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The Corticostriatal Pathway in Huntington's Disease

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Abstract

The corticostriatal pathway provides most of the excitatory glutamatergic input into the striatum and it plays an important role in the development of the phenotype of Huntington's disease (HD). This review summarizes results obtained from genetic HD mouse models concerning various alterations in this pathway. Evidence indicates that dysfunctions of striatal circuits and cortical neurons that make up the corticostriatal pathway occur during the development of the HD phenotype, well before there is significant neuronal cell loss. Morphological changes in the striatum are probably primed initially by alterations in the intrinsic functional properties of striatal medium-sized spiny neurons. Some of these alterations, including increased sensitivity of N-methyl-D-aspartate receptors in subpopulations of neurons, might be constitutively present but ultimately require abnormalities in the corticostriatal inputs for the phenotype to be expressed. Dysfunctions of the corticostriatal pathway are complex and there are multiple changes as demonstrated by significant age-related transient and more chronic interactions with the disease state. There also is growing evidence for changes in cortical microcircuits that interact to induce dysfunctions of the corticostriatal pathway. The conclusions of this review emphasize, first, the general role of neuronal circuits in the expression of the HD phenotype and, second, that both cortical and striatal circuits must be included in attempts to establish a framework for more rational therapeutic strategies in HD. Finally, as changes in cortical and striatal circuitry are complex and in some cases biphasic, therapeutic interventions should be regionally specific and take into account the temporal progression of the phenotype.

Keywords

Cortex; striatum; electrophysiology; mouse models; glutamate; pathway

1. Introduction

Huntington's disease (HD) is a genetic and progressive neurological disorder that is inherited in an autosomal, dominant fashion. The symptoms of HD include abnormal dance-like movements (chorea), cognitive disturbances, and disorders of mood, particularly depression which often precedes the onset of the motor abnormalities (Harper, 1996). The HD gene (IT15) is located on the short arm of chromosome 4 and contains an expansion in the normal number of CAG (glutamine) repeats (generally >40) (Huntington's Disease Collaborative Research Group, 1993). HD is typically a late onset disease although juvenile variants occur, usually when more CAG repeats are present. In young children with HD, the symptoms almost

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invariably include epileptic seizures (Gencik et al., 2002;Rasmussen et al., 2000). Neuropathologically, HD is primarily characterized by neuronal loss in striatum and cortex (for review see Vonsattel and DiFiglia, 1998). In the striatum, medium-sized spiny neurons (MSSNs) are most affected and degeneration of these neurons occurs progressively (Vonsattel et al., 1985). In addition, there is a gradient of striatal pathology progressing in a dorsolateral to ventral direction and another in a caudo-rostral direction (Vonsattel et al., 1985). Although it has been generally believed that the progression of symptoms in the disorder is due to the neurodegeneration, it has become apparent more recently that severe neuronal dysfunction precedes degeneration and is probably the major cause of many symptoms (Levine et al., 2004).

The protein coded by the HD gene (huntingtin) is a large protein (~350 kDa) that is highly conserved and expressed ubiquitously throughout the body (Strong et al., 1993). In the brain, it is predominantly found in neurons (Landwehrmeyer et al., 1995a) and although recent studies have provided important clues, its exact function still remains a mystery (Young, 2003). However, huntingtin is essential for embryogenesis and normal development, and the loss of normal huntingtin function may contribute to the pathogenesis of HD (reviewed in Cattaneo et al., 2001). Increasing normal huntingtin expression improves neuronal survival and attenuates the effects of the mutant protein (Cattaneo et al., 2005). Huntingtin is a cytoplasmic protein closely associated with vesicle membranes and microtubules, suggesting it may have a role in vesicle trafficking, exocytosis and endocytosis (DiFiglia et al., 1995). In addition, its distribution is very similar to that of synaptophysin (Wood et al., 1996) and it has been shown to associate with various proteins involved in synaptic function. Thus, it is probable that mutant huntingtin causes abnormal synaptic transmission in HD (Li et al., 2003;Smith et al., 2005a).

The mechanism by which mutant huntingtin causes dysfunction and ultimate degeneration of neurons is unknown. One possibility is that proteins with more than 40 glutamine residues precipitate as insoluble fibers (Perutz, 1999), allowing the formation of protein aggregates. Aggregates of mutant huntingtin localize in the nucleus and dystrophic neurites and may be part of the pathogenic mechanisms in HD (DiFiglia et al., 1997). Neuropil aggregates appear to be more common than nuclear aggregates and are more prevalent in cortex than in striatum (Gutekunst et al., 1999). Electron microscopic studies reveal many neuropil aggregates in axon terminals, which are co-localized with synaptic vesicles suggesting they may affect synaptic transmission (Li et al., 1999). However, recent evidence has questioned whether these aggregates are the cause of neuronal dysfunction and degeneration. Instead, they could represent a compensatory process to aid in neuronal survival (Slow et al., 2006).

There are several important unresolved questions concerning the progressive neuronal dysfunction in HD. One is, “What is the sequence of events that leads to neuronal dysfunction and ultimate cell death?” Another is, “Why is there selective vulnerability of specific neuronal types within the striatum?” Although the disease affects primarily MSSNs, a puzzling feature of HD is that MSSNs that project to the globus pallidus [these neurons are enkephalin-positive and are the source of the indirect striatal output pathway (Albin et al., 1989)] appear to be affected earlier than those that project to the substantia nigra [these neurons are substance P-positive and are the source of the direct striatal output pathway (Albin et al., 1989)] (Richfield et al., 1995;Sapp et al., 1995). In other words, MSSNs that originate the indirect pathway are more sensitive to the mutation than cells of the direct pathway.

With regard to the question of the sequence of events that lead to neuronal dysfunction and cell death, there either could be a single event that triggers a cascade of cellular alterations, similar to a chain reaction, or independent alterations may occur simultaneously or progressively in different neuronal systems. The idea that the initial and principal instigators of striatal dysfunction are not intrinsic to the striatum is not new. There is considerable evidence

that the earliest manifestations of HD are the emotional and cognitive disturbances. It is thus possible that areas related to these early alterations, such as the limbic system, the cerebral cortex or even the hypothalamus (Petersén et al., 2005) are the initial triggers of changes in motor functions ultimately mediated via the striatum. In fact, it has been speculated that cortical changes are fundamental to the onset and progression of the HD phenotype in humans and in mouse models (Laforet et al., 2001).

Because the key neuronal structures that display dysfunction and ultimate degeneration in HD are interconnected via long circuit loops (corticostriatal connections, striatal outputs to globus pallidus and substantia nigra, substantia nigra and globus pallidus projections to thalamus and thalamic projections back to the cortex), there are many synaptic interactions that can contribute to the functional alterations observed in HD. Ever since the pioneering studies by Wong et al. (1982) demonstrating perturbations in the synthesis of glutamate by corticostriatal neurons in HD, investigations of this pathway have been at the core of multiple attempts to understand the mechanisms of HD pathology. The remainder of this review primarily will concentrate on the electrophysiological changes that have been observed in MSSNs, cortical neurons, and in the corticostriatal pathway. We will also concentrate on findings obtained from genetic mouse models as they represent the best approach at the present time to unraveling the sequence of changes and determining why certain types of neurons may be more affected by the HD mutation.

2. Genetic mouse models of HD

The generation of genetic mouse models of HD has helped to understand the dysfunctions underlying behavioral phenotypes, neuronal abnormalities and neurodegeneration. A great advantage of these models, compared to the more classic excitotoxic models of HD, is that they allow examination of the evolution of the disease and the discovery of cause-effect relationships. Because a detailed description of these models is not the primary objective of the present article, we remit the reader to consult other recent reviews (Brouillet et al., 1999;Bates and Murphy, 2002;Hickey and Chesselet, 2003;Levine et al., 2004;Menalled and Chesselet, 2002;Rubinsztein, 2002).

At present, a number of transgenic, knock-in, and conditional mouse models have been developed and the electrophysiological and morphological cellular alterations have been extensively examined. We have primarily utilized transgenic animal models, including the R6/1 and R6/2 (Mangiarini et al., 1996), YAC72 and 128 (Hodgson et al., 1999;Slow et al., 2003), the Tg100 (Laforet et al., 2001), as well as several knock-in models, CAG71 and CAG94 (Levine et al., 1999).

