Differential vulnerability of neurons in Huntington's disease: The role of cell type-specific features

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Abstract

Abnormal expansion of a polyglutamine tract in huntingtin (Htt) protein results in Huntington's disease (HD), an autosomal dominant neurodegenerative disorder involving progressive loss of motor and cognitive function. Contrasting with the ubiquitous tissue expression of polyglutamine-expanded Htt (polyQ-Htt), HD pathology is characterized by the increased vulnerability of specific neuronal populations within the striatum and the cerebral cortex. Morphological, biochemical, and functional characteristics of neurons affected in HD that might render these cells more vulnerable to the toxic effects of polyQ-Htt are covered in this review. The differential vulnerability of neurons observed in HD is discussed in the context of various major pathogenic mechanisms proposed to date, and in line with evidence showing a "dying-back" pattern of degeneration in affected neuronal populations.

Introduction

Polyglutamine (polyQ) expansion diseases including Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA) and spinocerebellear ataxias are heritable neurological diseases characterized by abnormal expansion of CAG repeats in the coding region of structurally unrelated genes (Orr & Zoghbi 2007). Among these, HD represents the most commonly inherited neurological disorder, involving progressive loss of motor and cognitive function that mainly results from degeneration of selected neuronal populations within the basal ganglia and the cerebral cortex (reviewed in (Walker 2007). In recent years, much progress has been made regarding the etiology of HD, and a growing body of evidence suggests the involvement of multiple pathogenic pathways in this disease. However, little is known about mechanisms underlying the increased vulnerability of selected neuronal populations in HD. Here, we provide a detailed summary of the unique pathological topography of HD, and discuss the contribution of cell type-specific characteristics to this topography in the context of various pathogenic mechanisms proposed for HD. These mechanisms are discussed keeping in mind the "dying-back" pattern of degeneration of neurons affected.

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HD etiology

HD is inherited in an autosomal-dominant manner and typically presents in adulthood although juvenile forms of HD exist. Molecular mechanisms underlying HD remain elusive, and thus no effective therapeutic treatments are currently available beyond clinical symptomatic management of the movement disorder portion of this disease. HD patients typically die within 17 years of diagnosis from various complications such as accidents, aspiration and dysphagia (Walker 2007).

HD results from expansion of a polymorphic polyQ tract located near the N-terminus of the huntingtin (Htt) protein (HDCRG 1993). The polyQ tract in wild-type, non-pathogenic Htt (WT-Htt) ranges from 6 to 35 glutamines, but Htt variants with 36 or more Qs define a HD allele encoding pathogenic Htt (polyQ-Htt) (Brinkman *et al.* 1997, Snell *et al.* 1993). As in other polyQ diseases, the number of glutamine repeats in Htt correlates inversely with the age of HD onset (Andrew *et al.* 1993, Duyao *et al.* 1993). The temporal pattern of neuropathological features also relates to the number of glutamines in Htt, with the most damage seen in the brains of age-matched HD patients bearing longer polyQ tracts (Penney *et al.* 1997). However, HD is universally fatal and the ultimate pathological outcome is similar for all patients showing pathogenic expansions of the polyQ tract.

The widespread distribution of Htt (see below) and the lack of sequence homology with other proteins did not reveal significant information on the normal physiological function of this protein. Deletion of Htt in mice results in embryonic lethality, suggesting a critical, yet unidentified role of Htt during normal development (Nasir *et al.* 1995, MacDonald *et al.* 1996). Initial transgenic HD mouse models were illuminating in several respects (Beal & Ferrante 2004). These mice express randomly inserted Htt truncation constructs bearing unusually long polyQ stretches (>115 CAG repeats) that often result in severe early-onset neuropathology and behavioral syndromes (reviewed in (Ramaswamy *et al.* 2007b). In contrast, various knock-in mouse models expressing pathogenic, polyQ-expanded versions of full-length Htt at endogenous levels are viable, displaying a late onset phenotype with pathological features reminiscent of HD (Menalled 2005). Viability of these knock-in mice indicated that aspects of Htt functionality relevant to embryonic development are not compromised by polyQ tract expansion. The precise contribution that decreased Htt function plays in HD pathogenesis remains unclear, but the autosomal dominant pattern of HD inheritance and other genetic evidence strongly indicates that polyQ expansion confers a toxic gain of function upon Htt (Orr & Zoghbi 2007, Morfini *et al.* 2005). Consistent with this idea, several lines of experimental evidence showed that polyQ-Htt expression alters multiple, critical cellular processes including transcriptional regulation, cell survival, intracellular signaling, mitochondrial function and axonal transport, among others. However, the nature of molecular mechanisms underlying toxic gain of function(s) associated with polyQ-Htt continue to be debated (Morfini *et al.* 2005).

HD brain pathology

Motor impersistence (a term referring to the inability to maintain voluntary muscle contractions), represents a major clinical feature of HD that correlates well with disease progression (Reilmann *et al.* 2001). Involuntary, arrhythmic limb movements termed "chorea" represent a common clinical motor phenotype in most, but not all, HD patients (Barbeau *et al.* 1981), especially early in the disease. These movements were signature features in the original description of the disease as Huntington's chorea (Okun 2003). In addition to the relentless decline in motor function, non-motor disturbances such as cognitive impairments, personality changes, depression, and behavioral disturbances are commonly seen in HD patients and represent the more serious symptoms for their family,

friends and caregivers (Walker 2007). These anomalies are believed to represent the phenotypic manifestation of neuronal dysfunction and degeneration in selected areas of the basal ganglia and the cerebral cortex (Reiner *et al.* 1988, Storey & Beal 1993).

The basal ganglia comprise a set of subcortical brain structures involved in various aspects of motor control and cognition (Graybiel 1990, Mitchell *et al.* 1999) (Fig. 1). Within the basal ganglia, the neurodegenerative process characteristic of HD typically begins in the striatum (Vonsattel *et al.* 1985a), which serves the function of "filtering" multiple input pathways originating in different cortical regions (Mitchell *et al.* 1999). Information processed in the striatum ultimately returns to the cerebral cortex to complete the corticobasal ganglia-thalamocortical loop (Parent & Hazrati 1995) (Fig. 1). Within the striatum, signs of pathology initially appear in the caudate nucleus and putamen, with reactive gliosis and neurons showing neuritic dystrophy. As the disease progresses, these pathologies progressively extend along the caudal-rostral, and dorsal-ventral direction towards the putamen (Vonsattel & DiFiglia 1998). The prominent expansion of the lateral ventricles typical of advanced HD patients results from the dramatic degeneration of neurons within the adjacent caudate nucleus. A significant loss of neurons is also observed in the cerebral cortex of HD patients, including frontal, parietal, and temporal regions (Mann *et al.* 1993, Heinsen *et al.* 1994), although these changes are initially less obvious than those seen in the striatum.

