wild-type huntingtin upregulates expression of BDNF and other specific neuronal genes (Zuccato *et al.*, 2001; 2003), suggesting that there may well be an element of loss of function as well as gain of function in HD.

These and other results are consistent with a role for synaptic dysfunction and subsequent excitotoxicity, involving abnormal calcium regulation, mitochondrial dysfunction and free-radical damage, in HD (Fig. 3).

GENE-ENVIRONMENT INTERACTIONS IN HD

Although HD is caused by a CAG repeat expansion in a single gene, and is inherited in an autosomal dominant manner, recent evidence from a transgenic mouse model supports a role for environmental factors in disease onset and progression. Environmental enrichment of transgenic R6/1 HD mice, in-

volving exposure to novel objects of different shapes, sizes, textures and composition, was found to delay onset of motor symptoms (van Dellen *et al.*, 2000a). Histological quantification in this study also demonstrated that environmental enrichment delays the degenerative loss of cerebral volume in HD mice. This finding has recently been explored more exhaustively in R6/1 HD mice and extended to the early-onset R6/2 HD mouse model, suggesting that environmental enrichment's beneficial effect is a robust phenomenon (Hockly *et al.*, 2002; van Dellen & Hannan, 2004).

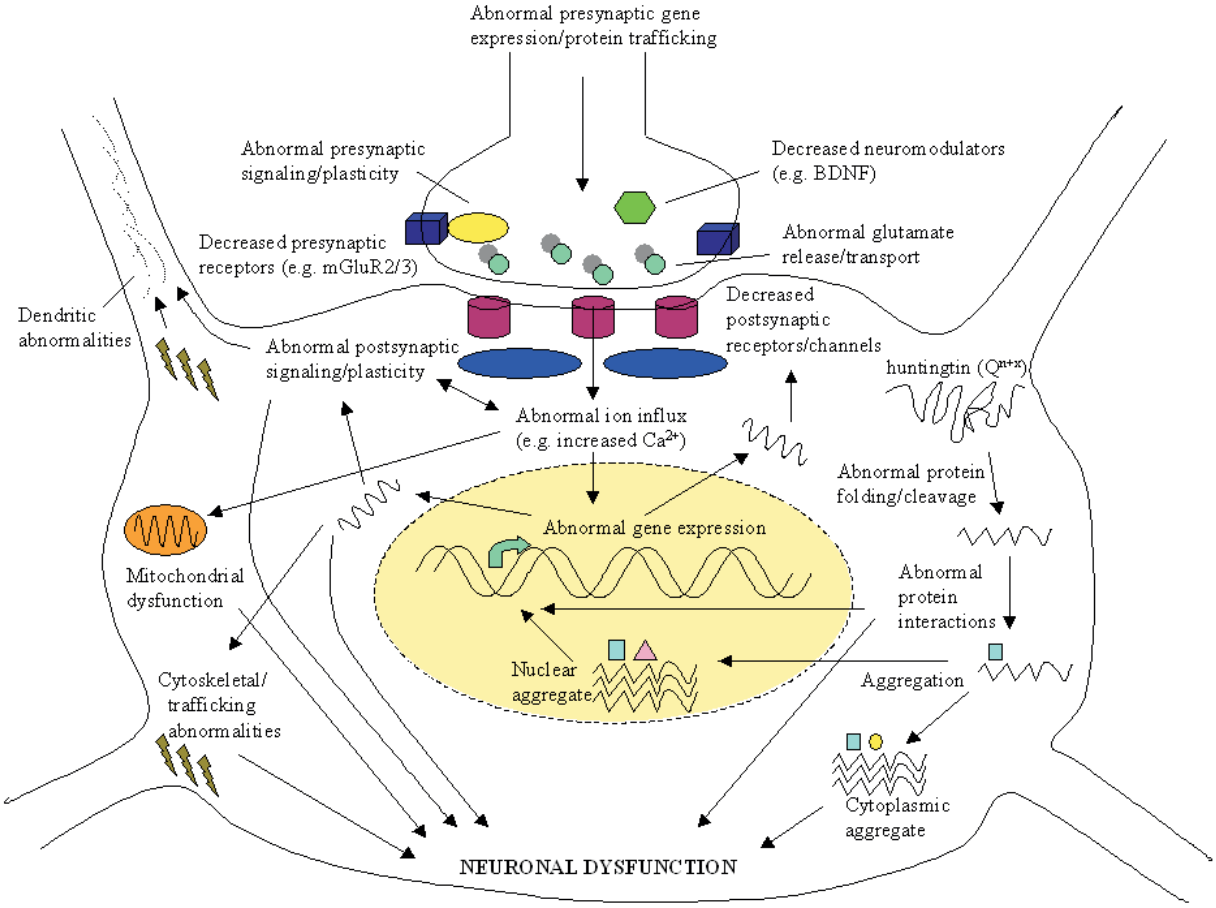

Figure 3. A model of polyglutamine-induced pathogenesis leading to neuronal dysfunction in HD.

