Huntington’s disease and striatal signaling

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Huntington’s Disease (HD) is the most frequent neurodegenerative disease caused by an expansion of polyglutamines (CAG). The main clinical manifestations of HD are chorea, cognitive impairment, and psychiatric disorders. The transmission of HD is autosomal dominant with a complete penetrance. HD has a single genetic cause, a well-defined neuropathology, and informative pre-manifest genetic testing of the disease is available. Striatal atrophy begins as early as 15 years before disease onset and continues throughout the period of manifest illness. Therefore, patients could theoretically benefit from therapy at early stages of the disease. One important characteristic of HD is the striatal vulnerability to neurodegeneration, despite similar expression of the protein in other brain areas. Aggregation of the mutated Huntingtin (HTT), impaired axonal transport, excitotoxicity, transcriptional dysregulation as well as mitochondrial dysfunction, and energy deficits, are all part of the cellular events that underlie neuronal dysfunction and striatal death. Among these non-exclusive mechanisms, an alteration of striatal signaling is thought to orchestrate the downstream events involved in the cascade of striatal dysfunction.

Keywords: polyglutamine, Huntingtin, excitotoxicity, mitochondrial dysfunctions, transcriptional deregulation

CLINICAL ASPECTS

Huntington’s disease (HD) is a fatal disorder with a general prevalence of about 10 per 100,000 births, with some regions of the world having a higher prevalence of up to 700 per 100,000 (Harper, 1992; Paradisi et al., 2008). The typical age of onset is usually between 35 and 50 years but is very variable ranging from 1 to 85 years or more. The disease begins before 30 years of age in about 15% of patients and is then referred to as juvenile HD. The duration of the disease from onset to death is about 15–20 years. Clinical features of HD can be divided into three groups: movement disorders, cognitive impairment, and psychiatric manifestations. Chorea is the most characteristic movement disorder of classical HD and is characterized by brief, involuntary, abnormal movements, which appear unpredictably in all the parts of the body (Quinn and Schrag, 1998). As the disease progresses, the choreic movements generally tend to diminish and be replaced by akineto-rigid parkinsonism that can be associated with dystonic postures (Penney et al., 1990; Kremer et al., 1992). At an advanced stage of the disease, a high proportion of HD patients have falls (Busse et al., 2009), and a loss of independent ambulation, which may precipitate admission to nursing homes (Wheelock et al., 2003). Other movement disorders can be occasionally observed during the course of the disease, including tics (Kerbeshian et al., 1991; Jankovic et al., 1995) and myoclonia (Vogel et al., 1991; Carella et al., 1993; Thompson et al., 1994). Cognitive impairment plays a major role in the functional decline and loss of autonomy of the patients. It can precede motor symptoms or occur during the course of the disease, and usually leads, in turn, to dementia. Cognitive alteration has a sub-cortical profile with predominant impairment of executive/attention functions (Caine et al., 1978; Bamford et al., 1995; Ho et al., 2003; Peinemann et al., 2005). Instrumental functions (language, praxia, and gnosis) and memory are generally better preserved in HD than in other types of dementia (Caine et al., 1977; Hodges et al., 1990; Pillon et al., 1993, 1994). Neurobehavioral symptoms are very frequent. They can be the initial manifestations of the disease or occur at any time during the course of the disease (Shiwach and Norbury, 1994; Kirkwood et al., 2002). Irritability, agitation, apathy, anxiety, social withdrawal, impulsiveness, alcohol abuse, obsessive–compulsive disorder (Cummings and Cunningham, 1992; Patzold and Brune, 2002), hostility, and sexual disorders are common (Pflanz et al., 1991; Fedoroff et al., 1994; Paulsen et al., 2001). Mood disorders are very frequent along HD, including depression (Caine and Shoulson, 1983; Folstein et al., 1983; Di Maio et al., 1993; Cummings, 1995; Jensen et al., 1998) and manic episodes (Mendez, 2000). Various types of psychotic disorders can also be observed (Cummings, 1995; Rosenblatt and Leroy, 2000). HD patients have a risk of suicide that is 10 times higher than in the general population. Sleep disorders and weight loss are also frequently encountered in HD patients (Morton et al., 2005; Arnulf et al., 2008; Aziz et al., 2008; Videnovic et al., 2009).

Contrary to patients with typical HD, those with the juvenile form (or the Westphal variant) do not display chorea. These forms are characterized by a combination of progressive akineto-rigid parkinsonism, dystonia, ataxia, dementia, and psychiatric disorders (Siesling et al., 1997; Gonzalez-Alegre and Afifi, 2006). Seizures can also occur. Patients with childhood-onset HD can develop non-specific encephalopathy resulting in seizures, myoclonus, and rapid cognitive deterioration (Siesling et al., 1997; Gambardella et al., 2001; Gonzalez-Alegre and Afifi, 2006).
GENETICS
The mutation responsible for HD is located at the 5’ terminal part of the HTT gene on chromosome 4p16.3 (The Huntington Collaborative Research Group, 1993). The mutation consists of an unstable expansion of the CAG repeat sequence, located in exon 1, at the NH2-terminal part of the protein. The mutated protein causes neuronal dysfunction and death, particularly in the striatum and cortex, although it is ubiquitously expressed. The penetrance of the mutation is almost complete. The HTT gene is normal when it contains less than 27 CAG repeats. Between 27 and 35 CAG repeats do not cause HD but may expand in successive generations. Intermediate alleles (between 36 and 39 repeats) repetitions are usually associated with late onset disease and may express a variable penetrance as the patient may die before disease onset. Individuals with 39 CAG repeats or greater will develop symptoms of HD (Kenney et al., 2007; Reynolds, 2008; Semaka et al., 2008). About 10% of HD patients have no family history of HD (Goldberg et al., 1993; Davis et al., 1994), with some of these patients receiving the mutant allele from an asymptomatic father with an intermediate allele. Such alleles do not cause HD but show instability on replication and tend to expand in successive generation with greater instability in spermatogenesis than in oogenesis (Zulhke et al., 1993; Ranen et al., 1995). This instability of increased number of CAG repeats over successive generations explains the phenomenon of genetic anticipation, which is defined by the tendency of an earlier disease onset in successive generations (Goldberg et al., 1993; Myers et al., 1993; Allord et al., 1996). The age of onset cannot be predicted from the CAG repeat length in clinical practice. However, the number of repeats inversely correlates with the age of onset (Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993; Wexler et al., 2004; Andresen et al., 2007).