One of the most studied models is the R6 line of transgenic mice (Mangiarini et al., 1996). In particular, R6/2 mice, with ~150 CAG repeats, manifest a very aggressive form of HD, somewhat similar to the juvenile variant. Transgenic animals display overt behavioral symptoms as early as 4–5 weeks of age and die of unknown causes at about 15 weeks. Affected animals display a number of alterations including the formation of neuronal intranuclear inclusions (Davies et al., 1997), changes in neurotransmitter receptor expression (Ariano et al., 2002;Cha et al., 1998), and altered signaling mechanisms (Bibb et al., 2000;Luthi-Carter et al., 2000;Menalled et al., 2000). There are also metabolic deficits in transgenic animals (Higgins et al., 1999;Tabrizi et al., 2000). These alterations are correlated with characteristic motor (Carter et al., 1999) and learning deficits (Lione et al., 1999;Murphy et al., 2000). R6/1 mice display a similar phenotype, but in a much more protracted form. Another model, Tg100, expresses the N-terminal one-third of huntingtin with normal (18) or expanded (100) glutamine repeats. These transgenic mice exhibit motor deficits beginning at 3 months and progress with

increasing age. Nuclear inclusions precede the onset of the phenotype, whereas pathological cortical changes predict the onset and severity of behavioral deficits (Laforet et al., 2001).

Other widely used transgenic mice were generated using yeast artificial chromosomes (YAC) expressing normal (YAC18) and mutant (YAC46 and YAC72) huntingtin (Hodgson et al., 1999). These mice show behavioral changes around 7 months of age, as well as selective degeneration of MSSNs in the lateral striatum by 12 months of age. Neurodegeneration can be present in the absence of aggregates in YAC mice, showing that they are not essential to initiation of neuronal death (Hodgson et al., 1999). YAC128 mice display similar but more severe alterations which occur earlier than in YAC72 mice (Slow et al., 2003).

Knock-in models have also emerged as a major contributor to our understanding of HD. Several models that differ mainly in the number of CAG repeats (from 48 to 150) have been generated (Levine et al., 1999;Lin et al., 2001;Shelbourne, et al., 1999;Wheeler et al., 2000;White et al., 1997). Although in knock-in mice overt behavioral changes are subtle, more sensitive and careful testing demonstrated behavioral abnormalities as early as 1–2 months of age (Menalled et al., 2002;2003). Further, a consistent feature in several models of knock-in mice is the presence of nuclear staining and microaggregates at 2–6 months, which is relatively early in the course of the disease. By contrast, nuclear inclusions are only observed when the mice are older (10–18 months, depending on the model), and extensive cell death has not yet been reported (Menalled and Chesselet, 2002).

Conditional mouse models of HD have also been generated. One model expresses exon 1 with 94 CAG repeats in a tetracycline-regulated manner (Yamamoto et al., 2000). These mice develop progressive motor decline and striatal atrophy in the absence of striatal neuronal loss up to 10 months of age, although cell loss occurs in older mice (Diaz-Hernandez et al., 2005). Abolishing transgene expression in symptomatic mice leads to the disappearance of inclusions and amelioration of the behavioral phenotype, even in mice presenting with striatal cell loss (Diaz-Hernandez et al., 2005;Yamamoto et al., 2000). More recently, Cre/LoxP conditional HD mice expressing mutant huntingtin with 103 glutamine repeats, either in all neurons of the brain or restricted to the vulnerable cortical pyramidal neurons, have been generated (Gu et al., 2005). Interestingly, in these models huntingtin aggregation was shown to be a cell-autonomous process, whereas motor deficits and cortical neuropathology were observed only when mutant huntingtin expression occurred in multiple neuronal types, including cortical interneurons, but not when it was restricted to cortical pyramidal neurons (Gu et al., 2005).

3. The corticostriatal pathway and its target neurons in the striatum

3.1 Cell types in the striatum and their vulnerability in HD

The striatum is the main input compartment of the basal ganglia. It receives massive glutamatergic and dopaminergic innervations. The excitatory glutamatergic input derives mainly from all regions of the cerebral cortex as well as specific thalamic nuclei (Fonnum et al., 1981;Jones, 1987). The dopaminergic input comes from the pars compacta of the substantia nigra (Carlsson et al., 1962). These inputs interact on MSSNs (Smith and Bolam, 1990). The mode of interaction between dopamine and glutamate has been an area of controversy, but it is generally believed that dopaminergic inputs modify the excitatory responses induced by glutamate (Cepeda and Levine, 1998;2006).

The ubiquitous MSSNs, comprising more than 90% of the striatal cell population, are projection neurons (Kemp and Powell, 1971) and, although all MSSNs are GABAergic, they differ in a number of properties including the expression of dopamine and acetylcholine receptor subtypes, peptide content, and their projection targets (Gerfen, 1992). Two major neuronal subpopulations of MSSNs have been described, the direct pathway that projects to

the substantia nigra pars reticulata and the internal segment of the globus pallidus (entopeduncular nucleus in rodents), and the indirect pathway that projects to the external segment of the globus pallidus (Smith et al., 1998). MSSNs at the origin of the direct pathway mainly express dopamine D1 and muscarinic M4 receptors, and colocalize substance P, whereas MSSNs of the indirect pathway mainly express dopamine D2 receptors and colocalize enkephalin, although some overlap exists (Aizman et al., 2000;Surmeier et al., 1996). Recent evidence supports differential cortical innervation of these subpopulations of MSSNs (Lei et al., 2004) which may be important in the development of symptoms in HD as the enkephalin-containing neurons of this pathway seem to be affected earlier (Richfield et al., 1995;Sapp et al., 1995).

In addition to MSSNs there are multiple classes of interneurons in the striatum. At least four classes of interneurons have been recognized: cholinergic, fast-spiking GABAergic, nitric oxide synthase-positive and calretinin-positive interneurons (Kawaguchi et al., 1995). Fast spiking interneurons receive direct inputs from the cerebral cortex and synapse onto MSSNs (Bennett and Bolam, 1994;Plotkin et al., 2005). Interneurons appear to be less affected in HD than projection MSSNs. Unfortunately, striatal interneurons have not been extensively studied as yet in mouse models. However, even though striatal interneurons are spared in the disease, they also could become dysfunctional and play a role in the HD phenotype (Picconi et al., 2006). For example, immunohistochemical evidence in humans indicates that the number of medium-sized calretinin-positive interneurons is selectively increased in HD (Cicchetti and Parent, 1996).

3.2 The gatekeepers of glutamate release in the corticostriatal pathway

Striatal cells, particularly the MSSNs and to a lesser extent interneurons, are constantly bombarded by excitatory cortical inputs. In fact, MSSNs remain hyperpolarized and silent (down state), unless synchronous cortical inputs induce a membrane depolarization (up state) (Wilson and Kawaguchi, 1996). Continuous exposure to glutamate inputs could make MSSNs particularly vulnerable to excitotoxic damage. For example, depolarization is critical for removal of the Mg^{2+} block of NMDA receptor-channels, which when open are generally believed to induce excitotoxicity. However, intrinsic conductances and presynaptic regulation of glutamate inputs can contribute to prevent excessive activation of MSSNs. First, inwardly rectifying K^+ conductances keep the membrane hyperpolarized and reduce input resistance and time constant, thereby effectively limiting the efficacy of glutamatergic synaptic inputs (Nisenbaum and Wilson, 1995). Second, a number of receptors strategically placed on the corticostriatal terminals exert presynaptic regulation of glutamate release. These include dopamine D2, group II metabotropic glutamate ($mGluR_2$ and $mGluR_3$), $GABA_B$, cannabinoid (CB_1) and adenosine (A_1) receptors (Calabresi et al., 1990;Cepeda et al., 2001b;Flores-Hernandez et al., 1997;Gerdeman and Lovinger, 2001;Hsu et al., 1995;Huang et al., 2001;Lovinger and Choi, 1995;Lovinger and McCool, 1995;Lovinger et al., 1993;Malenka and Kocsis, 1988;Nisenbaum et al., 1992). Alterations in the expression or function of these receptors could contribute to the dysfunction in HD, as unregulated release of glutamate would jeopardize the integrity of MSSNs, the main recipients of cortical inputs. In fact, the earliest behavioral manifestations of HD in mice coincide with reduced expression of striatal dopamine D2, mGlu and CB_1 receptors (Ariano et al., 2002;Cha, et al., 1998;Luthi-Carter et al., 2000). The mechanisms underlying receptor regulation of glutamate release are complex and in some cases controversial. Regardless of the mechanisms of presynaptic modulation of glutamate release, what is relevant in the present context is that functional alterations in cortical pyramidal neurons or in the receptor expression on presynaptic endings of the corticostriatal pathway, the gatekeepers of striatal excitation, could play an important role in HD neuropathology. The major issue then becomes what are the potential consequences of dysregulation of glutamate release along the corticostriatal pathway in HD?