Key processes that appear to be altered include protein–protein interactions, gene expression, synaptic function and plasticity. At the top of the figure is the pre-synaptic component of a synapse on to another neuron, whose cell body is illustrated in its entirety. To the right of the neuron's nucleus, the mutant huntingtin protein is shown undergoing abnormal folding/cleavage, protein interactions and aggregation. These abnormalities are then proposed to impact on gene expression in the nucleus *via* disruption of specific transcription factors. This transcriptional dysregulation is known to affect gene products required for post-synaptic neurotransmission, signaling and plasticity. In concert with the illustrated abnormalities of pre-synaptic function, the molecular changes leading to pathological plasticity of synapses would alter post-synaptic influx of ions (such as Ca^{2+}), causing chronic neuronal dysfunction *via* mitochondrial dysfunction, cytoskeletal/trafficking abnormalities, etc. Environmental enrichment could potentially alter one or more parallel pathways at different stages of pathogenesis. Abbreviations: BDNF, brain derived neurotrophic factor; mGluR2/3, metabotropic glutamate receptors 2/3; Q^{n+x}, a polyglutamine tract expansion in the huntington protein causing HD.

Over many decades, environmental enrichment of normal mice and rats has been shown to have beneficial effects on neuronal sur-

vival, intrinsic connectivity and functional organisation in diverse regions of the brain, but particularly the cortex. Rats reared in an enriched environment had significantly more dendritic branching in visual cortical neurons compared to non-enriched rats (Volkmar & Greenough, 1972). Enriched rats also showed increases in both excitatory post-synaptic potentials (EPSPs) and the magnitude of action potentials *in vivo* (Sharp *et al.*, 1985).

Another known cellular effect of environmental enrichment and wheel running, based on studies of wild-type rodents, is enhancement of adult neurogenesis (Kempermann *et al.*, 1997; 2004; Van Praag *et al.*, 1999; 2000). There is evidence of decreased hippocampal neurogenesis both in early-stage R6/1 HD mice (Lazic *et al.*, 2004) and enhanced neurogenesis close to regions of cell death in human HD brains at post-mortem (Curtis *et al.*, 2003). One hypothesis which we are currently exploring is that environmental enrichment ameliorates this failure of 'neuroregeneration' (Armstrong & Barker, 2001) in HD by enhancing adult neurogenesis and thus the capacity of the brain to repair itself (van Dellen & Hannan, 2004).

Mice exposed to an enriched environment also have altered expression in a subset of genes that are involved in transcription, neuronal signaling, neuronal growth and plasticity, and cell death regulation (Rampon *et al.*, 2000). Increased gene expression with relevance to synaptic function includes neurotropic factors (Pham *et al.*, 1999) and postsynaptic density protein 95 (PSD-95), which is important in NMDA receptor signaling, synaptic plasticity and memory formation (Migaud *et al.*, 1998). Environmental enrichment in rats increases the strength of specific hippocampal synapses, regulates the induction of LTP, and increases the binding of glutamate to the AMPA receptor (Foster *et al.*, 1996). These experimental examples suggest that enrichment affects activity-dependent neuronal gene expression as well as structural and functional organisation of neurons, particularly those within and connected to the cerebral cortex.

Environmental enrichment may delay the onset and progression of neurological signs in HD mice through various mechanisms. Enrichment provides increased opportunities for sensory stimulation, physical activity, learning and memory. Increased sensory input and/or motor activity may exert major effects within the cortex, as suggested by cerebral volume measurements (van Dellen *et al.*, 2000a). With regard to neuroprotection, it has been shown that environmental enrichment can protect against kainate-induced seizures and excitotoxic injury to the rat hippocampus (Young *et al.*, 1999). The beneficial effects of environmental enrichment with respect to synaptic connectivity are of particular interest, given the increasing evidence from HD mouse models, for the role of synaptic dysfunction in HD pathogenesis. There is recent evidence that environmental enrichment may selectively ameliorate, at transcriptional and post-transcriptional levels, deficits of expression of specific genes, including those encoding BDNF, DARPP-32 and the CB_1 cannabinoid receptor (Spires *et al.*, 2004b; Glass *et al.*, 2004; van Dellen & Hannan, 2004). Environmental enrichment may therefore overcome deficiencies of synaptic function and plasticity, particularly at intracortical and cortico-striatal synapses, and ameliorate the deficits in HD mice.

Dietary manipulations, namely dietary restriction and dietary supplementation with essential fatty acids from conception onwards, have recently been found to both slow disease progression and increase survival in HD transgenic mice (Clifford *et al.*, 2002; Duan *et al.*, 2003). Furthermore, administration of highly unsaturated fatty acids and the ethyl-ester of eicosapentaenoic acid (ethyl-EPA) reduced motor symptomatology in HD patients (Puri *et al.*, 2002; Vaddadi *et al.*, 2002). However, the underlying mechanisms whereby dietary factors may modulate HD pathogenesis as yet remain unknown. The

possibility that environmental factors may affect HD in humans is supported by two studies showing that monozygotic twins with identical CAG-repeat lengths can display different ages of onset, clinical symptoms and behavioral abilities (Georgiou *et al.*, 1999; Anca *et al.*, 2004). A recent analysis of Venezuelan HD kindreds also strongly implicates environmental factors as modulators of HD pathogenesis (Wexler *et al.*, 2004). One extrapolation of this work is that strategies of occupational therapy based on the principles of environmental enrichment might delay the onset and progression of disease in HD sufferers, whose deterioration is currently untreatable. A better understanding of how environmental enrichment induces its beneficial effects may also provide direction for the development of other therapeutic approaches.