Neuronal cell types affected in HD

At the cellular level, HD is characterized by differential vulnerability of specific neuronal subpopulations within the striatum and cerebral cortex (Fig. 1). The striatum, comprised of the caudate nucleus and putamen, represents the major "input" stage of the basal ganglia, being mainly composed of projection neurons (up to 95% of total striatal neurons) and a much smaller number of interneurons (approx. 5%). Golgi staining methods and electron microscopic studies identified and classified various subtypes of projection neurons and interneurons in the striatum with unique morphological and biochemical characteristics (DiFiglia *et al.* 1976, Difiglia *et al.* 1980, Parent *et al.* 1984). Striatal projection neurons (also known as Golgi type I cells) are all GABAergic and morphologically characterized by a long axon, medium-sized cell bodies, and spiny dendrites, hence the commonly used term of medium spiny neurons (MSNs) (Gerfen 1988, DiFiglia *et al.* 1976, Difiglia *et al.* 1980). MSNs project their axons over relatively long distances to targets in the globus pallidus (GP) and the substantia nigra pars reticulata (SNr), main "output" structures of the basal ganglia (Fig. 1). Striatal interneurons (also known as Golgi type II cells) represent key elements of the local striatal circuitry, displaying a wide range of morphological and biochemical heterogeneity (Parent *et al.* 1984, Parent *et al.* 1980). Striatal interneurons have unusually short axons, medium to very large-sized cell bodies, and display extensive dendritic arborization, making abundant synaptic contacts with multiple MSNs (Kawaguchi 1997, Kawaguchi *et al.* 1995). Intriguingly, MSNs represent the main and earliest striatal cell type affected in HD, whereas striatal interneurons are typically unaffected or only mildly affected at late stages of the disease.

The differential vulnerability of MSNs within the HD striatum extends to specific MSNs subtypes, as defined by their projection targets and neurochemical content (Mitchell *et al.* 1999) (Figs. 1-2). Based on their projection targets, MSNs in the striatum can be divided into two main groups: *a)* MSNs in the "direct" (or striatonigral) pathway, which project axons monosynaptically to the internal segment of the GP (GPi) or to the SNr (Smith *et al.* 1998), These neurons preferentially express the peptide enkephalin (ENK, a pentapeptide derived from the preproenkephalin gene). *b)* MSNs in the "indirect" (or striatopallidal) pathway, which project axons that polysynaptically contact the external segment of the GP

(GPe). These neurons preferentially express substance P (SP). Intriguingly, MSNs in the "indirect pathway" are affected at earlier stages and to a greater extent than MSNs in the "direct pathway" (Reiner *et al.* 1988, Albin *et al.* 1992a, Richfield *et al.* 1995b). Early functional abnormalities in the indirect pathway have been associated with development of the chorea-like movements in HD (Crossman *et al.* 1988, Crossman 1987). Degeneration of MSNs of the direct pathway late in the course of HD manifests as rigidity and bradykinesia (Berardelli *et al.* 1999).

Albeit less pronounced than in the striatum, differential vulnerability and loss of selected neuronal populations is also readily observed in the cerebral cortex of HD patients. Specifically, large pyramidal projection neurons in cortical layers V, VI and to a lesser extent, layer III, are preferentially lost (Cudkowicz & Kowall 1990, Hedreen *et al.* 1991). Long axons emanating from cortical projection neurons in layers V and VI innervate the striatum. In primates, these axons are thin and unbranched with a single target (Parent & Parent 2006). As in the striatum, there is remarkable preservation of small cortical interneurons (i.e., layer IV granule cells) in HD (Cudkowicz & Kowall 1990, Sotrel *et al.* 1991).

Vulnerability of different neuronal cell populations to Htt mutations: *Selective* or *differential*?

The earlier and more pronounced degeneration of specific neuronal populations within the striatum and cortex observed in HD prompted the phrase "*selective neuronal vulnerability*" to be used by a number of investigators (Sieradzan & Mann 2001, Perez-Navarro *et al.* 2006, Cowan & Raymond 2006). However, the unique cellular topography of HD pathology does not mean that the toxic effects of polyQ-Htt are *limited* to selected neuronal populations. Supporting this idea, a large body of pathological and experimental evidence demonstrates that polyQ-Htt expression can elicit toxic effects in additional neuronal cell types and even in some nonneuronal cells. Pathological examination in advanced HD patients revealed degeneration of neurons in other brain structures including the hippocampus, the angular gyrus in the parietal lobe, and the lateral tuberal nuclei of the hypothalamus (Lange *et al.* 1976, Vonsattel *et al.* 1985b, Oyanagi *et al.* 1989, Heinsen *et al.* 1999). Further, pronounced neuronal loss has been observed in the cerebellum of patients with juvenile HD onset (Byers *et al.* 1973, Rodda 1981). Although some of these neuronal losses may reflect secondary neuronal damage due to deafferentation, experiments involving tissue-specific overexpression of polyQ-Htt *in vivo* demonstrated that polyQ-Htt expression promotes functional abnormalities in many neurons not typically affected in HD (Senut *et al.* 2000, de Almeida *et al.* 2002). Additionally, nonneuronal cells appear affected in various peripheral tissues of HD patients and animal HD models (reviewed in (Sassone *et al.* 2009)). Finally, a plethora of studies documented functional abnormalities and decreased cell survival associated with the expression of pathogenic polyQ-Htt constructs across a range of cultured cell types including mouse (Ye *et al.* 2008, Lunkes & Mandel 1998) and human (Carmichael *et al.* 2002) neuroblastoma cells, PC12 cells (Li *et al.* 1999b), and kidney cells (COS-7) (Carmichael *et al.* 2002), among many others. Taken together, these observations indicate that the toxic effects of polyQ-Htt do not *selectively* affect specific neuronal populations. Instead, cell type-specific features might *differentially* render specific neuronal populations increasingly vulnerable to polyQ-Htt-induced toxicity.

Neurons affected in HD follow a "dying-back" pattern of degeneration

A discussion of cellular features modulating polyQ-Htt toxicity requires a revision of the sequence of pathogenic events in affected neurons. Historically, our understanding of the neurodegenerative process in HD was limited to the *post mortem* study of brain tissue

harvested from HD patients. The marked loss of neurons observed in these tissues logically focused research efforts into cell death-related mechanisms (Vila & Przedborski 2003, Portera-Cailliau *et al.* 1995), and the development of HD animal models based on acute intoxication and induction of cell death in the striatum. More recently, the development of various rodent HD models revealed important information on earlier pathogenic events (Menalled 2005). These animal models accurately reproduce the autosomal dominant pattern of inheritance as well as the major pathological characteristics of HD, including formation of Htt aggregates (see below), the development of motor and behavioral symptoms, and the differential vulnerability of discrete neuronal populations [reviewed in (Ramaswamy *et al.* 2007b)]. Variations in disease onset and severity among HD models can be attributed to differences in length of the polyQ tract, promoters driving transgene expression, and size of the exogenous Htt transgene introduced (Ramaswamy *et al.* 2007b, Vonsattel 2008, Menalled 2005). However, a common theme emerged from detailed pathological, electrophysiological and behavioral analysis of these animals. All models analyzed thus far have shown various degrees of behavioral and motor abnormalities well before apparent neuronal degeneration (Levine *et al.* 2004, Tobin & Signer 2000, Menalled 2005). For example, behavioral defects reminiscent of the HD human phenotype (i.e., increased motor activity, gait abnormalities, and altered stride length) were observed in HD transgenic mice models expressing truncated polyQ-Htt constructs, including R6/2 mice (Lione *et al.* 1999, Luesse *et al.* 2001, Murphy *et al.* 2000), N171-82Q mice (Klivenyi *et al.* 2006), and a transgenic rat model expressing a truncated Htt with 51 CAG repeats (von Horsten *et al.* 2003). Moreover, similar defects have been reported in various knock-in HD animal models expressing polyQ-Htt at endogenous levels in its appropriate genomic context (Menalled 2005). Remarkably, behavioral abnormalities in knock-in HD animal models were detected in the absence of neuronal loss (Menalled 2005) and prior to formation of polyQ-Htt aggregates, suggesting that aggregate formation may not be required for functional changes to occur in affected neurons. The relevance of these observations to HD is highlighted by functional MRI imaging studies revealing early changes in neuronal function in presymptomatic HD patients (Reading *et al.* 2004), and studies suggesting that the early manifestation of chorea does not result from neuronal cell loss (Rosenblatt *et al.* 2003).