NEUROPATHOLOGY
Brain weight may be reduced by as much as 25–30% in advanced HD cases. Gross pathology of HD is limited to the brain, with atrophy predominating in the caudate–putamen and to a lesser extent, the cerebral cortex. The neuropathological signature of HD atrophy predominating in the caudate–putamen and to a lesser extent, the cerebral cortex. The neuropathological signature of HD is normal when it contains less than 27 CAG repeats. Between 27 and 35 CAG repeats do not cause HD but may expand in successive generations. Intermediate alleles (between 36 and 39 repeats) repetitions are usually associated with late onset disease and may express a variable penetrance as the patient may die before disease onset. Individuals with 39 CAG repeats or greater will develop symptoms of HD (Kenney et al., 2007; Reynolds, 2008; Semaka et al., 2008). About 10% of HD patients have no family history of HD (Goldberg et al., 1993; Davis et al., 1994), with some of these patients receiving the mutant allele from an asymptomatic father with an intermediate allele. Such alleles do not cause HD but show instability on replication and tend to expand in successive generation with greater instability in spermatogenesis than in oogenesis (Zulhke et al., 1993; Ranen et al., 1995). This instability of increased number of CAG repeats over successive generations explains the phenomenon of genetic anticipation, which is defined by the tendency of an earlier disease onset in successive generations (Goldberg et al., 1993; Myers et al., 1993; Allord et al., 1996). The age of onset cannot be predicted from the CAG repeat length in clinical practice. However, the number of repeats inversely correlates with the age of onset (Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993; Wexler et al., 2004; Andresen et al., 2007).

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Another characteristic neuropathological change is a modification of increased number of CAG repeats over successive generations (Goldberg et al., 1993; Myers et al., 1993; Alford et al., 1996). The age of onset cannot be predicted from the CAG repeat length in clinical practice. However, the number of repeats inversely correlates with the age of onset (Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993; Wexler et al., 2004; Andresen et al., 2007).

MOLECULAR MECHANISMS OF THE DISEASE
Whether neuronal degeneration in HD is due to the loss of normal HTT properties or a gain of toxic functions, or both, is not fully elucidated. In addition, age-related “normal” alterations in cellular functioning may accelerate HD pathogenesis (Diguet et al., 2009). Importantly, HTT is required for normal embryonic development as the loss of the protein leads to lethality of mouse embryos around day 8.5 (Duyao et al., 1993; Zeitlin et al., 1995) and the selective knockdown of the protein in neurons and testis produces apoptosis in these tissues (Dragatsis et al., 2000). The wild-type HTT is a ubiquitous protein, expressed in most cells of the organism and within virtually all cellular compartments (DiFiglia et al., 1997; Gutekunst et al., 1999; Kegel et al., 2002, 2005; Hoffner et al., 2005; Caviston et al., 2007; Rockabrand et al., 2007; Strehlow et al., 2007). Cell-based assays have focused on striatal specific cell-autonomous effects of Exp-HTT on HD neuropathology, since striatal but not cortical neurons in culture, show spontaneous degeneration in presence of Exp-HTT (Saudou et al., 1998; Arrasate et al., 2004; Garcia et al., 2004). Evidence in favor of cell-autonomous effects also include that a lentiviral mediated delivery of Exp-HTT to rat striatum results in a progressive pathology characterized by the appearance of ubiquitinated HTT aggregates, loss of dopamine- and cAMP-regulated phosphoprotein of 32 kDa ( DARPP-32) staining, and cell death (De Almeida et al., 2002). Nevertheless, in a genetic model with striatal specific expression of Exp-HTT, cell-autonomous nuclear accumulation of Exp-HTT aggregates in striatal neurons were observed, but no significant locomotor deficits nor striatal neuropathology, were found (Gu et al., 2007). This work suggested a “two-hit” hypothesis in which both cell-autonomous toxicity and pathological cell–cell interactions are critical to HD pathogenesis.

Huntingtin has multiple interacting partners, some of them exhibiting enhanced binding with Exp-HTT, while a handful prefer associating with the wild-type HTT (Harjes and Wanker, 2003; Li and Li, 2004). Among the binding partners of HTT are a dozen transcription factors which appear to affect the transcriptional profile in HD brain tissue or cells (Luthi-Carter et al., 2000, 2002; Sipione et al., 2002; Sugars and Rubinsztein, 2003; Zhai et al., 2005; Kuhn et al., 2007). HTT is also considered as a scaffold protein, orchestrating the intracellular trafficking, signaling pathways, and transcriptional activity that are required for neuronal homeostasis; these functions being strongly hindered by the Exp-HTT expression (see below). Exp-HTT is cleaved by various intracellular proteases, including caspases, and this proteolytic processing plays a key role in the pathophysiology of HD since the cleaved N-terminal fragment is much more toxic than the full-length mutant protein. These cleaved versions of Exp-HTT can also undergo aggregate formation (Scherzinger et al., 1997; Huang et al., 1998; Perutz et al., 2002), which is thought to interfere with normal cellular functioning. Aggregates of insoluble proteins are found in the