One additional implication of these results is that drugs or other therapeutic approaches which have promising effects in standard-housed animal models should be repeated under conditions of environmental enrichment, which may more closely model normal levels of human sensorimotor stimulation, to assess whether the drug effects are robust. This could provide an important additional drug screening step prior to clinical trials to ensure that the strongest candidates are trialled first in the limited population of HD patients.

USING MOLECULAR MECHANISMS OF PATHOGENESIS AND GENE-ENVIRONMENT INTERACTIONS TO IDENTIFY THERAPEUTIC TARGETS

Understanding molecular mechanisms is a key step in the development of new therapeutics for HD (Bates & Hockly, 2003; Hersh, 2003; Hannan, 2004). Molecular targets currently under consideration or in trial as therapeutics include polyglutamine-induced protein interactions and aggregation, transcriptional regulators such histone deacetylases, various neurotransmitter receptors, trophic factors, oxidative stress pathways and mitochondrial molecules. In addition to compounds which may target key molecules involved in pathogenesis, the therapeutic potential of other approaches such as gene therapy, RNAi, intrabodies and cell therapy will no doubt be further explored in future.

A better understanding of gene-environment interactions mediating the beneficial effects environmental enrichment on HD mice may provide a direction for the development of therapeutic approaches. One speculation based on our findings are that drugs which could mimic the beneficial molecular and cellular effects of environmental stimuli may have therapeutic potential in HD and other brain diseases. We are currently searching for appropriate molecular targets which may facilitate the development of such 'enviromimetics'.

GENES, ENVIRONMENTS AND BRAIN DISEASES

New insights into HD pathogenesis and associated gene-environment interactions will have implications not only for treatment of HD, but for the many related neurological diseases. Abnormal protein–protein interactions link the polyglutamine diseases with pathological aggregation of different proteins in other major neurodegenerative diseases, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS or motor neuron disease) and prion diseases. Other common themes at later stages of pathogenesis may involve synaptic dysfunction and subsequent excitotoxicity. Identifying unifying mechanisms in neurodegeneration may be important as it could lead to the development of neuroprotective therapeutics suitable for use across a range of brain diseases. One hypothesis to explain why the CNS is so susceptible to toxicity associated with abnormal protein–protein interactions is that neurons are

the most structurally and functionally complex of cells and are therefore most vulnerable to disruption of metabolic homeostasis. For example, a single cortical pyramidal neuron can receive over 10 000 synaptic inputs from other neurons, which may make them exquisitely sensitive to synaptic dysfunction and subsequent excitotoxicity, as discussed above. Identifying unifying mechanisms in neurodegeneration would be important as it could lead to the development of neuroprotective therapeutics suitable for use across a range of brain diseases.

Parallel analysis of gene–environment interactions in the diseased and normal states has the potential to provide new information on pathogenesis as well as mechanisms of plasticity in the healthy cortex, which may underlie learning, memory and other experience-dependent aspects of brain function. Furthermore the dramatic effects of environmental enrichment on brain and behaviour observed in rodent models has implications for all neuroscientists working with animal models. If the aim is to model the function and dysfunction of the human brain, which in each individual's lifetime is differentially exposed to a breathtaking array of sensory, motor and cognitive stimuli, then animal researchers need to begin to model these environmental parameters, along with the more commonly investigated genetic and pharmacological parameters.

FUTURE DIRECTIONS

Since the discovery of the repeat expansion causing HD a decade ago there has been enormous progress in piecing together molecular and cellular mechanisms mediating the disease process. While we have a long way to go in linking molecular, cellular and behavioural deficits in HD, this information is gradually being used to identify intra- and inter-neuronal processes that provide therapeutic targets. Even though some interventions have demonstrated promising preclinical results, there is as yet no effective treatment or cure for HD. The availability of a genetic test means that future therapies may be targeted at presymptomatic individuals, to delay or prevent disease onset, as well as patients at early and late stages of HD. The number and complexity of disrupted molecular pathways appear to increase as the disease progresses, and one implication of this is that different therapeutic approaches may have optimal efficacy at presymptomatic, early and late stages of the disease. Another implication of this apparent complexity of pathogenic mechanisms is that combinations of drugs ('polypharmacy') may have additive or even synergistic therapeutic effects at specific disease stages. Candidate therapeutics will need to be thoroughly assessed and prioritized preclinically using optimal genetic, pharmacological and environmental parameters to ensure that a successful therapy for this devastating disease is achieved as quickly as possible.

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