4. Electrophysiology and morphology of the striatum and cortex in mouse models of HD

4.1 Morphology in striatum and cortex

Electrophysiological alterations in the corticostriatal pathway are likely to produce morphological changes in postsynaptic neurons as a consequence of dysregulation of glutamate release. Neuronal death is not prominent in most HD mouse models, although it does occur. It is a late event that seems dependent on which transgenic or knock-in model is examined. In the R6 line neuronal loss is modest and occurs very late in the life of the animal (Turmaine et al., 2000). However, we have observed early and significant changes in striatal somato-dendritic morphology that would indicate dysfunctional neurons and synaptic connections (Klapstein et al., 2001;Levine et al., 1999). Somatic areas and dendritic fields are reduced. Recurving dendrites are apparent in striatal neurons, similar to those found in HD patients (Graveland et al., 1985). Loss of spines may be an early morphological change. Alterations in cortical pyramidal neurons also occur (Klapstein et al., 2001;Laforet et al., 2001). In symptomatic R6/1 mice there is a decrease in dendritic spine density and dendritic spine length in striatal MSSNs and cortical pyramidal neurons (Spires et al., 2004). HD also causes a specific reduction in the proportion of bifurcated dendritic spines on basal dendrites of cortical pyramidal neurons. Decreases in the number of dendritic spines on MSSNs will disrupt corticostriatal networks and spine decreases on cortical pyramidal neurons will lead to cortical information processing abnormalities. In contrast to the R6 line, the YAC72 and YAC128 models display selective degeneration of MSSNs in the lateral striatum after several months of age (Hodgson et al., 1999;Slow et al., 2003). In another full-length transgenic mouse model with 48 or 89 CAG repeats, a decrease in the number of dendritic spines occurred without significant cell loss (Guidetti et al., 2001).

Other cortical changes also are apparent. There is clear evidence for a progressive thinning of the cortical ribbon and pyramidal neuron loss in HD patients (Cudkowicz and Kowall, 1990;de la Monte et al., 1988;Halliday et al., 1998;Hedreen et al., 1991;MacDonald and Halliday, 2002;Rosas et al., 2002;Sotrel et al., 1991). Early degeneration of the corticostriatal pathway may occur in conjunction with the accumulation of mutant huntingtin in axonal swellings in striatal neuropil and in the cytoplasm of cortical neurons (MacDonald and Halliday, 2002;Sapp et al., 1999). These changes in cortical projection neurons may lead to alterations in synaptic function and receptor responsiveness. For example, huntingtin alters axonal transport and the mutated form disrupts neurotransmitter release which will affect neuronal circuitry (Li et al., 1998;Li et al., 2003).

The alterations in cortical pyramidal neurons may not be primary nor sufficient to cause the HD phenotype. The question then becomes, which mechanism can better explain HD neuropathology? Is neuronal dysfunction and degeneration caused by cell-autonomous toxicity of mutant huntingtin (cell-autonomy model) or by altered cellular interactions (cell-cell interation model)? As exemplified in a conditional model of HD, neuropathology in different areas seems to occur only when mutant huntingtin is widely expressed in the brain, supporting the cell-cell interaction, not the cell-autonomy, model for cortical and striatal pathogenesis (Gu et al., 2005).

4.2 Electrophysiology in cortex

In the same conditional model electrophysiological studies showed a reduction of GABAergic inhibitory input onto cortical pyramidal cells only in mice expressing mutant huntingtin widely in the brain, but not when it was restricted to the cortical pyramidal neurons alone (Gu et al., 2005). This is significant because some models of HD display spontaneous epileptic seizures and/or have a reduced epileptic threshold after systemic injection of $GABA_A$ receptor

antagonists bicuculline or picrotoxin (Cummings et al., 2006b;Uzgil et al., 2004). This implies that cortical hyperexcitability due to impaired inhibition could be an early event in HD. Other types of cortical abnormalities occur in R6/2 mice and these may underlie changes in information processing. We have shown that currents induced by glutamate receptor agonists are decreased in isolated cortical pyramidal neurons from R6/2 mice, possibly contributing to changes in cortical integration and output that underlie the cognitive and motor impairments in this animal model of HD (André et al., 2006). Interestingly, high voltage-activated (HVA) Ca^{2+} currents in cortical pyramidal neurons are increased in symptomatic mice, suggesting complex changes that may effectively increase excitability altering corticostriatal function (André et al., 2006;Cherry et al., 2002). Electrophysiological alterations also occur in the striatum and at similar time points. Thus, we do not know if changes occur first in cortex or striatum or if they occur simultaneously.

4.3 Passive and active cellular membrane properties in striatum

One of the earliest and most consistent alterations in the basic membrane properties of MSSNs in the R6/2 transgenic mouse model is an increase in input resistance. This increase probably reflects loss of conductive membrane channels due to morphological changes such as reduced membrane area possibly as a consequence of the loss of spines. Consistent with this observation, cell capacitance is significantly reduced in symptomatic animals (Cepeda et al., 2001a;Klapstein et al., 2001;Levine et al., 1999). The increase in membrane input resistance could also be due to alterations in the number and/or properties of K^+ channels. This possibility is supported by gene expression studies showing decreases in inwardly rectifying K^+ channels and the β1 subunit of the K^+ channel (Luthi-Carter et al., 2000). Furthermore, in R6/2 and Tg100 transgenic mice, membrane expression of proteins responsible for inwardly and outwardly rectifying K^+ currents is diminished in striatal projection neurons (Kir2.1 and Kir2.3 for inward and Kv2.1 for outward rectification) (Ariano et al., 2005a,b). As a consequence, many MSSNs have a depolarized resting membrane potential (Klapstein et al., 2001;Levine et al., 1999) and are less able to repolarize (Ariano et al., 2005a). These alterations are particularly relevant because membrane depolarization can remove the Mg^{2+} block of the NMDA receptor causing neurons to become more depolarized when glutamatergic inputs are activated and they will stay in a depolarized state for longer periods of time.

Other voltage-gated conductances may also be affected as alterations in firing patterns occur in some striatal cells from symptomatic R6/2 mice (Klapstein et al., 2001). For example, there is a reduction in HVA Ca^{2+} conductances (Bibb et al., 2000;Cepeda et al., 2001a;Starling et al., 2005). This effect appears to occur after 7 weeks of age in the R6/2 transgenics, and is also likely to affect the firing patterns of MSSNs. In recent preliminary experiments we have also observed an increase in voltage-gated Ca^{2+} conductances in MSSNs from younger (3–6 weeks of age) R6/2 mice (Plotkin and Levine, 2006;Starling et al., 2005). This, in conjunction with other changes in membrane properties, could explain increased spontaneous firing rates in some striatal neurons from R6/2 mice at 6–9 weeks of age, an effect that is reversed by repeated ascorbate treatment (Rebec et al., 2006). Therefore, the changes in Ca^{2+} conductances may be biphasic and region specific. This could mean that the effects of mutant huntingtin on some voltage-gated currents in MSSNs are not unidirectional and can change over time, either as a consequence of the natural evolution of the disease or as a compensatory mechanism.

Taken together the complex set of alterations in voltage-gated conductances of MSSNs will produce dysfunctional cells that have altered responses to inputs. Early increases in Ca^{2+} conductances will predispose cells to more easily become depolarized while subsequent decreases might be protective. Early increases in input resistance will decrease electrotonic decay of conductances allowing peripheral inputs to depolarize over longer distances while specific changes in K^+ channel function can also predispose neurons to remain depolarized

and more excitable. In particular, decreased inward rectification could amplify excitatory inputs. These postsynaptic changes in voltage-gated currents stress the level of complexity of events when trying to determine if striatal neuron pathology is a primary effect or the consequence of alterations in other brain regions. They also emphasize that striatal MSSNs are dysfunctional and may be primed to be affected by abnormal cortical inputs.

4.4 Glutamate receptors

The main hypothesis underlying striatal neurodegeneration in HD has been excitotoxicity (DiFiglia, 1990). This hypothesis emanated from many studies demonstrating parallels in the effects of excitotoxic or chemical lesions of the striatum with those observed in HD in patients. In general, excitoxicty can result from a number of changes, either together or in isolation. These include an increase in release of excitatory neurotransmitters like glutamate, and an increase in responsiveness of glutamate receptors either due to an increase in receptor density or number or a change in receptor composition or their signaling properties. Since NMDA receptors are intimately associated with excitoxicity, they were one of the first glutamate receptors studied in mouse models of HD.