Providing a structural basis for these early alterations in neuronal function, histopathological studies documented a marked reduction in the number of axonal fibers and synaptic proteins early in the course of HD (DiProspero *et al.* 2004b, Reiner *et al.* 1988, Levine *et al.* 2004, Li *et al.* 2001). These alterations in axonal connectivity and synaptic function were consistent with the progressive electrophysiological disturbances reported in association with polyQ-Htt expression (Klapstein *et al.* 2001, Bibb *et al.* 2000, Cepeda *et al.* 2001, Laforet *et al.* 2001). Diffusion tensor imaging studies further demonstrated early signs of axonal degeneration in white matter of living, presymptomatic HD patients (Weaver *et al.* 2009, Rosas *et al.* 2009). Together, these observations suggested the existence of critical pathogenic events affecting neuronal functionality *prior* to cell death in HD. The accumulated evidence indicates that alterations in neuronal connectivity play a major role in HD pathology, and that neurons affected in HD follow a "dying back" pattern of degeneration (Fig. 3) (Li *et al.* 2001, Ferrante *et al.* 1991, Morfini *et al.* 2005, Wade *et al.* 2008). This emerging concept has far reaching implications regarding experimental therapeutic strategies. For instance, trophic factor therapies, which have been proposed for clinical testing (Ramaswamy *et al.* 2007a), have primarily focused on preserving striatal perikarya. However, few of these studies (Emerich *et al.* 1997) have employed tools to demonstrate that basal ganglia circuitry, including the essential aspect of sustained innervation and appropriate connectivity, was maintained following trophic factor delivery.

Cellular factors influencing mutant huntingtin-induced toxicity

Projection neurons in the striatum and the cerebral cortex are major regions of the HD pathology, whereas interneurons within these structures largely survive the neurodegenerative process (Albin *et al.* 1992b, Reiner *et al.* 1988, Richfield *et al.* 1995a). In addition, MSNs in the direct pathway are affected earlier and to a larger extent than MSNs in the indirect pathway. Differences in biochemical content, morphology and connectivity among these neuronal cell types could provide clues towards an explanation of their differential vulnerabilities in HD. In the case of striatal neurons, one or more unique characteristics of MSNs could exacerbate the toxic effects of polyQ-Htt in these cells, rendering an otherwise "manageable" insult into a deadly one. Alternately, a unique set of protective characteristics might confer upon striatal interneurons an advantage to deal with the toxic effects of polyQ-Htt. Similar speculations can apply to projection neurons and interneurons in the cortex, but mechanisms underlying the differential vulnerability of cortical neurons are rarely addressed (Cepeda *et al.* 2007, Levine *et al.* 2004).

Because a molecular basis for the toxic gain of function associated with polyQ-Htt has been unclear, the contribution of cell type-specific traits in the modulation of polyQ-Htt-induced toxicity can only be speculative. Below, we discuss the potential contributions of various cell type-specific factors to the differential vulnerability of neurons characteristic of HD (Table I). These factors are discussed within the context of several major pathogenic mechanisms proposed for HD.

Htt distribution, expression levels, and somatic instability

In some familial forms of human diseases, the increased vulnerability of cell types affected can be explained by differential expression of the pathogenic gene product. Following the discovery of the Htt gene, multiple studies examined whether heterogeneities in Htt mRNA and/or protein expression could underlie the increased vulnerability of MSNs and cortical neurons in HD. However, extensive mRNA and protein expression analyses indicated that Htt is expressed in nearly all tissues (Trottier *et al.* 1995, Li *et al.* 1993, Fusco *et al.* 1999). Moreover, Htt expression levels were comparable in normal and HD patients (Bhide *et al.* 1996, Landwehrmeyer *et al.* 1995a). Immunochemical studies showed widespread distribution of Htt protein throughout the brain (DiFiglia *et al.* 1995), with no evidence of increased Htt expression in brain regions most affected in HD (Gutekunst *et al.* 1995, Ide *et al.* 1995). In fact, detailed studies showed that striatal interneurons, largely unaffected in HD, express higher levels of Htt than MSNs (Bhide *et al.* 1996), suggesting that differences in mutant Htt expression levels do not account for the increased vulnerability of MSNs.

Recent studies in HD patients and animal HD models showed that the mutant CAG repeat tract in the *IT15* gene coding for Htt can undergo both inter- and intra-generational variability in expansion size (Shelbourne *et al.* 2007, Ishiguro *et al.* 2001). Studies on end-stage human HD autopsy material indicated that approximately 10% of sampled striatal cells contained hyperexpansions of over 200 repeats (Kennedy *et al.* 2003). Further, age-dependent instability of Htt was observed in the striatum and the cerebral cortex of knock-in HD mice (Ishiguro *et al.* 2001, Kennedy & Shelbourne 2000). These findings led to the proposal that increased instability of Htt's CAG expansion might contribute to the marked vulnerability of striatal neurons in HD (Shelbourne *et al.* 2007). However, greater instability of CAG repeats in the striatum was also observed in other polyQ-expansion diseases displaying little or no striatal pathology (Lopes-Cendes *et al.* 1996, Watase *et al.* 2003). Moreover, observations from a bacterial artificial chromosome-based HD mouse model expressing polyQ-Htt with a stable CAA-CAG tract appeared inconsistent with a role of somatic repeat instability in HD pathogenesis (Gray *et al.* 2008). These observations argued

against a direct causal relationship between somatic CAG expansion mosaicism and the increased vulnerability of striatal MSNs. Collectively, the evidence indicates that neither heterogeneities in Htt expression levels nor somatic instability of the Htt gene play a role in the differential vulnerability of striatal neurons affected in HD.

Mutant Htt aggregation

Following the discovery of the Htt gene, various antibodies mapping to different Htt epitopes were generated (Li & Li 1998). These antibodies revealed N-terminal fragments of polyQ-Htt that accumulate to form microscopically visible aggregates (or inclusions) in both the nucleus (DiFiglia *et al.* 1997b) and neurites (Li *et al.* 1999a) of some, but not all, neurons affected in HD patients (Kuemmerle *et al.* 1999, DiFiglia *et al.* 1997a). These aggregates are also found in most HD rodent models (Li & Li 2004, Perez-Navarro et al. 2006), and thus represent a major histopathological feature of HD.