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brain of HD patients and in various HD models. They are enriched in striatal neurons and first appear in the neuropil of striatal MSNs (Li et al., 2000, 2001; Lee et al., 2004). By sequestering the wild-type HTT (Martindale et al., 1998) or associated proteins involved in transcription (Kazantsev et al., 1999; Steffan et al., 2000; Nucifora et al., 2001) or transport (Gunawardena et al., 2003; Trushina et al., 2004), these aggregates are thought to alter the fate of neuronal cells. Aggregate-mediated toxicity could be attributed to defects in RNA synthesis, cell survival, microtubule-dependent trafficking, or the ubiquitin–proteasome system (DiFiglia et al., 1997; Harjes and Wanker, 2003; Li and Li, 2004; Bennett et al., 2007). Nevertheless, the toxicity of aggregates still remains an issue of debate. Several studies have indicated that Exp-HTT aggregates are connected with neurodegeneration or cytotoxicity (Davies et al., 1997; DiFiglia et al., 1997; Ordway et al., 1997), whereas other studies have suggested that aggregate formation is either not intimately correlated with cytotoxicity (Saudou et al., 1998; Arrasate et al., 2004; Slow et al., 2005; Sawada et al., 2007; Mitra et al., 2009) or plays a protective role in cells (Arrasate et al., 2004; Mitra et al., 2009). Some authors argue that smaller oligomeric aggregates may be more toxic than larger ones (Gong et al., 2008). Furthermore, Exp-HTT can misfold into distinct β-sheet aggregates, called amyloids, which can be either toxic or non-toxic depending on their conformation (Nekooki-Machida et al., 2009). Aggregate toxicity can also depend on the cellular compartment in which they are localized, for example they could be more toxic in the neurites than in the nucleus (Li et al., 2000, 2001; Lee et al., 2004). Importantly, aggregates cannot be cleared by the ubiquitin–proteasome system (Bence et al., 2001; Jana et al., 2001; Verhoef et al., 2002; Venkatraman et al., 2004) and alter the normal efficacy of the clearance-machinery (Bennett et al., 2007; Hunter et al., 2007).

The lower basal activity of the ubiquitin–proteasome system in neurons as compared to glial cells may account for the preferential accumulation of aggregates in neurons (Tydlacka et al., 2008). It is noteworthy that inhibiting the aggregation of Exp-HTT can alleviate the symptoms in various models of HD (Carmichael et al., 2000; Jana et al., 2006; Vacher et al., 2005; Ravikumar et al., 2006; Chopra et al., 2007; Herbst and Wanker, 2007; Perrin et al., 2007; Sarkar et al., 2007; Seo et al., 2007).

**CHANGES IN AXONAL TRANSPORT AND SYNAPTIC DYSFUNCTION**

Vesicular transport is altered in HD and is linked to a subsequent synaptic dysfunction (Gunawardena et al., 2003; Szebenyi et al., 2003; Gauthier et al., 2004; Trushina et al., 2004; Caviston and Holzbaur, 2009; Sinadinos et al., 2009). These defaults of trafficking are mainly due to an impaired interaction between Exp-HTT and motor proteins (Szebenyi et al., 2003; Lee et al., 2004), but can also be a consequence of neuritic aggregates that act as physical roadblocks (Gunawardena et al., 2003; Szebenyi et al., 2003; Trushina et al., 2004). According to the non-autonomous theory, the “neurotrophin disorder hypothesis” is the most widely accepted (Zuccato and Cattaneo, 2009). The release of brain derived neurotrophic factor (BDNF) from cortical afferences, which provides an important neurotrophic support to striatal neurons, is impaired in HD. Transcriptional dysregulation of BDNF in cortical neurons was first described (Zuccato et al., 2001; see Transcriptional Dysregulation chapter below). Then, altered axonal transport deficit of BDNF from cortical neurons, was shown to participate in the default of BDNF release in the striatum (Gauthier et al., 2004). Wild-type HTT interacts with the molecular motor complex that transports organelles along the microtubules in axons (Gauthier et al., 2004; Caviston and Holzbaur, 2009). This interaction is altered in HD, due to Exp-HTT expression, which decreases axonal transport and the release of BDNF from cortical neurons to their terminals within the striatum (Figure 1). This is thought to participate in the striatal vulnerability in HD. One approach
to compensate for the defective BDNF transport is to mimic the phosphorylation of Exp-HTT on Ser421, in order to restore the interaction between Exp-HTT and dynactin, and their association with microtubules (Colin et al., 2008). Interestingly, increasing tubulin acetylation using a specific histone deacetylase (HDAC6) inhibitor restores the recruitment of motor proteins, including kinesin-1 and dynein to microtubules, and increases BDNF axonal transport in cortical neurons (Dompierre et al., 2007).

Huntingtin is also involved in the trafficking and secretion of vesicles from the Golgi apparatus (Strehlow et al., 2007). In particular, it promotes, acting in concert with transglutaminase 2 (TGarase 2) and HJSJ1b, the budding of vesicles containing BDNF from the Golgi to the cytoplasm (Borrell-Pages et al., 2006a; Del Toro et al., 2006). Modulation of TGase 2 and HJSJ1b expression by cystamine or cysteamine increases the release of BDNF in mice and monkey models of HD (Borrell-Pages et al., 2006b). The trafficking of neural proteins from the Golgi is also regulated by HTT-interacting protein 14 (HIP14), which normally interacts with HTT to regulate the trafficking of neuronal proteins and their synaptic release through palmitoylation of cysteine string protein (CSP; Yanai et al., 2006; Ohyama et al., 2007). Finally, Exp-HTT increases c-Jun-Kinase3 (JNK3) activity, which phosphorylates kinesin on Ser176 and reduces its binding to microtubules (Morfini et al., 2009). Thus, inhibition of the neuron-specific JNK3 can also protect from defects in fast axonal transport induced by Exp-HTT.