In all models of HD examined thus far we and others have found that many MSSNs are more sensitive to exogenous application of NMDA. We first examined NMDA-induced cell swelling in the R6/2 and two knock-in mouse models of HD, CAG71 and CAG94 (Levine et al., 1999). There was an overall increase in cell swelling in transgenic and CAG94 mice compared to controls indicating cells from these HD models are more sensitive to NMDA. Interestingly, the increase in sensitivity was limited to NMDA receptors, as sensitivity to kainate was not affected. Electrophysiological and Ca^{2+} imaging studies supported these observations (Cepeda et al., 2001a). A subpopulation of cells from transgenic animals (R6/2, YAC72 and Tg100) displayed larger NMDA currents and NMDA-induced Ca^{2+} influx than cells from littermate controls, whereas the remainder of cells displayed normal responses (Cepeda et al., 2001a;Laforet et al., 2001). The more sensitive cells could correspond to the enkephalin-containing MSSNs that are more affected in HD. Similar increases in NMDA receptor sensitivity have been observed in the YAC72 model (Zeron et al., 2002). Interestingly, acute treatment with succinate dehydrogenase inhibitors (e.g., 3-nitropropionic acid, 3-NP) augments NMDA receptor-mediated corticostriatal excitation in striatal MSSNs (Centonze et al., 2001).

Cells from transgenic animals also displayed reduced NMDA receptor Mg^{2+} sensitivity (Cepeda et al., 2001a). Changes in Mg^{2+} sensitivity occur very early in R6/2 mice. In dissociated striatal neurons a group of cells from transgenic mice displayed increased responses to NMDA and decreased Mg^{2+} sensitivity as early as 15 days of age, suggesting the presence of constitutively abnormal NMDA receptors (Starling et al., 2005). Early changes in NMDA receptor sensitivity were also found in the YAC72 mouse model, supporting the presence of constitutively abnormal NMDA receptors (Zeron et al., 2002). Further, increased sensitivity was specific for this type of receptor as the sensitivity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors was unchanged (Zeron et al., 2002). This agrees with the observation that cell swelling is not differentially affected by non-NMDA receptor activation in control and symptomatic HD mice (Levine et al., 1999). However, in a more detailed study on the evolution of changes in postsynaptic sensitivity of AMPA receptors in dissociated MSSNs from R6/2 mice, we have shown a delayed developmental reduction in AMPA current amplitude. Whereas in control mice AMPA current amplitude decreases from 21 to 40 days, in transgenic animals AMPA current amplitude remains high and does not decrease until later, during the symptomatic stage, when the amplitude becomes similar in transgenic and control mice (Joshi et al., 2006). These results suggest that abnormal AMPA

receptor function in striatal MSSNs occurs in pre-symptomatic and early symptomatic phases in the R6/2 mouse model.

The mechanism that causes increases in NMDA receptor sensitivity in HD remains unknown. One explanation is that huntingtin with expanded polyQ tracts interferes with the binding of PSD95, a scaffolding protein found at the postsynaptic density, to the NR2 NMDA and GluR6 kainate receptor subunits, causing both receptors to become hypersensitive to glutamate (Sun et al., 2001). Another possible explanation is that there is a change in the subunit composition of NMDA receptors. Increased responsiveness to NMDA correlates with an increase of NR1 subunit protein expression and reduced NR2A/B protein expression (Ariano et al., 2005b;Cepeda et al., 2001a). We used single cell RT-PCR to demonstrate further that in the R6/2 transgenic there was an early decrease in the number of MSSNs expressing mRNA for the NR2A receptor subunit (Ali and Levine, 2006), providing evidence that different types of NMDA receptors are expressed in mutant mice. This decrease in NR2A expression would thus cause NMDA receptors to express the NR2B subunit more exclusively. A similar conclusion has been reached for the YAC72 and YAC128 mouse models of HD (Li et al., 2003; 2004;Shehadeh et al., 2006).

4.5 Synaptic responses

Mutant huntingtin has been shown to impair directly the cellular machinery involved in synaptic transmission. Proteins involved in the control of neurotransmitter release such as complexin II, synaptobrevin and synapsin I are affected early (Liévens et al., 2002;Morton and Edwardson, 2001;Morton et al., 2001). Rabphilin 3A, another protein involved in exocytosis, is also substantially decreased in synapses of most brain regions in R6/1 mice. This reduction coincides with the onset of behavioral deficits and may be the cause of impaired synaptic transmission in these mice (Smith et al., 2005). Recent studies have demonstrated an important role for huntingtin and its N-terminal fragments in the uncoupling of syntaxin 1A (another protein that plays an essential role in synaptic transmission) with the N-type Ca^{2+} channel (Swayne et al., 2005). Huntingtin and its fragments influence synaptic transmission by enhancing Ca^{2+} influx and uncoupling the exocytotic machinery from the N-type Ca^{2+} channel (Swayne et al., 2005). Alterations in cross-talk between these two essential proteins have the potential of playing a crucial role in synaptic perturbations in HD.

In the corticostriatal pathway, cellular pathology caused by mutant huntingtin in the presynaptic terminals might result in an increased release of glutamate. Alternatively, impaired clearance of glutamate from the synaptic cleft might increase glutamatergic neurotransmission. In both cases, striatal excitotoxicity could occur (Beal et al., 1986;Zeron et al., 2002). Intracerebral microdialysis has shown that depolarizing concentrations of potassium chloride increase the extracellular concentrations of glutamate substantially more in R6/1 mice than in wildtype mice (NicNiocaill et al., 2001). In addition, the glial glutamate transporter (GLT-1) is downregulated in R6/2 mice before any evidence of neurodegeneration (Liévens et al., 2001). This indicates that there is an impairment in glutamate transport and glutamate–glutamine cycling, and suggests that a defect in astrocytic glutamate uptake could contribute to the phenotype and to neuronal cell dysfunction in HD. Finally, mutant huntingtin binds to synaptic vesicles with a higher affinity than does the wildtype form and inhibits the uptake of glutamate into synaptic vesicles in a dose-dependent manner (Li et al., 2000). These alterations combined could lead to increased glutamate in and around the synaptic cleft.

4.5.1 Evoked synaptic responses—One of the first indications of electrophysiological changes in the corticostriatal pathway was the observation that the stimulus intensity necessary to evoke an excitatory postsynaptic potential (EPSP) in MSSNs was significantly increased in symptomatic R6/2 and Tg100 transgenic mice (Klapstein et al., 2001;Laforet et al., 2001). A

similar trend occurred in YAC72 mice, although the effect was much smaller. Another important observation was that symptomatic R6/2 transgenics displayed slower rise and incomplete decay of the EPSP. This phenomenon was hypothesized to indicate a larger contribution of a slower kinetic current, such as the one mediated by activation of NMDA receptors. This idea is supported by the observation of enhanced NMDA responses associated with increased NR1 subunit expression (Levine et al. 1999;Cepeda et al. 2001a). In addition, synaptic responses mediated by activation of NMDA receptors are enhanced in R6/2 mice at 40 days of age, when overt symptoms are just beginning to occur (Wu et al., 2004).

In other mouse models similar and specific enhancement of synaptic responses mediated by activation of NMDA receptors has been found. For example, in YAC72 mice a larger NMDA to AMPA receptor-mediated current ratio occurs (Li et al., 2003) and may be caused by increased surface expression of NMDA receptors containing the NR2B subunit (Li et al., 2004). Recently, we recorded evoked synaptic responses in MSSNs from YAC128 mice. These mice are similar to the YAC72 model but the phenotypic changes occur earlier and are more dramatic (Slow et al., 2003). Interestingly, the synaptic alterations were age-dependent. At 40 days mean peak AMPA and NMDA receptor-mediated current amplitudes were significantly increased in YAC128 compared to wildtype mice. In contrast, at 7 months, mean peak amplitudes of AMPA and NMDA responses were smaller in YAC128 than in wildtype mice (Levine et al., 2005). These findings are consistent with the biphasic motor phenotype observed in YAC128 mice, hyperactivity followed by hypoactivity. These results emphasize that synaptic alterations in some HD mouse models are not static but change with disease progression and that different models may display contrasting alterations in synaptic responses.

4.5.2 Spontaneous excitatory postsynaptic currents—In addition to alterations in evoked synaptic responses, we demonstrated both transient and progressive changes in spontaneous synaptic currents in transgenic R6/2 mice (Cepeda et al., 2003). Spontaneous excitatory postsynaptic currents showed a progressive reduction in frequency that became more evident as the neurological phenotype advanced. We interpreted these effects as a progressive disconnection between the striatum and its cortical inputs. Reduced glutamatergic synaptic currents were correlated with a marked reduction in the expression of synaptic marker proteins synaptophysin and PSD95 (Cepeda et al., 2003). This could be associated with the loss of dendritic spines.