Initial focus on polyQ-Htt aggregates as a pathogenic agent of HD was fueled by biochemical findings suggesting that elongated polyQ stretches form insoluble structures toxic to cells (Perutz 1996, Rubinsztein & Carmichael 2003). Cellular HD models based on overexpression of truncated polyQ-Htt constructs first proposed a positive correlation between the abundance of polyQ-Htt aggregates and cellular toxicity (Cooper *et al.* 1998, Hackam *et al.* 1998). However, Htt toxicity and aggregation were experimentally dissociated in both cellular (Arrasate *et al.* 2004) and animal (Perrin *et al.* 2009) HD models. At present, it remains unclear whether polyQ-Htt aggregates promote neuronal dysfunction and death, or whether polyQ-Htt aggregation represent the outcome of endogenous cellular mechanisms conferring protection against soluble, toxic polyQ-Htt species (Truant *et al.* 2008, Wang *et al.* 2008).

Despite the large body of research on polyQ-Htt aggregates, little evidence exists linking these structures to the preferential degeneration of MSNs and cortical neurons in HD. As observed in SBMA (La Spada & Taylor 2003), and other polyQ diseases (Michalik & Van 2003), a poor correlation was found between polyQ-Htt aggregation and neuronal vulnerability (Saudou *et al.* 1998). Moreover, the presence of polyQ-Htt aggregates in surviving neurons of advanced HD patients suggested these structures might even promote neuronal survival (Truant *et al.* 2008). Experiments in cellular (Arrasate *et al.* 2004) and animal (Perrin *et al.* 2009) HD models further supported this view. Finally, prominent polyQ-Htt aggregates have been reported in striatal interneurons (Kuemmerle *et al.* 1999), and in brain regions largely spared in HD such as the hippocampus (Becher *et al.* 1998, Gutekunst *et al.* 1999). The precise contribution of polyQ-Htt aggregation to HD pathogenesis remains unknown, but no definitive evidence exists linking the formation and abundance of polyQ-Htt aggregates to increased neuronal cell vulnerability or survival in HD.

Abnormalities in BDNF signaling

Mechanisms underlying neural degeneration in HD are unknown, but pathology has been linked to alterations in trophic factor function, specifically the function of brain-derived neurotrophic factor (BDNF) (reviewed in (Zuccato & Cattaneo 2007)). BDNF is normally synthesized by neurons in the cortex and the SN, and subsequently transported along axons to the striatum (Baquet *et al.* 2004). Results from experiments in various knockout mouse models suggested that BDNF supports the survival of MSNs, leading to the proposal that abnormalities in BDNF signaling could contribute to the reduced survival of striatal neurons in HD [reviewed in (Zuccato & Cattaneo 2007)]. Supporting this idea, reductions in BDNF levels were demonstrated in a number of cellular and animal HD models, as well as in HD patients (Zuccato & Cattaneo 2007). Further, genetic studies indicate that reductions in

BDNF levels selectively exacerbate polyQ-Htt-induced degeneration of enkephalinergic striatal projection neurons in the indirect pathway (Canals *et al.* 2004).

Functional studies indicated WT-Htt promotes BDNF expression in both cortex and striatum (Zuccato *et al.* 2001, Canals *et al.* 2001). Interestingly, this function of WT-Htt appears compromised by polyQ expansion, raising the possibility that reductions in striatal BDNF levels might result from polyQ-Htt-induced transcriptional changes (Zuccato *et al.* 2001, Canals *et al.* 2001). Alternatively, reductions in striatal BDNF could result from polyQ-Htt-induced reductions in anterograde axonal transport in cortical neurons (Gauthier *et al.* 2004b, Szebenyi *et al.* 2003a, Trushina *et al.* 2004), decreased BDNF endocytosis by MSNs (Her & Goldstein 2008), or both. Mechanisms underlying BDNF deficits remain a matter of debate.

Recent studies in a conditional knock out model indicated that total number of striatal neurons remained unaffected by BDNF depletion, challenging a long-standing assumption that BDNF serves as a critical survival factor for these neurons (Rauskolb *et al.* 2010). Instead, results from studies in these mice suggest BDNF is required for dendritic growth of striatal neurons (Rauskolb *et al.* 2010). The degree to which defects in BDNF signaling contribute to the degeneration of striatal and cortical projection neurons in HD remains unknown, but deserves further study.

Mitochondrial Alterations

Mitochondria are the chief cellular producers of chemical energy and major regulators of metabolism, as well as crucial modulators of intracellular signaling and survival (reviewed in (McBride *et al.* 2006)). Observations of cellular metabolism disturbances in HD patients suggested that mitochondrial dysfunction might represent a critical pathogenic component (Sanchez-Pernaute *et al.* 1999, Jenkins *et al.* 1993). *Post-mortem* studies on HD brain tissue further supported this idea, showing decreased activity in complex II, III, and IV of the mitochondrial respiratory chain (Gu *et al.* 1996)s. Experimental evidence using cultured neurons (Seong *et al.* 2005) and HD animal models (Browne *et al.* 1997) showed deficits in mitochondrial respiration in association with polyQ-Htt expression. Consistent with these observations, various mitochondrial inhibitors generate striatal pathology and phenotypes reminiscent of HD when administered systemically (Browne 2008). For example, accidental ingestion of the irreversible mitochondrial inhibitor 3-nitropropionic acid (3-NP) caused chorea, dystonia, and basal ganglia degeneration in humans (Ludolph *et al.* 1991). Also, systemic administration of 3-NP in rats (Beal *et al.* 1993) and primates (Palfi *et al.* 1996) caused striatal cell loss, inducing the accompanying movement deficits. However, unbiased gene expression analysis comparing HD and 3-NP changes in energy metabolism found significant differences and indicated that HD effects on metabolism were extramitochondrial (Lee *et al.* 2007). Further, any treatment compromising the connectivity and survival of neurons in the striatal pathway would produce similar clinical symptoms. Significantly, functional experiments indicated that activation of the cJun Amino Terminal kinase (JNK) pathway represented an essential step in 3-NP-induced striatal degeneration (Garcia *et al.* 2002), but mechanisms linking reductions in mitochondrial function and JNK activation in HD remain elusive.

Several mechanisms have been proposed linking polyQ-Htt to mitochondrial dysfunction in HD (Grunewald & Beal 1999), including polyQ-Htt-induced reductions in ATP generation (Seong *et al.* 2005), Ca^{2+} buffering (Reddy *et al.* 2009, Panov *et al.* 2002), and mitochondrial trafficking (Li *et al.* 2010, Reddy *et al.* 2009, Orr *et al.* 2008). While tissue-specific patterns of mitochondrial protein composition have been described (Mootha *et al.* 2003), no evidence exists showing that polyQ-Htt differentially affects mitochondria from

specific cell types, making unclear how polyQ-Htt-induced mitochondrial dysfunction might differentially affect selected neuronal populations. Alternatively, it has been proposed that MSNs are uniquely susceptible to defects in mitochondria-dependent energy production (Beal 1992). Unlike other neurons in the basal ganglia, MSNs display unusually low levels of spontaneous discharge (Mitchell *et al.* 1999). This distinctive electrophysiological characteristic of MSNs could place a higher energy demand on these neurons, because a large portion of their ATP would presumably be used for the maintenance of a hyperpolarized state (Calabresi et al. 1995). The susceptibility of striatal neurons to mitochondrial inhibitors would therefore reflect unique energy requirements by these cells (Lee *et al.* 2007). However, disruption of mitochondrial function does not typically produce HD-like pathology. For example, systemic application of 3-NP induced neuronal cell pathology in the hippocampus and the thalamus, structures which are normally affected only at late HD stages (Bossi *et al.* 1993). Further, different mouse strains display differential vulnerability to 3-NP administration (Alexi *et al.* 1998), and different patterns of neural degeneration have been described for different mitochondrial inhibitors (McLin *et al.* 2006). Most studies of mitochondrial pathology in HD look at advanced stages of the disease, when mitochondrial-based cell death pathways may be activated as a secondary response to primary pathogenic mechanisms (Bredesen *et al.* 2006, Jellinger 2006). Such observations indicate that much remains to be learned regarding molecular factors that underlie the selective vulnerability of striatal neurons secondary to mitochondrial changes.