EXCITOTOXICITY AND STRIATAL SIGNALING

In HD, increased glutamate levels within the striatum are thought to arise from reduction of glial glutamate uptake (Liévens et al., 2001; Behrens et al., 2002). This is because of selective down-regulation of the glutamate transporter GLT1, which is mainly expressed in astrocytes. In Drosophila glia, Exp-HTT antagonize epidermal growth factor receptor (EGFR) Ras-extracellular signal-regulated kinase (ERK) signaling pathway, resulting in down-regulation of the glutamate transporter levels (Liévens et al., 2006). In addition, the expression of glutamine synthetase, an enzyme that converts glutamate to glutamine in glia, was also found to be altered (Liévens et al., 2001; Behrens et al., 2002). These findings demonstrated that the HD mutation results in a progressively deranged glutamate handling in the brain, beginning before the onset of symptoms in mice. They also provided evidence for a contribution of excitotoxicity to the pathophysiology of HD.

NMDAR-MEDIATED EXCITOTOXICITY IN HD

Ineffective management of Ca2+ homeostasis by striatal neurons ultimately leads to cell death via numerous signaling pathways. This excitotoxicity mostly implicates the N-Methyl-D-Aspartate type glutamate receptors (NMDAR) due to their high calcium permeability and slow activation/deactivation kinetics (Rothman and Olney, 1995; Dingledeen et al., 1999; Cull-Candy et al., 2001). The earliest evidence in support of a role for NMDAR-mediated excitotoxicity in HD came from rodent studies where the administration of NMDAR agonists mimicked some clinical and pathological features of the disease (Real et al., 1986; Sanberg et al., 1989; Ferrante et al., 1993). Studies have since switched from these chemical HD models to genetic mouse models where the expression of Exp-HTT protein has been linked to NMDAR-mediated excitotoxicity (Levine et al., 1999; Cepeda et al., 2001; Zeron et al., 2004). However, comparisons between HD models are complicated as the mRNA and protein expression levels of the NMDAR subunits vary between models and the disease state (Fan et al., 2007). Furthermore, age-related dependence to excitotoxicity has been recently highlighted in the transgenic YAC128 HD mice model, which display enhanced sensitivity to excitotoxicity in the early phase of the disease, prior to development of cognitive dysfunction and motor abnormalities, and resistance to excitotoxic stress as the disease progresses (Graham et al., 2009).

TARGETING NMDAR SUBUNITS

Pharmacological analyses have indicated that striatal NMDARs are most commonly formed from heterotetramers containing two obligatory NMDAR type 1 subunits (GluN1, previously known as NR1) plus a combination of two NMDAR type 2 subunits, GluN2A and GluN2B, as heterodimers or as heterotrimers (GluN1 plus GluN2A and GluN2B). Some literature points to NMDARs containing principally GluN2A as being pro-survival whereas GluN2B-containing NMDARs act as the excitotoxic mediators (Zeron et al., 2002; Liu et al., 2007). As the expression of GluN2B is significantly higher than GluN2A in the striatum than in other brain regions (Landwehrmeyer et al., 1995; Kuppenbender et al., 2000), a GluN2B-mediated excitotoxicity is consistent with the striatal vulnerability for neurodegeneration in HD. Interestingly, recent work has demonstrated a greater contribution by GluN2A containing NMDAR in the D1 expressing MSNs than D2 expressing MSNs which degenerate first in HD (Jocoy et al., 2011). In the YAC transgenic FVB/N mouse model of HD, NMDA-induced cell death is prevented by a specific GluN2B antagonist ifenprodil (Zeron et al., 2002). Likewise, double mutant mice expressing Exp-HTT and overexpressing GluN2B displayed an exacerbated striatal degeneration (Heng et al., 2009). The logical conclusion from these studies is that selective antagonists of GluN2B such as ifenprodil, RO-25,6981, and CP101,606 should offer some neuroprotection. However, the use of three different GluN2B antagonists had no beneficial effects in the R6/2 mouse model of HD (Tallaksen-Greene et al., 2010). In addition, both ifenprodil and RO-25,6981 increase cell death induced by oxidative stress (Papadia et al., 2008) and blockade of spontaneous GluN2B activity exacerbates staurosporine-induced cell death (Martel et al., 2009). Therefore, as the outcome depends on the considered model and the particular excitotoxic insult the argument is left open as to whether GluN2B merits specific targeting in HD excitotoxicity.