In R6/2 animals there was also a transient expression of complex, large amplitude (>100 pA) synaptic currents at 5–7 weeks of age that coincided with the onset of behavioral symptoms (Cepeda et al., 2003). We hypothesized that these large currents reflect dysregulation of glutamate release and/or an increase in cortical synchronization. Dysregulation of glutamate release can also be contributed by increased HVA Ca^{2+} currents in cortical pyramidal neurons (André et al., 2006;Cherry et al., 2002). The fact that R6 mice often develop epileptic seizures implies that the cortex in these HD mice becomes hyperexcitable. Interestingly, synchronous cortical input, similar to that produced by local application of picrotoxin in the cortex, appears to target enkephalin-positive neurons preferentially (Berretta et al., 1997). These neurons are more vulnerable in HD (Mitchell et al., 1999;Richfield et al., 1995;Sapp et al., 1995) and enkephalin expression seems to depend on intact cortical inputs (Uhl et al., 1988). In addition, alterations in the function or density of presynaptic D2, mGluR, endocannabinoid, and adenosine receptors regulating glutamate release could contribute to the occurrence of large synaptic events (Ariano et al 2002;Cha et al., 1998). Finally, postsynaptic AMPA receptor dysfunction in R6/2 mice (Joshi et al., 2006), in conjunction with transient increases in HVA Ca^{2+} currents in MSSNs (Plotkin and Levine, 2006;Starling et al., 2005), could also favor the occurrence of large synaptic events.

Our hypothesis that, concomitant to the transient dysregulation of glutamate release, there is a progressive disconnection between cortex and striatum in R6/2 transgenics has important implications. First, it casts doubts on the belief that chronic excess glutamate release is the sole mechanism underlying striatal cell death. Indeed, release studies have been inconclusive. Either no change or a reduction of glutamate in the striatum has been observed (Behrens et al., 2002;Liévens et al., 2001;NicNiocaill et al., 2001). Second, the progressive disconnection between MSSNs and their cortical inputs may deprive these cells of important trophic factors necessary for normal function such as brain derived neurotrophic factor [BDNF (Zuccato et al., 2001)].

This progressive disconnection could help explain the surprising and seemingly paradoxical observation that, in some mouse models of HD, striatal lesions produced by injections of quinolinic acid or kainate are dramatically reduced compared to control animals (Hansson et al., 1999;Morton and Leavens, 2000). Reduced receptor sensitivity to these excitatory amino acid receptor agonists can be ruled out because immediate early gene responses do not appear impaired, suggesting that resistance may be conferred by other processes further along the toxic cascade (MacGibbon et al., 2002). We have proposed that the progressive loss of cortical inputs explains neuroprotection at least in R6/2 mice. It has long been recognized that in order to produce an excitotoxic lesion in the striatum the integrity of the excitatory cortical projection is required (Bizière and Coyle, 1979;McGeer et al., 1978;Orlando et al., 2001). The integrity of this projection is severely compromised in R6/2 mice, which then contributes to the neuroprotection. This hypothesis is supported by the observation that young transgenic animals and other mouse models are not protected against excitotoxic lesions (Petersén et al., 2002), indicating that the HD mutation *per se* is not neuroprotective. Because neuroprotection develops against various insults such as cerebral ischemia (Schiefer et al., 2002a), 3-NP (Hickey and Morton, 2000), dopamine-induced toxicity (Petersén et al., 2001) and methamphetamine (MacGibbon et al., 2002), it is likely that other factors may also be involved. Alternatively, the progressive development of neuroprotection may reflect compensatory mechanisms. In a recent study, we showed that striatal field potentials of 3–4 week R6/2 transgenic mice show significantly more sensitivity to ischemic challenge than do their WT counterparts. However, the R6/2 responses do not become more sensitive over age but rather maintain a relative tolerance to ischemia compared to controls (Klapstein and Levine, 2005). Metabolic deficiencies could explain increased sensitivity to ischemia in presymptomatic mice, but compensatory mechanisms may take place in striatal neurons to induce ischemic tolerance.

4.6 GABA function in HD

Glutamate release can be regulated by $GABA_B$ receptors located on corticostriatal terminals (Charara et al., 2000;Lacey et al., 2005). Activation of these receptors exerts significant inhibitory effects (Calabresi et al., 1990;Nisenbaum et al., 1992). In contrast to the progressive down-regulation of glutamate synaptic transmission, GABAergic function was unexpectedly increased in symptomatic R6 mice. These effects were manifested by increased frequency of spontaneous GABAergic synaptic currents, increased responses to exogenous GABA application, and increased expression of the $GABA_A$ receptor α1 subunit (Centonze et al., 2005;Cepeda et al., 2004a). Changes in GABAergic synaptic currents occur relatively early in R6/2 mice (5–7 weeks), concurrent with the first overt behavioral manifestations of the disease, and are also observed in R6/1 mice which display a much slower disease progression.

The onset of increased GABA synaptic activity in R6/2 mice coincides with the presence of large synaptic events in a subpopulation of MSSNs. This phasic glutamatergic surge may induce postsynaptic changes that cause increased GABAergic input into MSSNs and corticostriatal terminals. It is tempting to speculate that this increase represents a compensatory mechanism to reduce the potentially deleterious effects of glutamate increases. This

mechanism would reduce glutamate release via activation of $GABA_B$ receptors on presynaptic terminals, and by shunting the effects of excitatory inputs via activation of $GABA_A$ receptors on MSSNs.

Changes in $GABA_A$ receptor function may contribute to symptoms in HD. In particular, increased inhibition of enkephalin-positive GABAergic neurons would reduce striatal output along the indirect pathway, similar to a functional ablation. This may lead to disinhibition of the external globus pallidus and could explain why lesions in this area ameliorate some HD symptoms (Ayalon et al., 2004;Reiner, 2004).

5. Synaptic Plasticity in HD

Alterations in synaptic plasticity in genetic mouse models of HD were first conducted in the hippocampus. The rationale was twofold: first, because cognitive changes precede motor alterations and second, because the hippocampus shows early neuronal intranuclear inclusions (Morton et al., 2000). A number of studies concluded that hippocampal long-term potentiation (LTP) is altered in HD mouse models (Hodgson et al., 1999;Murphy et al., 2000;Usdin et al., 1999). In R6/2 mice alterations in synaptic plasticity occur at both CA1 and dentate granule cell synapses, and are accompanied by impaired spatial cognitive performance. Further, deficits in synaptic plasticity at CA1 synapses occurred before an overt phenotype suggesting that altered synaptic plasticity contributes to the presymptomatic changes in cognitive function reported in human HD (Murphy et al., 2000). In R6/1 mice aberrant long-term depression (LTD) in the hippocampus has also been observed. LTD is developmentally regulated, dependent on NMDA receptors, and normally declines by early adulthood. Young R6/1 mice follow the same pattern of hippocampal LTD expression as controls, but later regain the ability to support LTD (Milnerwood et al., 2006). Mossy fiber LTP in the CA3 region of the hippocampus is also severely impaired in slices from R6/2 mice (Gibson et al., 2005). Interestingly, a similar impairment is observed in mice lacking complexin II, a presynaptic protein that modulates neurotransmitter release and that is depleted in the brains of HD patients and R6/2 mice (Morton and Edwardson, 2001).

Synaptic plasticity is also altered in the cortex of R6/1 mice. Thus, a progressive derailment of LTD at perirhinal synapses is observed in association with early nuclear localization of mutant huntingtin in layers II/III (Cummings et al., 2006a). Interestingly, similar to the changes in membrane properties observed in striatal MSSNs, cortical pyramidal neurons display depolarization and reduced capacitance. More importantly, reduced expression of dopamine receptors occurs in the perirhinal cortex and application of a dopamine D2 agonist can reverse abnormal synaptic plasticity (Cummings et al., 2006a).

It is a natural consequence that cellular and synaptic alterations in MSSNs should affect synaptic plasticity in the striatum. Striatal synaptic plasticity is complicated and remains controversial. Although it was initially believed that LTD was the physiological form of synaptic plasticity after high-frequency stimulation of the corticostriatal pathway, a growing number of studies have demonstrated that this is not the case and that, in fact, both LTD and LTP can be induced in physiological conditions (Charpier and Deniau, 1997;Dos Santos Villar and Walsh, 1999;Mahon et al., 2004;Smith et al., 2001;Spencer and Murphy, 2000). Furthermore, in a corticostriatal slice preparation that better preserves cortical inputs, high-frequency stimulation consistently induced LTP, whereas low-frequency stimulation reliably induced LTD (Fino et al., 2005).