Neurochemical content

Based on their neurochemical content, MSNs can be classified either as part of the "striosomes" (also referred to as "patches") or as part of the "extrastriasome" (also known as "matrix") compartments (Graybiel 1990, Gerfen 1992). Projection MSNs represent the main cell type present in striosomes, while striatal interneurons are the dominant cell type at the matrix compartment. According to this classification, MSNs in the striosomal compartment are among the first to degenerate in HD (Hedreen & Folstein 1995). Various biochemical markers have been identified showing differential expression between the striosomal and matrix compartments, including neuropeptides and neurotransmitter receptors (Table I).

Neuropeptide and calcium-binding proteins

Besides expressing the neurotransmitter GABA, striosomal MSNs express higher levels of various neuropeptides including ENK, SP, dynorphin (DYN, a class of opioid peptides derived from the precursor protein prodynorphin) and neurotensin (NT, a 13 amino acid neuropeptide), among others (Holt *et al.* 1997, Angulo & McEwen 1994). Interestingly, the expression of specific neuropeptides is associated with increased vulnerability of MSN subtypes. As mentioned above, MSN neurons in the "direct pathway" express DYN and/or SP, whereas MSNs in the "indirect pathway" express ENK (Gerfen & Young 1988). However, it remains unclear whether expression of DYN and/or SP exacerbates polyQ-Htt toxicity, or whether ENK expression might provide a protective effect. Similarly, interneurons expressing nitric oxide synthase (NOS), somatostatin and neuropeptide Y (Ferrante *et al.* 1985) are particularly resistant in HD, but mechanisms making these proteins protective remain elusive and thus such associations are correlative.

A positive association has been observed between the level of expression of some calcium-binding proteins (i.e., calbindin, parvalbumin and caretinin) and the survival of interneurons in HD (Gerfen *et al.* 1985). Such associations led to the proposal that higher levels of calcium-binding proteins in striatal interneurons may protect these cells from glutamate-mediated excitotoxic mechanisms (Mitchell & Griffiths 2003). However, these proteins are not exclusively distributed in the striasomal compartment (Gerfen *et al.* 1985), and a small fraction of calbindin or parvalbumin positive interneurons degenerate in HD (Mitchell *et al.*

1999). Conversely, decreased expression of hippocalcin and other calcium sensor proteins in MSNs was proposed to contribute to the increased vulnerability of these cells in HD (Luthi-Carter *et al.* 2000). However, functional experiments based on lentivirus-mediated hippocalcin expression yielded results in direct contradiction with this latter hypothesis (Rudinskiy *et al.* 2009).

Glutamate-related factors

Glutamate is the most abundant excitatory neurotransmitter in mammalian brain, activating both N-methyl-D-aspartate (NMDA) and non-NMDA ionotropic glutamate receptors (i.e., AMPA and kainate receptors) (Gasic & Hollmann 1992). Abnormally sustained stimulation of NMDA receptors by glutamate can lead to prolonged increases in intracellular calcium, triggering various intracellular events including activation of kinases and phosphatases, calcium-dependent proteases, synthesis of nitric oxide synthase (NOS), generation of reactive oxygen species, mitochondrial dysfunction, and activation of apoptotic pathways (reviewed in (Aarts & Tymianski 2004)). Relevant to the subject of this review, both striatal MSNs and cortical neurons receive a rich supply of excitatory glutamatergic inputs (Bouyer *et al.* 1984). Striatal MSNs in particular are constantly stimulated by these inputs, remaining hyperpolarized much of the time (Wilson & Kawaguchi 1996). These observations led to suggestions that increased exposure of MSNs to cortical glutamate stimulation could render these cells more vulnerable to excitotoxic damage. This idea provided the rationale for the use of NMDAR antagonists in HD (Kieburtz *et al.* 1996, Bonelli & Hofmann 2004, Handley *et al.* 2006), but these treatments had no beneficial effects in HD patients (Handley *et al.* 2006).

Experimental evidence using intrastriatal injection of agonists for NMDA (e.g., quinolinic acid) and non-NMDA (e.g., kainic acid) receptors in rodent and non-primate animals demonstrated greater vulnerability of MSNs to glutamate-induced excitotoxicity, compared to striatal interneurons (McGeer & McGeer 1976, Coyle & Schwarcz 1976, Emerich *et al.* 1996). However, mechanisms linking polyQ-Htt expression to the increased vulnerability of these neuronal subtypes to glutamate toxicity have not yet been established. Despite this, various HD models have been proposed based on the administration of glutamate receptor agonists (McGeer & McGeer 1976, Coyle & Schwarcz 1976). While these models generally resemble the HD phenotype of striatal dysfunction, their time window for inducing cell death contrasts sharply with the dying-back pattern of degeneration observed in HD (Fig. 3). Further, some studies showed that the pattern of striatal neuron degeneration resulting from systemic quinolonic acid injection differs significantly from that of HD, suggesting different pathogenic mechanisms (Figueredo-Cardenas *et al.* 1994). Relevant HD animal models need to replicate the sequence of changes in neuronal connections and neuronal populations seen in the disease, including the "dying back" pattern of neuronal degeneration. Since the neurological symptoms in HD reflect loss of functional connections made by affected neurons, any treatment that disrupted these synaptic relationships would be expected to exhibit similar clinical symptoms, without necessarily involving the pathogenic mechanisms initiated by polyQ-Htt.

A molecular basis underlying the differential vulnerability of striatal neurons to glutamate excitotoxicity is currently unknown, but reductions in levels of calcium-binding proteins, heterogeneous expression of NMDA receptor subtypes, and abnormalities in glial function have all been proposed as contributing factors (reviewed in (Mitchell *et al.* 1999)).

NMDA glutamate receptors exist as heteromeric dimers of NR1 and NR2 (A, B, C and D) subunits (Rigby *et al.* 1996). In the brain, levels of NR1 expression greatly exceeds that of the other subunits combined, whereas NR2A, B, C and D subunits varied widely (Goebel & Poosch 1999). NR1 subunits are essential for NMDA receptor function, but

heteromerization with NR2 subunits increases both the permeability of the channel (over 100 fold), and its deactivation time (Schoepfer *et al.* 1994). Significantly, differential expression of NMDA subunits have been observed among striatal neurons (Cicchetti *et al.* 2000), with MSN projection neurons reportedly expressing higher levels of the NR2B subunit, and striatal interneurons predominantly expressing NR2D (Landwehrmeyer *et al.* 1995b, Kuppenbender *et al.* 2000). While differences in NMDA receptor subtype expression could help explain the increased vulnerability of MSNs over striatal interneurons to NMDA agonists, these do not explain the minimal HD pathology observed in the hippocampus and olfactory bulb, two other CNS regions showing higher levels of NR2B expression than the striatum (Goebel & Poosch 1999, Laurie *et al.* 1997). Recently, experiments involving selective expression of polyQ-Htt in astrocytes suggested that reduced expression of glutamate transporter in these cells might contribute to increases in extracellular glutamate levels (Bradford *et al.* 2010). Currently, no consensus exists on mechanisms by which polyQ-Htt expression might promote imbalances in glutamate signaling (Mitchell *et al.* 1999, Sieradzan & Mann 2001, Estrada Sanchez *et al.* 2008), nor is clear how the contribution of glutamate signaling relates to the early axonal and synaptic degeneration phenotype of HD.