GLUTAMATE RECEPTOR LOCALIZATION AND EXCITOTOXICITY

Instead of a definite GluN2B subunit-specific implication for excitotoxic signaling, work by Hardingham and Bading fueled the hypothesis that activation of extrasynaptic NMDAR (those located at the cell body, dendritic shaft or on the neck of spines) promotes cell death whereas stimulation of synaptic NMDAR promotes cell survival (Hardingham and Bading, 2010). These hypotheses may not be in complete opposition as extrasynaptic NMDAR contain more GluN2B than synaptic ones (Tovar and Westbrooke, 1999; Steigerwald et al., 2000; Jocoy et al., 2011). Stimulation of calcium entry via synaptic NMDAR is well tolerated and coupled to
activation of the MAP kinase/ERK signaling pathway along with its target the transcription factor cyclic AMP-response element binding (CREB), which regulates genes such as bdnf (Hardingham et al., 2001, 2002). On the other hand these pro-survival mediators are dominantly opposed by the activation of extrasynaptic NMDAR which leads to the loss of mitochondrial membrane potential, inhibition of ERK signaling, CREB shut off (Vanhouthe and Bading, 2003), and an induction of a distinct genomic program including the gene clca1a, which encodes a calcium-activated chloride channel sufficient to kill neurons (Zhang et al., 2007). In HD, the striatal specific signaling partners of synaptic versus extrasynaptic NMDAR have begun to be analyzed. Ras homolog enriched in striatum (Rhes) is localized in the striatum, where it specifically bind to Exp-HTT and elicits both a decrease in ubiquitination and an increase in sumoylation of Exp-HTT, which leads to its disaggregation and favors the formation of neurotoxic soluble microaggregates (Subramaniam et al., 2009). Okamoto et al. (2009) found that Rhes expression is reduced when extrasynaptic receptors are blocked, whereas antagonism of synaptic NMDAR leads to a decrease in Exp-HTT aggregates and cell death. This study distinguished between the two receptor pools by the use of the uncompetitive NMDAR antagonist memantine, which selectively antagonizes extrasynaptic NMDAR at low concentrations (Rammes et al., 2008). The formation of non-toxic Exp-HTT inclusions is dependent on synaptic NMDAR activation and the induction of the T-complex-1 (TCP-1) subunit of TCP-1 ring complex (TRiC), which associates with heat shock protein 70 (Hsp 70) to favor the formation of these inclusions. By contrast, activation of extrasynaptic NMDAR in the presence of Exp-HTT down-regulates the protective PPAR alpha-co-activator-1z (PGC-1z) cascade (see below) via an inhibition of ERK activation and CREB phosphorylation (Okamoto et al., 2009). Inhibition of extrasynaptic NMDAR after in vivo treatment with a low dose of memantine over a period of 8 months increased TCP-1 protein levels, inclusion formation, and improved the motor function of YAC128 HD mice. By using the same approach, Milnerwood et al. (2010) showed that a blockade of extrasynaptic NMDAR restores basal levels of CREB activation and significantly overcomes motor learning deficits of YAC128 mice. Even at presymptomatic stages, YAC128 mice express more NMDAR subunits at extrasynaptic sites than YAC18 control mice, and consequently have a heightened response to glutamate spillover dependent on an extrasynaptic GluN2B-containing NMDAR (Milnerwood et al., 2010).

In addition to lateral NMDAR receptor localization, altered NMDA receptor trafficking may also participate to neuronal excitotoxicity in the striatum. Accelerated NMDA receptor trafficking and increased expression at the cell surface were found in striatal neurons from the YAC72 HD mouse model (Fan et al., 2007). This phenomenon can be related to an altered interaction between Exp-HTT and postsynaptic density 95 (PSD-95), a scaffold protein necessary for NMDAR stability, which has been previously described (Roche et al., 2001; Sun et al., 2001). Recently, association of PSD-95 with GluN2B in striatal tissue has been shown to be enhanced by Exp-HTT (Fan et al., 2009). Treatment of cultured MSNs with a TAT coupled peptide that blocks binding of GluN2B with PSD-95, reduces NMDAR surface expression in both YAC transgenic and WT MSN and rescues cells from NMDAR excitotoxicity.

The HIP1, which normally interacts with HTT, is involved in the intracellular trafficking of glutamate receptors of the AMPA subtypes. Exp-HTT, which interacts less efficiently with HIP1 than its normal counterpart, participates to increased membranal expression of AMPA receptors and hence to excitotoxic neuronal death in HD (Metzler et al., 2007). Altered calcium homeostasis in HD could be due to an abnormal interaction between Exp-HTT and the type 1 inositol 1,4,5-trisphosphate receptor (InsP3R1), which regulates the cytoplasmic calcium clearance by the endoplasmic reticulum (Tang et al., 2004, 2009). Disrupting the interaction between InsP3R1 and Exp-HTT normalizes calcium signaling, protects from glutamate-induced apoptosis in striatal neurons in vitro, and reduces neuronal pathology and motor deficits in a mouse model of HD in vivo.

**STRIATAL VULNERABILITY: THE DOPAMINERGIC HYPOTHESIS**

In addition to the glutamatergic stimulation, some evidence indicate that Dopamine (DA) stimulation may play a key role in excitotoxicity in HD (Reynolds et al., 1998; Charvin et al., 2005, 2008; Cyr et al., 2006; Stack et al., 2007; Tang et al., 2007; Benchoua et al., 2008); Knock-out mice for the DA transporter (DAT) show spontaneous striatal death accompanied by behavioral alterations that resemble HD specifically during aging (Cyr et al., 2003). In an elegant study, a double mutant mouse strain with both enhanced dopamine transmission and endogenous expression of a mutant HTT gene was generated. This strain was generated by crossing the DAT knock-out mouse with a knock-in mouse model of HD containing 92 CAG repeats (Cyr et al., 2006). These double mutant mice exhibited increased behavioral and neuropathological hallmarks of HD, including neuropil aggregates in MSN projection neurons. DA released from nigro-striatal inputs, is present in high concentrations within the striatum and enhances sensitivity to glutamatergic inputs. It may also produce oxidative stress via the production of reactive oxygen species (ROS), a cellular process that increases with aging (Jakel and Maragos, 2000). In particular, cultures of striatal neurons from R6/2 HD mice are sensitized to DA-induced oxidative stress, leading to neuronal autophagy (Petersen et al., 2001). ROS produced by low doses of DA potentiate activation of the pro-apoptotic JNK pathway induced by Exp-HTT (Garcia et al., 2004; Charvin et al., 2005), the pharmacological inhibition of which is neuroprotective in the R6/2 transgenic mouse model of HD (Apostol et al., 2008). DA may also render striatal neurons more vulnerable to Exp-HTT via dopamine receptor-mediated mechanisms (Charvin et al., 2005, 2008). Depending on the cell line model of HD, expressing either the full length or truncated versions of Exp-HTT, D1, or D2 receptors stimulation seems to be different. Full-length Exp-HTT is required for alteration of calcium signaling (Zhang et al., 2008). In striatal neurons from YAC128 transgenic or Q111 knock-in mice, both expressing full-length Exp-HTT, D1 receptor stimulation potentiates calcium influx via NMDA receptors, and hence excitotoxic processes, including mitochondrial depolarization, and caspase activation (Cepeda et al., 2001; Zeron et al., 2002, 2004; Starling et al., 2005; Tang et al., 2007). More recently, a
calcium-dependent activation of calpain was shown to be involved in striatal death after convergent activation of NMDA and D1 receptors in HD cell models (Paoletti et al., 2008). Increases in calcium influx lead to the cleavage of Cdk5 co-activator p35 into p25, which enables an aberrant toxic activation of Cdk5 (Paoletti et al., 2008). By contrast, when associated with p35 as a co-activator, Cdk5 is known to be protective via phosphorylation of Exp-HTT and the blockade of caspase-induced cleavage, resulting in attenuated aggregate formation and toxicity (Luo et al., 2005; Anne et al., 2007). Consistently, Cdk5/p35 suppresses the formation of aggregates induced by a short fragment of Exp-HTT (exon 1), via a new, unexpected role on microtubule stability and hence inclusion formation (Kaminsomo et al., 2008). Together, these data highlight the complexity of Cdk5 activity and the importance of targeting selectively p25 to block Exp-HTT-induced inclusion formation and neuronal death.