Little is known about changes in striatal synaptic plasticity in HD models. In a recent study, synaptic plasticity in dorsolateral striatal slices from control and 3-NP-treated rats demonstrated that both forms of activity-dependent synaptic plasticity can be recorded in control rats, whereas in 3-NP slices a suppression of LTD expression occurred (Dalbem et al.,

2005). This is consistent with the observation that acute application of 3-NP in striatal slices produced a LTP of the NMDA receptor-mediated synaptic excitation in striatal MSSNs but not in cholinergic interneurons (Calabresi et al., 2001). However, this does not mean that cholinergic interneurons play no role in spiny neuron vulnerability. Using the 3-NP rat and the R6/2 mouse models, a recent study suggested that defective plasticity of cholinergic interneurons could be the primary event mediating abnormal functioning of striatal circuits (Picconi et al., 2006).

6. Selective neuronal vulnerability in HD

6.1 Why are the MSSNs more vulnerable?

A puzzle in HD is the selective vulnerability of striatal MSSNs and the resistance of interneurons to neurodegeneration. Clearly, multiple factors must contribute to this selective vulnerability. These could include differing levels of expression of huntingtin, differences in the density of NMDA receptors and the degree of cortical innervation, to name a few (Sieradzan and Mann, 2001;Uhl et al., 1988).

One hypothesis is that huntingtin expression differs in various types of neurons and this may account for selective vulnerability. Thus, high levels of expression are confined to neurons and neuropil within the matrix compartment of the striatum, with lower levels of expression in the patch compartment of the striatum (Ferrante et al., 1997). Furthermore, large cholinergic interneurons do not appear to express huntingtin and they do not degenerate, although these findings are controversial (Fusco et al., 1999). What is consistent is that corticostriatal neurons are enriched in huntingtin, suggesting that the HD mutation may render corticostriatal neurons dysfunctional first and potentially destructive upon some MSSNs, rather than render all striatal neurons vulnerable (Fusco et al., 1999). Interestingly, huntingtin is expressed in a higher proportion in substance P-positive neurons forming the direct striatonigral pathway than in the enkephalin-positive neurons forming the indirect striatopallidal output (Fusco et al., 2003).

A growing number of studies have demonstrated differential expression of specific membrane ion channels, glutamate receptor subunits, and intracellular enzymatic activities that could be responsible for opposite glutamate receptor-mediated toxicity between MSSNs and striatal interneurons (Calabresi et al., 2000). There is little doubt that NMDA receptors play an important role in degeneration of MSSNs in HD. Since the cellular distribution, density, and subunit composition of NMDA receptors is not equal throughout the striatum (Landwehrmeyer et al., 1995b), these factors could help explain differential vulnerability. For example, striatal interneurons have reduced density of NMDA receptors and the subunit composition is different from that expressed by MSSNs (Standaert et al., 1999).

Taking advantage of cell identification with infrared videomicroscopy we examined cell swelling induced by NMDA in MSSNs compared to large, putative cholinergic interneurons. We observed that, in contrast to MSSNs, cell swelling was not induced in large interneurons by bath application of NMDA (Cepeda et al., 2001c). This effect was not due to the inability of large interneurons to swell, because kainate application could induce cell swelling. Electrophysiological experiments confirmed reduced NMDA current density in large interneurons (Cepeda et al., 2001c). Although previous reports suggested that cholinergic interneurons were less responsive to all glutamate receptor agonists (Calabresi et al., 1998), our results demonstrated that the reduced sensitivity was not indiscriminate, but specific to activation of NMDA receptors. Similar studies in HD mouse models remain to be done in order to provide confirmatory evidence.

Another factor that could contribute to the selective vulnerability of MSSNs is the degree of cortical innervation (Fusco et al., 1999). Our observations suggest that a progressive

disconnection between cortex and striatum occurs in HD. We could expect that striatal neurons that receive less cortical inputs would be more resistant to degeneration. At least one class of striatal interneuron, the cholinergic large aspiny cell, which has been shown to be less densely innervated than the MSSNs (Bennet and Wilson, 1999;Cepeda et al., 2001c;Lapper and Bolam, 1992), is spared in HD. This conclusion lends support to the idea that a critical determinant of neuronal vulnerability is the extent to which cells receive input from cortical and other huntingtin-rich glutamate neurons (Fusco et al., 1999).

The question then becomes what is the mechanism of MSSN degeneration in human HD? One potential hypothesis for a mechanism is that early changes in cortical projection neurons alter their ability to release glutamate and possibly BDNF into target areas. This decrease induces changes in postsynaptic glutamate receptor density, distribution, or subunit composition leading to denervation supersensitivity. Although studies reporting this phenomenon in the striatum are relatively rare, one set of experiments on striatal glutamate receptor expression after cortical ablations found evidence for excitatory amino acid receptor changes in gene expression, supporting the concept of denervation supersensitivity (Wüllner et al., 1994). In addition, there is evidence that the composition of postsynaptic NMDA receptors is under tight presynaptic control (Gottman et al., 1997). Alterations in presynaptic activity thus may affect the types of postsynaptic NMDA receptors activated.

Recent studies are attributing an increasingly important role to extrasynaptic NMDA receptors (Kullman and Asztely, 1998). In view of the fact that the number of synaptic contacts may be reduced in HD, the role of these extrasynaptic receptors may be increased. In normal conditions extrasynaptic NMDA receptors appear to signal glutamate spillover [extrasynaptic diffusion of neurotransmitter (Kullman and Asztely, 1998;Lozovaya et al., 1999)]. Receptor subunit composition is different between synaptic and extrasynaptic NMDA receptors. Thus, in hippocampal neurons, extrasynaptic NMDA receptors contain NR1 and NR2B subunits, whereas synaptic NMDA receptors also contain the NR2A subunit (Tovar and Westbrook, 1999). This has led to the suggestion that synaptic and extrasynaptic NMDA receptors may have differing roles in excitotoxicity (Sattler et al., 2000). In support, there is evidence that activation of synaptic and extrasynaptic NMDA receptors have opposing effects on the cAMP response element binding protein (CREB), gene regulation and neuronal survival (Hardingham et al., 2002). Thus, whereas Ca^{2+} entry through synaptic NMDA receptors induces CREB activity and BDNF gene expression, Ca^{2+} entry through extrasynaptic NMDA receptors activates a dominant CREB shut-off pathway that blocks induction of BDNF expression (Hardingham et al., 2002). These results imply that synaptic NMDA receptors have anti-apoptotic activity, whereas stimulation of extrasynaptic NMDA receptors causes loss of mitochondrial membrane potential and cell death (Hardingham et al., 2002).

Considering that there is a progressive disconnection between the cortex and the striatum, associated with reductions in synaptophysin and PSD95, and knowing that the density of NMDA receptors is not reduced in HD, one reasonable assumption is an increased role of extrasynaptic NMDA receptors as the disease advances. The fact that there is a progressive reduction in synaptic contacts does not mean that glutamate is not being released, it just indicates that the topography of receptor activation is likely to change in HD. Enhanced activation of extrasynaptic NMDA receptors may facilitate cell dysfunction and eventual death. Indeed, recent studies have indicated that reduced expression of PSD95 in neurons may be responsible for neuronal vulnerability (Gardoni et al., 2002).

Finally, another factor that affects neuronal vulnerability is the presence or absence of dendritic spines. We do not know the cause of the progressive loss of spines in transgenic HD mice (Klapstein et al., 2001). We can only speculate that early dysregulation of glutamate release, manifested by the presence of large synaptic events, in conjunction with an increase in cortical

excitability, may induce postsynaptic changes. Studies of hippocampal neurons show that exposure to glutamate or NMDA for short periods of time can produce a rapid loss of dendritic spines (Halpain et al., 1998). However, a decrease in synaptic activity observed in later stages of the disease, could also cause elimination of spines (Segal, 1995). Whatever the mechanism of spine elimination in R6/2 transgenics, one consequence of spine loss is to make these neurons more vulnerable to subsequent excitotoxic stimuli (Halpain et al., 1998). In that sense spines, as well as normal levels of synaptic activity, can be viewed as neuroprotective (Segal, 1995). Supporting this suggestion, it has recently been shown that environmental stimulation can increase the life expectancy of R6/2 and R6/1 mice (Carter et al., 2000;Hockly et al., 2002;van Dellen et al., 2000) and prevents the occurrence of seizures. Environmental stimulation increases spine density (Schrott, 1997) and possibly reduces the rate of spine loss in MSSNs in HD.