Dopamine signaling

Like glutamate, dopamine (DA) is a key neurotransmitter in several CNS circuits, and the striatum is the brain region most heavily innervated by dopaminergic afferents. These fibers originate from the SN (Albin *et al.* 1989) (Figs. 1-2). Interestingly, the striatal DA content exhibits a dorsal to ventral gradient (Cass 1997) that is consistent with the progression of pathology in HD (Vonsattel & DiFiglia 1998). Based on these observations, and findings of DA signaling deregulation in HD models and patients (Tang *et al.* 2007), a role of DA in the increased vulnerability of MSNs has been proposed (Jakel & Maragos 2000). DA in the striatonigral circuit exerts excitatory signals by activation of D1 receptors, and inhibitory signals by activation of D2 receptors (Albin *et al.* 1989) (Fig. 2). MSNs of the "indirect pathway" express high levels of D2, in contrast with the MSNs in the "direct pathway", which express high levels of D1 (Gerfen *et al.* 1990), suggesting that differences in DA-induced signaling could modulate the toxic action of polyQ-Htt. Consistent with this idea, activation of the JNK pathway induced by polyQ-Htt (Phelan *et al.* 2001, Apostol *et al.* 2006, Morfini *et al.* 2009b) was reportedly exacerbated by D2 receptor activation (Luo *et al.* 1998, Charvin *et al.* 2005). However, both direct and indirect pathways are eventually affected in HD. Again, the loss of synaptic connections early in the disease make it difficult to determine whether altered dopamine signaling represents a primary or secondary element in HD pathogenesis.

The cumulative evidence indicates that dopamine and perhaps other neurotransmitters might modulate the toxic effects of polyQ-Htt and thus may represent factors contributing to the differential vulnerabilities of striatal neurons in HD. While most studies have focused in altered calcium homeostasis and induction of apoptosis as a consequence of abnormal neurotransmitter signaling (Tang *et al.* 2007, Sieradzan & Mann 2001), little emphasis has been placed on well-established events downstream of neurotransmitter receptor activation, including the modulation of kinase-dependent signaling pathways (Luo *et al.* 1998, Zhen *et al.* 1998). Indeed, specific neurotransmitters and neuropeptides might act synergistically with polyQ-Htt-induced pathogenic kinase-mediated pathways (i.e., JNK activation) to increase the vulnerability of specific neuronal populations (Morfini *et al.* 2005). Alternatively, some neurotransmitters could promote activation of kinase pathways (e.g., the Akt pathway) that counteracting toxic ones elicited by polyQ-Htt (Humbert *et al.* 2002, Kim *et al.* 2002). Accordingly, cell type-specific changes in kinase activity and patterns of protein phosphorylation have been found in association with drugs that target the striatum

(Bateup *et al.* 2008). Additional studies are needed to illuminate molecular mechanisms by which specific neurotransmitters might modulate polyQ-Htt-induced toxicity. Such studies will help determine the precise contribution of each neurotransmitter system to the differential vulnerability of neuronal subtypes in HD.

Alterations in Gene Expression

A plethora of gene studies in transgenic HD models and HD human tissue initially described polyQ-Htt-induced transcriptional alterations (reviewed in (Thomas 2006, Cha 2007)). Major advances in molecular biological and computer technology allowed for the screening of large numbers of candidate genes in an unbiased fashion. Specifically, microarray studies screened HD-related changes in the expression levels of thousands of RNAs encoding molecular components involved in various cellular processes including calcium homeostasis, intracellular signaling, energy metabolism and the transcriptional machinery (Thomas 2006, Cha 2007). Changes in the expression levels of mRNAs encoding neurotransmitters and their receptors, synaptic proteins, energy metabolism and mediators of intracellular signaling have all been described (reviewed in (Cha 2007)). However, data obtained thus far have not provided an explanation for the differential cellular vulnerability of HD. Further, it is unclear whether changes in gene expression identified thus far play a direct role on HD pathogenesis or represent a secondary response to primary pathogenic events. Changes in the levels of specific genes could result from compensatory mechanisms, making difficult to establish the relevance of such changes to HD pathogenesis. Additionally, most gene expression studies screened for transcriptional changes in the striatum or cortex, but few established quantitative comparisons between the most affected MSNs or pyramidal neurons and mildly affected or unaffected cells such as striatal and cortical interneurons. No signature pattern of gene expression changes has been defined for neurons affected in HD. Currently, there is no direct evidence linking changes in the transcription of specific genes to the differential vulnerability of neuronal populations in HD.

Deficits in axonal transport

Although no common biochemical features have been found among the most vulnerable neuronal cell types in HD, an analysis of their morphological characteristics does reveal a common theme. Specifically, neurons affected in HD within the striatum and the cortex are principally projection neurons (Cicchetti *et al.* 2000) (Table I). Indeed, MSNs and cortical neurons affected in HD project axons to anatomically distant target structures outside the striatum and the cortex, respectively (Fig. 2). In contrast, striatal and cortical interneurons that are mainly spared in HD bear short axons that remain within the boundaries of these brain structures. This morphological and functional difference has been proposed to play a role in the differential vulnerability of neurons observed in HD (Cicchetti *et al.* 2000), as well as other neurodegenerative diseases (Mattson & Magnus 2006, Morfini *et al.* 2009a, Morfini *et al.* 2009b). The lack of protein synthesis machinery in axons and the enormous distances separating the cell body from the axonal and synaptic domains impose a unique set of challenges to neuronal cells. One such challenge includes the transport and delivery of proteins and lipid components along axons, a process collectively referred to as axonal transport (AT) [reviewed in (Morfini *et al.* 2006b, Morfini *et al.* 2005)]. In mature neurons, AT of membrane-bounded organelles (MBOs, including mitochondria, synaptic vesicles, and plasma membrane components) from their sites of synthesis in the neuronal cell body to their final destination in axons is mainly executed by the microtubule-based motor protein *conventional kinesin*. The multi-subunit motor *cytoplasmic dynein* on the other hand, translocates signaling endosomes, multivesicular bodies, and lysosomes from axons back to the neuronal cell body [reviewed in (Morfini *et al.* 2006b)]. The crucial dependence of

neuronal function and axonal maintenance on AT is highlighted by observations linking loss of function mutations in these molecular motors above to various neurological diseases (Reid *et al.* 2002, Hafezparast *et al.* 2003, Roy *et al.* 2005). Significantly, pathological studies revealed a "dying-back" pattern of neuronal degeneration in these diseases, suggesting that alterations in AT might also represent a critical pathogenic event in HD (Roy *et al. 2005*, Morfini *et al. 2005*, Morfini *et al.* 2009a).