A central role of DARPP-32 (Dopaminergic and cAMP-regulated phosphoprotein) has also been proposed (Metzler et al., 2010). DARPP-32 phosphorylation at Thr34 is induced by a D1 agonist (SKF 81297) and inhibits in turn the activity of PP1, a phosphatase that dephosphorylates the Ser421 residue of the HTT protein. Of interest, inhibition of PP1 can offer protection from NMDA-induced excitotoxicity in YAC128 mice, through increased phosphorylation of Ser421-HTT. The loss of DARPP-32 expression described in HD results in an increase of PP1 activity followed by a decrease of Ser421-Exp-HTT phosphorylation (Metzler et al., 2010). As its cleaved version, Exp-HTT is not sensitive to D1 agonists, probably because it is not sensitive to calcium overload and calcium-dependent proteolytic processes produced by D1 receptor stimulation. By contrast, D2 receptors stimulation potentiates Exp-HTT-induced aggregate formation, deficiency of mitochondrial complex II protein activity, and neuronal death (Charvin et al., 2005; Benchoua et al., 2008). In vivo, in a rat model of HD based on lentiviral-mediated expression of Exp-HTT exon 1 in the striatum (De Almeida et al., 2002), an early and chronic treatment with the D2 antagonist, haloperidol decanoate, protects striatal neurons from Exp-HTT-induced dysfunction, and aggregates formation (Charvin et al., 2008). Striatal signaling mediated by D2 receptor stimulation on Exp-HTT toxicity has been recently elucidated. Inhibition of the Rho/ROCK pathway using selective inhibitors or knockdown of ROCK-II expression reversed D2 agonist-mediated aggregate formation, neuritic retraction and neuronal death induced by Exp-HTT (Deyts et al., 2009).

Mitochondrial Dysfunction and Energy Deficits

Defects in energy metabolism in brain and muscles, has long been proposed to be involved in HD, from clinical (Djoussé et al., 2002; Hamilton et al., 2004) bioenergetic (Arenas et al., 1998; Turner et al., 2007) and neuroimaging studies (Jenkins et al., 1998). In HD patients there is strong evidence for reduced glucose consumption in the brain, more specifically in the basal ganglia (Grafton et al., 1992; Kuwert et al., 1993) as well as increased lactate concentrations in the basal ganglia and occipital cortex (Jenkins et al., 1993), and lactate-to-pyruvate levels in the CSF (Jenkins et al., 1998). Various mechanisms that underlie the energy deficit in the HD brain have been proposed (Mochel et al., 2007; Mochel and Haller, 2011). They include impaired oxidative phosphorylation, oxidative stress, impaired mitochondrial calcium handling, abnormal mitochondria trafficking, decreased glycolysis, and transcriptional deregulation of PGC-1α. A deficiency of respiratory chain complex II, i.e., succinate dehydrogenase (SDH), in HD has been proposed since the observation that accidental ingestion of 3-nitropropionic acid (3-NP), an irreversible inhibitor of SDH, reproduces the clinical and neuropathological characteristics of HD in humans (Brouillet et al., 1999). In rodents, systemic 3-NP administration reproduces selective striatal degeneration, despite an altered SDH activity in multiple brain regions (Brouillet et al., 1998). Conversely, restoration of the complex II activity level is neuroprotective in a cellular model of HD (Benchoua et al., 2006). Activation of the pro-apoptotic JNK pathway is observed selectively in striatal neurons of 3-NP-administered rats in vivo, and overexpression of a dominant negative, non-phosphorylatable version of c-Jun in vitro inhibits striatal degeneration induced by 3-NP (Garcia et al., 2002). DA signaling regulates SDH enzymatic activity (Benchoua et al., 2008) and hence may account for the vulnerability of striatal neurons in HD. Furthermore, as detailed in the next section Exp-HTT-induced transcriptional dysregulation is now thought to contribute to altered bioenergetics.

Transcriptional Dysregulation

Transcriptional dysregulation is an early event in the neuropathological process. Altered levels of dopaminergic receptor and neuropeptide mRNAs observed in patient's brain tissues (Augood et al., 1996, 1997) are also observed in pre-symptomatic HD's transgenic mice, suggesting that changes in transcription underlie neurodegeneration rather than reflecting non-specific degradation of all RNAs in affected neurons (Cha et al., 1998, 1999). Subsequently, multiple genes encoding neurotransmitter receptors, enzymes, and proteins involved in neuron structure, stress responses, and axonal transport were found to be dysregulated (Luthi-Carter et al., 2000, 2002; Sugars and Rubinsztein, 2003; Cha, 2007; Runne et al., 2007), with overlaps of altered transcripts between various mouse models of HD and brain of HD patients (Kuhn et al., 2007). Interestingly, more than 80% of classically admitted striatal-enriched genes (genes with higher relative expression in the striatum compared with other brain regions) are decreased in a mouse model of HD as well as in human HD postmortem brain (Desplats et al., 2006). A down-regulation of novel striatal-enriched genes involved in vesicle transport and trafficking, tryptophan metabolism, and neuroinflammation were identified more recently in both HD mouse striatum and caudate from HD patients (Mazarei et al., 2010). Of interest, most of HD-induced dysregulation of the striatal transcriptome can be largely attributed to the intrinsic effects of mutant HTT, in the absence of expression in cortical neurons (Thomas et al., 2011).