6.2 Selective vulnerability of enkephalin-containing cells

What makes MSSNs originating the indirect pathway more vulnerable in HD? Taking advantage of the generation of mice expressing enhanced green fluorescent protein (EGFP) in cells containing dopamine D1 (direct pathway) or D2 (indirect pathway) receptors (Gong et al., 2003), we were able to tease apart electrophysiological properties specific to each cell type. For example, D2-EGFP cells displayed more spontaneous inward synaptic currents than D1-EGFP cells and large-amplitude events (similar in amplitude, but not identical to those seen transiently in a subset of MSSNs from R6/2 mice) occurred only in D2 cells (Cepeda et al., 2004b). This means that D1- and D2-EGFP-positive MSSNs differ in the type of synaptic inputs they receive. Increased frequency of small-amplitude synaptic currents could indicate increased inputs and glutamate release on D2 cells. Large-amplitude synaptic events are usually dependent on the firing of action potentials from the presynaptic neuron, indicating that D2 cells more faithfully reflect ongoing cortical activity.

These findings are reinforced by anatomical data demonstrating that the size of corticostriatal terminals making synaptic contacts with D2-immunolabeled spines is significantly larger than those making contact with D1-immunolabeled spines (Lei et al., 2004). The idea that D2 cells receive more glutamatergic input was also reinforced by the observation that application of $GABA_A$ receptor antagonists induced large-amplitude membrane depolarizations preferentially in D2 cells. These depolarizations reflect increased cortical synchronization typically produced by blockade of $GABA_A$ receptors. The preferential propagation of epileptiform activity onto D2 cells thus confirms a tighter synaptic coupling between cortical pyramidal neurons and this particular subpopulation of MSSNs, in support of previous data demonstrating that enkephalin-positive neurons are selectively activated by cortical stimulation (Berretta et al., 1997) and that preproenkephalin expression is under the control of cortical inputs (Uhl et al., 1988).

These findings could help explain the observation that in HD the striatal projection to the external pallidal segment (indirect pathway) is the most vulnerable (Deng et al., 2004). One of the earliest morphological changes in HD is the reduction in enkephalin expression in neurons of the indirect pathway (Menalled et al., 2000;Reiner et al., 1988;Sapp et al., 1995). Our electrophysiological studies in R6/2 mice have demonstrated a transient increase (around 5–7 weeks) of large synaptic events in a subset of MSSNs followed by a progressive reduction of cortical inputs into the striatum (Cepeda et al., 2003). It is tempting to speculate that the transient surge occurs primarily on the D2 (enkephalin-expressing) neurons because these neurons have greater cortical synaptic inputs and are more directly affected by cortical activity. Thus, these D2-expressing neurons would be more vulnerable to dysfunction in the corticostriatal pathway.

7. Rescuing synaptic dysfunction

How can these findings on corticostriatal synaptic dysfunction help design a more rational treatment for HD? A number of important considerations have to be taken into account to answer this question. First, timing is of paramount importance. Data from multiple laboratories indicate that cellular and synaptic alterations occur very early in genetic mouse models of HD, often before overt symptoms or major neuropathological changes can be observed (Levine et al., 2004). This fact offers a unique opportunity for intervention. Second, regional alterations (e.g., cortex versus striatum) are also important. Should we try to reduce cortical hyperexcitability or should we try to rescue the progressive decline in spontaneous synaptic activity in the striatum? How can we prevent selectively the increased NMDA receptor sensitivity of striatal neurons? If, according to the chain reaction model there is a single, probably cortical, trigger of striatal dysfunction we could concentrate on preventing this primary alteration. However, if changes in the intrinsic membrane properties of MSSNs are the primary event, it is possible that targeting the cortical pyramidal neurons would be fruitless. It has been generally assumed that treatment of HD should be aimed at reducing glutamate release in the corticostriatal pathway. But as we demonstrated, with disease progression, synaptic activity decreases until the striatum becomes functionally disconnected from the cortex. Thus, reducing glutamate release at this stage would not be effective. Furthermore, reducing glutamate release deprives the striatum of important neurotrophic factors. However, reducing glutamate release when the first signs of dysregulation in the corticostriatal pathway occur could be therapeutic.

7.1 Drugs that reduce cortical excitability and glutamate release

If the cortex becomes hyperexcitable in HD (Cepeda et al., 2003;Cummings et al., 2006b;Gu et al., 2005;Uzgil et al., 2004), drugs that reduce cortical neuronal excitability must be beneficial. Indeed, drugs that reduce glutamate release, such as riluzole, can be neuroprotective both in clinical trials and in animal models of HD (Centonze et al., 1998;Cepeda et al., 2003;Huntington Study Group, 2003;Mary et al., 1995;Rosas et al., 1999;Schiefer et al., 2002b). Furthermore, a short-acting benzodiazepine, alprazolam improved cognitive function in a mouse model of HD (A. J. Morton, personal communication). The fact that benzodiazepines are allosteric agonists that increase $GABA_A$ receptor mediated inhibition explains that this drug also has antiepileptic properties (Kubova and Mares, 1993). Activation of group II mGluRs, either on striatal cells or presynaptic corticostriatal terminals, has neuroprotective effects in the quinolinic acid model (Orlando et al., 1995). In addition, group I mGluRs play a major role as antagonism of these receptors can be also neuroprotective (Orlando et al., 2001). In the R6/2 model both a $mGluR_2$ agonist or a $mGluR_5$ antagonist increased survival time compared to placebo treated transgenic animals (Schiefer et al., 2004). The relative success in this trial can be attributed to prompt initiation of treatment at 3.5 weeks of age.

Electrophysiological studies have provided evidence for presynaptic regulation of glutamate release by D2 receptors either directly (Bamford et al., 2004;Cepeda et al., 2001b;Flores-Hernandez et al., 1997;Hsu et al., 1995) or via a retrograde signal involving endocannabinoid production and activation of presynaptic CB_1 receptors (Yin and Lovinger, 2006). As dopamine release may be compromised in HD, and dopamine receptors are decreased early in the disease, attempts to restore or enhance dopamine function have been assessed. Apomorphine, a D1/D2 receptor agonist, seemed to ameliorate HD symptoms (Albanese et al., 1995;Corsini et al., 1978). In the R6/2 model, replacement therapy with L-DOPA caused short-term behavioral improvements but long-term treatment was deleterious on survival and rotarod performance (Hickey et al., 2002). Dopamine D2 receptor blockers do not appear to affect the long-term progression of HD. Bromocriptine, rather than improving chorea, induced an exacerbation

(Kartzinet et al., 1976). However, dose-dependent effects were also observed. Low doses produced clinical improvement but higher doses potentiated the symptoms (Loeb et al., 1979). Finally, another D2 blocker, sulpiride, produced no functional improvement but reduced abnormal movements (Quinn and Marsden, 1984). In contrast, there is growing consensus that D2 agonists are neuroprotective, probably by pre- and postsynaptic mechanisms, and could be used to prevent striatal neuronal damage (Bozzi and Borrelli, 2006;Cepeda et al., 1998).

Because of early alterations in adenosine receptor signaling in HD (Tarditi et al., 2006), the potential therapeutic effects of adenosine receptor agonists or antagonists are beginning to be examined (Blum et al., 2003a). In the 3-NP model administration of an A_1 receptor agonist, ADAC prevented the development of dystonia (Blum et al., 2002). In addition, another agonist was able to reduce 3-NP-induced seizures in mice (Zuchora et al., 2001) via disruption of glutamate neurotransmission. The role of A_{2A} receptors is more complex, as these receptors have a pre- and postsynaptic distribution that could result in biphasic effects (Blum et al., 2003b). Blockade of presynaptic A_{2A} receptors has been proved beneficial in a number of neurological conditions, including HD (Popoli et al., 2002). On the other hand, activation of postsynaptic A_{2A} receptors has potential therapeutic effects. For example, in the R6/2 model, administration of CGS21680, an A_{2A} adenosine receptor selective agonist, delayed the progressive deterioration of motor performance and prevented a reduction in brain weight (Chou et al., 2005).