Multiple independent studies provided evidence of AT deficits in HD. Ultrastructural observations first showed reduced number of synaptic vesicles, and abnormal MBO profiles within axons of affected neurons (Li 1999,Li *et al.* 2001,Li & Li 2004). Subsequently, reports from various experimental models demonstrated that inhibition of AT represents an important pathogenic event in HD (Gunawardena *et al.* 2003,Szebenyi *et al.* 2003b,Lee *et al.* 2004,Sinadinos *et al.* 2009,Morfini *et al.* 2009b) and other polyQ-expansion diseases (Morfini *et al.* 2006a). Studies in isolated squid axoplasm first showed that polyQ-Htt inhibits AT in a manner independent of alterations in the neuronal cell body (Szebenyi *et al.* 2003b,Morfini *et al.* 2009b). Subsequent experiments in cultured cells (Gauthier *et al.* 2004a,Her & Goldstein 2008) and Drosophila neurons (Sinadinos *et al.* 2009,Lee *et al.* 2004) further documented reductions in AT and accumulation of axonal vesicle cargos in association with polyQ-Htt expression. These observations, the absolute reliance of neurons on AT, and the "dying-back" pattern of neuronal degeneration seen in HD all support the concept that AT deficits might represent a major pathogenic event underlying the increased vulnerability of projection neurons in this disease (Morfini *et al.* 2009b).

Reductions in AT observed in various HD experimental models raised the question of *how* polyQ-Htt inhibits AT. An explanation to this question appears to be that polyQ-Htt inhibits AT by promoting alterations in the activity of kinases involved in the phosphorylation of molecular motor proteins (Morfini et al. 2005, Morfini et al. 2009b). Consistent with this notion, aberrant patterns of proteins phosphorylation including neurofilaments (Nihei & Kowall 1992, DiProspero *et al.* 2004a) and synapsin (Lievens *et al.* 2002), as well as increased activation of kinases all represent well-established HD features (Apostol et al. 2006, Garcia *et al.* 2004, Liu 1998). Expression of polyglutamine-expanded huntingtin activates the SEK1-JNK pathway and induces apoptosis in a hippocampal neuronal cell line (Liu 1998). Accordingly, studies in isolated squid axoplasm and a knock-in mouse model further showed polyQ-Htt inhibits AT through a mechanism involving activation of the JNK pathway and phosphorylation of the molecular motor protein conventional (Morfini et al. 2009b). Three JNK isoforms exist in mammals (JNK1, JNK2 and JNK3)(Brecht et al. 2005). Neuron-specific JNK3 (Yang *et al.* 1997), but not ubiquitously expressed JNK1, mediated the inhibitory effects of polyQ-Htt on AT, thus providing a partial explanation for the increased vulnerability of neurons to polyQ-Htt (Morfini *et al.* 2009b). Increased activation of JNK3 in HD would promote reductions in AT of various MBO cargoes, leading to deficits in synaptic and axonal function and maintenance. Increased activation of the JNK pathway in HD is also consistent with the changes in gene transcription and activation of apoptotic pathways widely reported in association with polyQ-Htt expression (Phelan *et al.* 2001, Merienne *et al.* 2003).

Deficits in AT appear to play a role in the degeneration of neurons observed in HD. Obviously, longer axons characteristic of projection neurons mean that larger cellular volumes and surface area must be maintained, placing greater demands on AT-related mechanism. However, *why* deficits in AT in HD would affect projection neurons in the striatum and the cortex to a greater extent than projection neurons in other brain structures remains to be established. Several possibilities exist. Among these, MSNs and cortical projection neurons affected in HD may have unique AT requirements or specializations that makes them more vulnerable to polyQ-Htt-induced toxicity. Consistent with this idea,

cytotypic differences in AT have been documented *in vivo* for different neuronal populations (Oblinger *et al.* 1987). Genetic evidence also demonstrates cell type-specific AT specializations. For example, whereas some mutations in the molecular motor protein subunit dynactin primarily cause motor neuron disease (Puls *et al.* 2005, Puls *et al.* 2003), a different set of mutations in this protein result in Perry's syndrome, which lack motor neuron pathology and instead is characterized by degeneration of cortical and extrapyramidal neurons (Farrer *et al.* 2009). Alternatively, one or more components mediating the effects of polyQ-Htt on AT (i.e., JNK3) might be expressed at higher levels in neurons affected in HD. An exhaustive examination of JNK isoforms in the brain has not been done, but some reports suggest differential expression of each isoform in different areas (Brecht *et al.* 2005). A molecular basis underlying the increased vulnerability of MSNs and cortical projection neurons to polyQ-Htt-induced alterations in AT is currently unknown, but likely reflects unique AT specializations of these neuronal cell types (Oblinger *et al.* 1987, Morfini *et al.* 2001, Her & Goldstein 2008).

Conclusions

In HD, the ubiquitous pattern of polyQ-Htt expression contrasts sharply with the increased vulnerability of specific populations of neurons in the striatum and cerebral cortex. The consistent loss of these neuronal populations has been proposed to result from "*selective*" vulnerability of these cells to the toxic gain of function associated with polyQ expansion in Htt. However, multiple lines of evidence clearly indicate that the toxic effects of polyQ-Htt are not restricted to specific neuronal populations. Instead, the evidence suggests that cell type-specific features might render such populations increasingly vulnerable to polyQ-Htt-induced toxicity.

Several scenarios, not mutually exclusive, appear consistent with the unique cellular topography of neuronal degeneration in HD. One or more molecular components involved in polyQ-Htt toxicity could be enriched in affected cells, but the identity of such component(s) remains elusive. Alternatively, cell type-specific features could render some neurons more vulnerable to the toxic effects of polyQ-Htt. Such features would represent the "weakest link in the chain" and likely be associated with critical functional needs of affected cells. In this regard, it is noteworthy that thus far, the presence of long axons constitutes the only common characteristic observed among neuronal cell types affected in HD. Indeed, it is striatal and cortical projections neurons bearing axons that project to anatomically remote structures that mainly degenerate in HD, whereas interneurons bearing short axons are largely spared. Significantly, polyQ-Htt has been shown to induce decrements in axonal transport, a cellular process critical for the function and maintenance of axons. Moreover, degeneration of neurons with defective axonal transport follows a "dying back" pattern that is consistent with that of neurons affected in HD. At present, it is unclear why deficits in axonal transport induced by polyQ-Htt would affect projection neurons in the striatum and the cortex to a greater extent than projection neurons in other brain structures, but differences in the composition, amounts, and regulation of axonal transport have all been documented.

An understanding of the interactions between polyQ-Htt and cell type-specific characteristics should provide a novel conceptual framework for the development of effective therapeutic strategies in HD. Such knowledge could yield treatments that specifically address neuronal populations affected in this disease. Regardless, preventing loss of neuronal connectivity should represent a primary goal of any effective therapeutic strategy.