Transcriptional dysregulation can be found in large genomic regions in a coordinated fashion and this dysregulation is associated with disease progression. Attempts were made to use transcriptional dysregulation as a biomarker in HD. Genome-wide expression profiling of the blood from HD’s patients revealed significant differences in symptomatic patients (Borovecki et al., 2005), but not moderate-stage patients (Runne et al., 2007). Thus, these biomarkers need to be further validated before their widespread use in clinical trials.
MOLECULAR MECHANISMS OF TRANSCRIPTIONAL DYSREGULATION IN HD

Within the nucleus Exp-HTT, under its soluble or aggregated form, interacts with and inhibits the activity of proteins involved in the normal transcriptional machinery. These include TATA binding protein (TBP), transcription factor II F (TFIIF), and tyrosine-aminotransferase II (TATII) 130 (Shimohata et al., 2000; Suhr et al., 2001; Dunah et al., 2002; Li et al., 2002). Exp-HTT also sequesters transcription factors involved in cell viability, including CREB protein (CBP), p53, specificity protein 1 (Sp1), nuclear factor-kappa B (NF-kB), nuclear receptor co-repressor (NCoR), and CA150 (Boutell et al., 1999; Li et al., 2000; Steffan et al., 2000; Nucifora et al., 2001; Dunah et al., 2002; Bae et al., 2005; Arango et al., 2006). Expression levels of BDNF, and its receptor TrkB, are decreased in the striatum of HD patient’s, suggesting a deficit in cortical neurotrophic support of the striatum (Ferrer et al., 2000; Zuccato et al., 2001; Lynch et al., 2007; Strand et al., 2007). In animal models of HD, cortical BDNF expression is reduced (Zuccato et al., 2001). Moreover, downregulating BDNF in striatum in mice worsens the HD phenotype, whereas elevating BDNF expression in the forebrain alleviates the HD phenotype (Canals et al., 2004; Strand et al., 2007; Gharami et al., 2008; Xie et al., 2010). The molecular mechanisms by which Exp-HTT drives the down-regulation of BDNF expression in cortical neurons have been unraveled. Wild-type HTT sequesters R element-1 silencing transcription factor (REST), a transcriptional repressor of neuronal survival factors including BDNF, within the cytoplasm. The HTT mutation leads to REST release within the nucleus, where it exerts a potent inhibitory role on the transcription of BDNF and other neuronal genes (Zuccato et al., 2001, 2003, 2007). Furthermore, REST mRNA levels are increased in R6/2 mouse model of HD and NG108 neuronal-like model of HD. At the transcriptional level, Sp1 binds to the Sp factor binding sites contained in the promoter of REST and contributes to Exp-HTT-mediated REST upregulation (Ravache et al., 2010). BDNF expression is also a component of the neuroprotective transcriptional response mediated by NF-kB in neurons (Lipsky et al., 2001). In addition, the loss of BDNF expression and low levels of NF-kB activity in neurons could lead to impairments of cognitive functions (Kalschmidt et al., 2005; Meffert and Baltimore, 2005), a common feature of neurodegenerative disorders such as HD.

A LINK BETWEEN TRANSCRIPTIONAL DYSREGULATION AND ENERGY DEFICITS IN HD

A link between Exp-HTT-induced transcriptional dysregulation and energy deficits has been recently described. Exp-HTT binds to the tumor suppression gene p53 more avidly than wild-type HTT and has been reported to increase p53 protein levels, nuclear localization and transcriptional activity in neuronal cultures and transgenic mice (Bae et al., 2005). Augmented p53 activity mediates mitochondrial membrane depolarization and decreases complex IV activity, and p53 inhibition or genetic deletion ameliorates these changes in a cell culture model. PGC-1α is a transcriptional co-activator that regulates mitochondrial biogenesis and oxidative phosphorylation (Cui et al., 2006; Weydt et al., 2006). A role of PGC-1α in HD pathogenesis was suspected from the observation of selective striatal lesions in PGC-1α knock-mice (Lin et al., 2004).

A direct link between CREB phosphorylation and transcriptional regulation at the PGC-1α promoter has been observed in neuronal cells (Cui et al., 2006). Impairment of the CREB/PGC-1α signaling cascade by suppression of excitatory synaptic activity or by stimulation of extracellular NMDA receptors increases the vulnerability of HD neuronal cells (Okamoto et al., 2009). Mitogen and stress-activated protein kinase-1 (MSK-1), a nuclear protein kinase activated downstream of ERK, was shown to control the expression levels of PGC-1α via increased binding of phosphorylated-CREB and Histone H3 at the promoter region of PGC-1α. Overexpression of MSK-1 was protective against Exp-HTT-induced striatal dysfunctions in vitro (Roze et al., 2008) and in vivo (Martin et al., 2011; Figure 1).