Alterations in endocannabinoid receptors occur early in mouse models of HD. In R6/1 transgenic mice CB_1 receptor mRNA is severely downregulated between 8–10 weeks of age, before overt symptoms occur (McCaw et al., 2004;Naver et al., 2003). Importantly, as shown in another mouse model, the decrease in CB_1 receptor levels is accompanied by a decrease in proenkephalin- but not in substance P-mRNA levels, suggesting that the loss of CB_1 receptors might be preferential to striatopallidal neurons (Lastres-Becker et al., 2002). These data demonstrating that the endocannabinoid system becomes hypofunctional in HD open a new venue for therapeutic intervention using highly selective CB_1 agonists (Lastres-Becker et al., 2003).

Our results on changes in GABA synaptic activity are applicable to studies testing the efficacy of GABA mimetic compounds in the treatment of HD. Although some can reduce dystonia, at least in animal models (Hamann and Richter, 2002), for the most part clinical trials have been unsuccessful (Shoulson et al., 1978;Waddington and Cross, 1984). Specifically, in spite of early reports of limited success in retarding disease progression using baclofen, a $GABA_B$ receptor agonist, controlled trials have been unsuccessful, casting doubt on the efficacy of reducing presynaptic release of glutamate (Shoulson et al., 1989). This is not unexpected in view of our findings showing increased GABAergic tone and reduced glutamate synaptic activity in mouse models. Interestingly, abnormal sensitivity of endocannabinoid receptors may contribute to aberrant GABA synaptic transmission (Centonze et al., 2005).

7.2 Manipulating BDNF

Another promising therapeutic venue is to restore trophic factors lost because of the progressive decrease in cortical inputs. Decreased striatal BDNF has been reported in HD mouse models and may contribute to cell dysfunction (Zuccato et al., 2001). Normal huntingtin contributes to the BDNF pool produced in the cerebral cortex and its loss affects the stability of cortical afferents and decreases support to striatal targets (Cattaneo et al., 2005). Furthermore, normal huntingtin enhances vesicular transport of BDNF and this transport is markedly attenuated in the context of HD (Gauthier et al., 2004). The expression of TrkB, the principal BDNF receptor, is also severely reduced in HD (Gines et al., 2006). Finally, mice that lack cortical BDNF develop progressive symptoms and neuropathology similar to that found in HD (Baquet et al., 2004).

Among a growing number of therapeutic trials, attempts to restore neurotrophic factors in HD models have yielded promising results (Alberch et al., 2004;Zucatto et al., 2005). In fact, dietary restriction (Duan et al., 2003), as well as several candidate drugs to treat HD such as cisteamine (Borrell-Pages et al., 2006) and riluzole (Mizuta et al., 2001), appears to be neuroprotective via increasing BDNF levels in the brain. Biologically delivered neurotrophins can also attenuate striatal damage caused by 3-NP (Frim et al., 1993) or quinolinic acid (Alberch et al., 2002;Perez-Navarro et al., 2000). Furthermore, environmental enrichment can slow the progression of the disease in R6/2 mice (Hockly et al., 2002) presumably, among other factors, by increasing BDNF levels. A key component of environmental enrichment is exercise, which is known to increase BDNF levels (Cotman and Berchtold 2002) and is being considered as a potential tool for slowing progression of some neurodegenerative diseases (Smith and Zigmond, 2003). In the R6/1 model of HD, voluntary exercise delays the onset of behavioral and cognitive deficits, although the exact relationship with BDNF protein levels was not established (Pang et al., 2006). Recently we began to examine the effects of exercise on electrophysiological parameters known to be altered in R6/2 mice. In transgenic mice, there is a significant reduction in membrane capacitance of MSSNs, probably associated with a reduction in spine density and dendritic branching. After 3–5 weeks of voluntary exercise, the decrease in cell membrane capacitance was rescued, suggesting that exercise may prevent the loss of membrane observed in HD mice. In contrast, the progressive reduction in spontaneous synaptic currents did not appear changed by exercise, possibly due to the fact that transgenic mice exercise much less than wildtype animals (Cepeda et al., 2006;Hickey et al., 2005). Despite this finding, further exploration into the effects of BDNF on corticostriatal synaptic transmission is warranted. Interestingly, voluntary exercise markedly increased spontaneous synaptic currents in control mice.

Evidence indicates that bath application of BDNF produces differential effects on spontaneous synaptic activity. It increases glutamatergic (Li et al., 1998) but decreases GABAergic currents (Tanaka et al., 1997). In that sense, BDNF could be ideal because it could rescue the progressive decline in glutamatergic currents and, at the same time, prevent the increase in GABA currents. We showed that BDNF reduced GABAergic currents in R6/2 mice (Cepeda et al., 2004a). This effect could be caused by changes in receptor expression. In hippocampal cultures, BDNF reduces miniature inhibitory postsynaptic currents by rapid down-regulation of $GABA_A$ receptor surface expression (Brünig et al., 2001). Thus, it becomes important to test whether or not BDNF can fully restore normal striatal synaptic function in HD.

8. Conclusions

Evidence obtained from genetic mouse models of HD has changed our views about how the symptoms of this disorder emerge. First, neuronal dysfunction is sufficient to induce symptoms (Tobin and Signer, 2000;Levine et al., 2004) and cell death is not a prerequisite for their occurrence. Second, neuronal circuits in both the striatum and cortex are important in the development of the HD phenotype. The corticostriatal pathway is the primary provider of the excitatory glutamatergic inputs into the striatum. The effects of these inputs are regulated by presynaptic receptors on corticostriatal terminals that function as the gatekeepers of glutamate release, as well as by the intrinsic membrane properties of MSSNs. When the neurons of this pathway become dysfunctional, excitation of striatal neurons will become abnormal. Furthermore, it is becoming increasingly clear that major morphological alterations in the striatum are probably primed initially by alterations in the intrinsic functional properties of MSSNs, but ultimately require abnormalities in corticostriatal inputs for the phenotype to be expressed. When viewed in this context, reasons for the selective degeneration of MSSNs and the earlier predisposition to loss of MSSNs in the indirect striatal output pathway become apparent.

The changes within the corticostriatal pathway are just beginning to be unraveled. They are complex and consist of early increased excitability which may involve a combination of changes in inhibitory GABAergic cortical microcircuits and presynaptic dysregulation of neurotransmitter release, followed by a loss of connectivity between the cortex and striatum. This sequence of events also may cause increased striatal GABA function which will severely impair the integrative and output capabilities of MSSNs and cause a lack of regulation of pallidal and nigral neurons. From a clinical perspective, early disturbances of cortical function point to potential mechanisms underlying the cognitive and emotional abnormalities associated with the disorder that often precede the sensorimotor symptoms. Alterations in striatal output, in the absence of significant cell loss, will ultimately lead to the disruption of sensorimotor control. Taken together, the primary implications from these conclusions are that interventions to ameliorate or ultimately prevent the development of the HD phenotype should occur early to target neuronal dysfunction and should be aimed at abnormalities in both cortex and striatum.

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Abbreviations

HD
Huntington's disease

CAG
(cytosine adenine guanine) DNA triplet sequence coding for glutamine

YAC
yeast artificial chromosome

Tg
transgenic

MSSN
medium-sized spiny neuron

NMDA
N-methyl-D-aspartate

AMPA
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

D1
dopamine D1 receptor subtype

D2
dopamine D2 receptor subtype

A_1
adenosine 1 receptor subtype

A_{2A}
adenosine 2A receptor subtype

$mGluR_{2/3}$
group II metabotropic glutamate receptor subtypes

$mGluR_5$
group I metabotropic glutamate receptor

CB_1
cannabinoid 1 receptor subtype

GABA
γ-aminobutyric acid

$GABA_A$ and $GABA_B$
ionotropic and metabotropic GABA receptor subtypes

Kir2.1 and 2.3
inwardly rectifying potassium channels

Kv2.1
voltage-activated potassium channel underlying delayed rectification

HVA
high voltage-activated

EPSP
: excitatory postsynaptic potential

NR1 and NR2A/B
: N-methyl-D-aspartate receptor subunits

GluR6
: glutamate receptor subunit constitutive of kainate receptors

3-NP
: 3-nitropropionic acid

BDNF
: brain derived neurotrophic factor

TrkB
: tyrosine kinase receptor subtype that binds neurotrophins, in particular BDNF

EGFP
: enhanced green fluorescent protein

RT-PCR
: reverse transcriptase polymerase chain reaction

ADAC
: adenosine amine congener, a selective A_1 adenosine receptor agonist

CGS21680
: a selective A_{2A} adenosine receptor agonist

L-DOPA
: levodopa, metabolic precursor of dopamine

PSD95
: postsynaptic density 95

CREB
: cAMP response element binding protein

LTD
: long-term depression

LTP
: long-term potentiation