Acknowledgments

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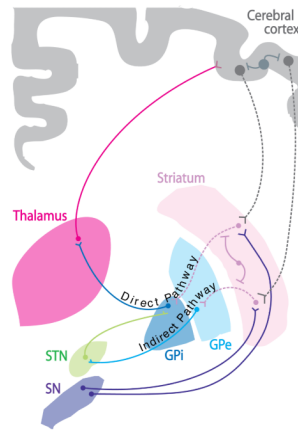
Figure 1. Overview of HD pathology
A subset of projection neurons in the striatum and the cortex (represented by dashed lines) are particularly vulnerable in HD. These include medium spiny neurons (MSNs, pink dashed lines) of the striatum and large pyramidal projection neurons in cortical layers V, VI and III of the cerebral cortex (gray dashed lines). MSNs in the "indirect pathway" of the basal ganglia project to the external segment of the globus pallidus (GPe) and are affected early in the course of the disease. As HD progresses, MSNs projecting to the internal segment of the globus pallidus (GPi) via the "direct pathway" and cortical pyramidal cells projecting to the striatum are also impaired. Remarkably, most interneurons in both the striatum (pink solid lines) and the cerebral cortex (gray solid lines) are largely spared. This morphological and functional difference has been proposed to play a role in the differential vulnerability of neurons observed in HD (Cicchetti *et al.* 2000), as well as other neurodegenerative diseases (Mattson & Magnus 2006, Morfini *et al.* 2009a, Morfini *et al.* 2009b). Abbreviations: STN: subthalamic nucleus; GPe: external globus pallidus; GPi: internal globus pallidus; SN: substantia nigra.
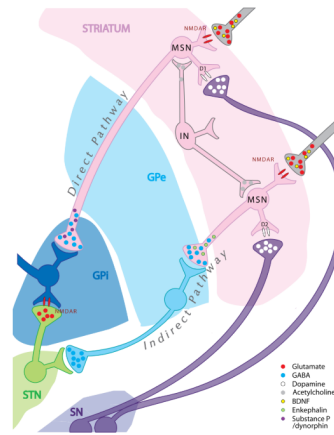
Figure 2. Cell type-specific characteristics of neuronal populations affected in HD
Cumulative pathological and experimental evidence indicates that cell type-specific characteristics modulate the vulnerability of specific neuronal populations to mutant huntingtin expression. Striatal medium spiny neurons (MSN) and cortical neurons affected in HD project axons to anatomically distant target structures outside the striatum and the cortex, respectively. In contrast, striatal and cortical interneurons (IN) that are largely spared in HD bear short axons that remain within the boundaries of these brain structures. Differences in biochemical content may also contribute to the differential vulnerability of these neuronal populations, but the underlying pathogenic mechanisms remain unknown. MSNs are GABA-ergic projection neurons (GABA, blue circles) and receive brain-derived neurotrophic factor (BDNF, yellow circles) from cortical glutamatergic (Glutamate, red circles), as well as dopaminergic afferents (Dopamine, white circles) from the substantia nigra (SN). Interestingly, more vulnerable MSNs in the "indirect pathway" express enkephalin peptides (Enkephalin, green circles) and D2 dopamine receptors (white ovals, bottom), while less vulnerable MSNs in the "direct pathway" express substance P/dynorphin (purple circles) and D1 receptors (white ovals, top). Abbreviations: MSN: medium spiny neuron; IN: interneuron; BDNF: brain-derived neurotrophic factor; D1: dopamine receptor subtype 1; D2: dopamine receptor subtype 2; NMDAR: N-methyl-D-aspartic acid receptor; GABA: γ-aminobutyric acid; GPe: external globus pallidus; GPi: internal globus pallidus; SN: substantia nigra; STN: subthalamic nucleus.
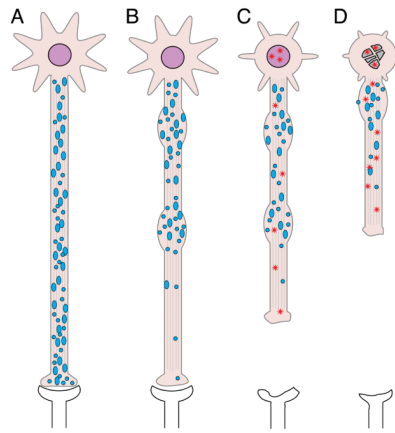
Figure 3. "Dying back" pattern of neuronal degeneration in HD
A) Neurons undergo normal development, retaining normal connectivity and functionality prior to disease state. **B)** Affected neurons begin to exhibit signs of synaptic and axonal alterations early in the disease process, including abnormalities in the phosphorylation of axonal proteins, abnormal accumulation of membrane-bounded organelles (blue circles) in axons (Davies & Scherzinger 1997, DiFiglia *et al.* 1997a, Sapp *et al.* 1999, Davies *et al.* 1997), and loss of synaptic proteins (DiProspero *et al.* 2004b). These changes correspond to functional impairments in synaptic function that appear very early on, even in presymptomatic stages (Cepeda *et al.* 2003, Levine *et al.* 2004). **C)** Axonal degeneration steadily advances in a retrograde fashion, and nuclear/neuritic Htt aggregates (red stars) become evident. As HD progresses, dysfunction of striatal and corticostriatal projection neurons manifest in clinical symptoms such as motor deficits and cognitive decline long before evidence of cell death (Mizuno *et al.* 2000). **D)** Disruption of functional synaptic connectivity and eventual loss of appropriate trophic support (Zuccato & Cattaneo 2007) ultimately result in cell death, likely by apoptosis-related mechanisms (Vis *et al.* 2005).

Table I

Differential vulnerability of specific cell populations in HD and its relationship to morphological and biochemical characteristics

Different subpopulations of neurons in the striatum and cerebral cortex display varying degrees of vulnerability (indicated by a "+" sign) in HD. No common biochemical characteristic have been found among the main neuronal populations affected in HD. However, an analysis of morphological characteristics suggests increased vulnerability of neurons bearing longer and more prominent axons. Accordingly, MSNs and cortical projection neurons represent the main neuronal cell types affected in this disease, while interneurons are largely spared. Other cell type-specific properties including afferents, targets, and biochemical content (i.e., neurotransmitter receptors, peptides, etc.) could further modulate mutant huntington toxicity. Accordingly, several biochemical features characterize more vulnerable MSNs in the "indirect" pathways from those in the "direct" pathway, which are affecter later in the disease.

Anatomical location	Cell type	Relative vulnerability	Morphology	Afferents	Target	NT receptors	NT	Peptides	Other molecular markers
	MSN (direct pathway)	+ + +	projection neuron, long axon	Cortex (Glu), SNc (DA), Thalamus (Glu)	GPi, SNr	D1, NMDA, AMPA	GABA	Substance P/Dynorphin	DARPP-32, GAD
Striatum	**MSN (indirect pathway)**	+ + + + +	projection neuron, long axon	Cortex (Glu), SNc (DA), Thalamus (Glu)	GPe	D2, A2a, NMDA, AMPA	GABA	Enkephalin	DARPP-32, GAD
	Interneurons	+	extensive dendritic network, axon projects locally	MSNs, other interneurons	MSNs, other interneurons	D2, NMDA, AMPA	Ach	neuropeptide Y, parvalbumin	iNOS, somatostatin
Cerebral Cortex	Pyramidal neurons (layers V/VI)	+ + +	projection neuron, long axon	Thalamus, brainstem nuclei	Striatum, brainstem, thalamus	Glu, ACh, DA, NE, 5HT	Glu	-	MAP2, CaMK
	Interneurons	+	extensive dendritic network, axon projects locally	Thalamus	Pyramidal neurons	Glu, GABA	GABA	Somatostatin, neuropeptide Y	GAD