ACTING ON CHROMATIN REMODELING TO IMPROVE TRANSCRIPTIONAL DYSREGULATION IN HD

Chromatin remodeling that underlies DNA decompaction was first described in dividing cells, but is also one of the prime events of transcription in post-mitotic mature neurons (Taniura et al., 2007). This “above the genome” molecular mechanism, also called an epigenetic mechanism, gates DNA access, and hence transcription. It is critically controlled by post-translational modifications of histones (H2A and H2B, H3 and H4), a group of highly basic proteins tightly linked to DNA. In particular, the methylation and acetylation state of histones is closely linked to the regions of transcriptional activity by regulating transcription factor access to promoter regions in the DNA. Histone acetylation at a promoter generally increases transcription and the enzymes that catalyze these reactions are histone acetyltransferases (HATs). By contrast, HDACs catalyze deacetylation. Exp-HTT interacts with CBP and blocks its intrinsic HAT activity (Steffan et al., 2001). Administration of HDACs inhibitors, including SAHA, sodium butyrate, and phenylbutyrate, has demonstrated their therapeutic role in several HD models (Steffan et al., 2000; Ferrante et al., 2003; Hockly et al., 2003; Gardian et al., 2005), as they improved behavioral performance and neuronal survival. Interestingly, administration of a new benzamide-type HDAC inhibitor with lower potential toxicity than previous HDAC inhibitors, HDAC4 4b, also restores the transcription of critical striatal genes and improves motor and neuropathological phenotype of R6/2 HD mice (Thomas et al., 2008). All these HDAC inhibitors act broadly across various classes of HDACs (Lesort et al., 1999). Inhibitors targeting a specific class of HDACs may result in a better benefit to side effect ratio (Pallos et al., 2008). Finally, it must be emphasized that the levels of acetylated histones are not decreased globally in HD mice models, but rather selectively in the promoters of genes that are specifically down-regulated in HD (Sadri-Vakili et al., 2007).

Methylation of histones plays the opposite, inhibitory role on transcription. One of the proteins involved in methyltransferase activity at histone H3 (K9) is ERG-associated protein with SET domain (ESET). ESET expression is increased in HD patients and R6/2 HD mice (Ryu et al., 2006). Sp1 acts as a transcriptional activator of the ESET promoter at guanosine–cytosine (GC)-rich DNA binding sites (Yang et al., 2003). Inhibiting Sp1 binding to these sites using mitramycin (a clinically approved antitumor antibiotic) suppressed basal ESET promoter activity in a dose-dependent manner. The combined pharmacological treatment of
mimethramycin and cystamine, down-regulates ESET gene expression and hypertrimethylation of histone H3. This treatment significantly ameliorates the behavioral and neuropathological phenotype of R6/2 HD mice and improves their survival. Owing to its HEAT repeat α-solenoid structure, HTT acts as a facilitator of the epigenetic silenced polycomb repressive complex 2 (PRC2; Seong et al., 2010). The polyglutamine region augments PRC2 stimulation and hence H3 trimethylation on specific promoters, including Hoxb9. In general, the DNA/RNA binding agents anthracyclines are thought to provide a significant therapeutic potential by correcting the pathological nucleosome changes and realigning transcription. Two such agents, chromomycin and mimethramycin, were found to improve altered nucleosomal homeostasis, and by virtue of normalizing the shift in the balance between methylation and acetylation in HD mice, could alter a subset of down-regulated genes accompanied by a significant improvement of the behavioral and neuropathological phenotype observed in HD mice (Stack et al., 2007).

The transcriptional co-repressor transglutaminase 2 (TG2), which is up-regulated in HD, interacts physically with Histone H3 and could contribute to gene silencing via hyperpolyamination of histone tails (McConoughey et al., 2010). The inhibition of TG2 increases PGC-1α expression, but also that of 40% of genes that are dysregulated (Karpuj et al., 1999; Lesort et al., 1999) in HD striatal neurons. Histone H2A ubiquitylation is increased in R6/2 HD mice and the association of ubiquitylated H2A with the promoters of down-regulated genes is increased in an in vitro model of HD (Kim et al., 2008). This transcriptional repression is rescued by restoration of the ubiquitylated H2A level. In addition, histone H2B ubiquitylation is decreased in R6/2 HD mice and association of ubiquitylated H2B with promoters positively correlates with transcriptional level in R6/2 mice. This transcriptional modulation by H2 ubiquitylation is thought to occur through a subsequent interference with methylation of histone H3 (Kim et al., 2008).

Histone H3 phosphorylation is also critical to induce the nucleosomal response and gene transcription at some promoters. MSK-1 is critically involved in Histone H3 phosphorylation in the striatum (Brami-Cherrier et al., 2005, 2009). It is deficient in the striatum of R6/2 mice and postmortem caudate of HD patients (Roze et al., 2008). Restoring MSK-1 expression and subsequent striatal H3 phosphorylation in an in vitro model of HD protects against neuronal alteration induced by the Exp-HTT including neuritic retraction, aggregate formation, and neuronal death (Roze et al., 2008). In vivo, in a rat model of HD based on striatal lentiviral expression of Exp-HTT, overexpression of MSK-1 induced hyperphosphorylation of H3 and CREB, along with an overexpression of PGC-1α (Martin et al., 2011). Similarly to PGC-1α, MSK-1 protects from Exp-HTT-induced striatal dysfunctions, including DARPP-32 down-regulation and neuronal death. Furthermore MSK-1 knock-out mice are more susceptible to 3-NP-induced striatal lesion, and aging MSK-1 knock-out mice show spontaneous striatal degeneration (Martin et al., 2011).

CONCLUSION

The regulation of neuronal death has been intensely investigated and, due to its paramount implications for neurodegenerative disease, has sparked one of the most prolific research fields in the past decades. In particular, basic research has provided novel insights into the molecular machinery of neuronal signaling, and how it mediates neuronal dysfunction and death in progressive neurodegenerative diseases. HD involves a complex pathological cascade with multiple deleterious mechanisms, affecting predominantly the striatal neurons. This striatal vulnerability to HD-induced neuronal dysfunction reflects both the particular characteristics of striatal neurons (cell-autonomous alterations) and their location within the functional neuronal networks (non-cell-autonomous alterations). The various pathological events are not proceeding in succession but instead take place in parallel with continuous reciprocal interactions. This parallel and interactive nature should be taken into account for both the general understanding of the HD-related neurodegeneration and any therapeutic approach.

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