Genetic mouse models of Huntington’s disease: focus on electrophysiological mechanisms

Carlos Cepeda¹, Damian M Cummings, Véronique M André, Sandra M Holley and Michael S Levine

Intellectual and Developmental Disabilities Research Center, David Geffen School of Medicine, University of California Los Angeles, 760 Westwood Plaza Los Angeles, CA 90095, U.S.A.

Cite this article as: Cepeda C, Cummings DM, André VM, Holley SM and Levine MS (2010) Genetic mouse models of Huntington’s disease: focus on electrophysiological mechanisms. ASN NEURO 2(2):art:e00033.doi:10.1042/AN20090058

ABSTRACT

The discovery of the HD (Huntington’s disease) gene in 1993 led to the creation of genetic mouse models of the disease and opened the doors for mechanistic studies. In particular, the early changes and progression of the disease could be followed and examined systematically. The present review focuses on the contribution of these genetic mouse models to the understanding of functional changes in neurons as the HD phenotype progresses, and concentrates on two brain areas: the striatum, the site of most conspicuous pathology in HD, and the cortex, a site that is becoming increasingly important in understanding the widespread behavioural abnormalities. Mounting evidence points to synaptic abnormalities in communication between the cortex and striatum and cell–cell interactions as major determinants of HD symptoms, even in the absence of severe neuronal degeneration and death.

Key words: excitatory amino acid, Huntington’s disease, mouse model, neurodegeneration, striatum, synaptic activity.

WHAT IS HUNTINGTON’S DISEASE?

HD (Huntington’s disease) is a progressive, debilitating, and fatal neurological disorder. Its principal symptoms include chorea (uncontrollable dance-like movements), cognitive disturbances, depression and other psychiatric changes (Harper, 1996). HD is inherited in an autosomal dominant fashion. The mutated gene is located on the short arm of chromosome 4 and contains an expansion in the normal number of CAG (glutamine) repeats, generally >40 (The Huntington’s Disease Collaborative Research Group, 1993). It is believed that the severity of symptoms is directly correlated with the number of CAG repeats (Harper and Jones, 2002). HD is typically a late-onset disease, although juvenile variants occur, generally when more CAG repeats are present. In young children with HD, the symptoms also include epileptic seizures (van Dijk et al., 1986; Rasmussen et al., 2000; Gambardella et al., 2001; Seneca et al., 2004). The protein encoded by the HD gene, htt (huntingtin), is normally a cytoplasmic protein closely associated with vesicle membranes and microtubules. Although its normal function is not completely understood, considerable evidence suggests it has a role in vesicle trafficking, exocytosis and endocytosis (DiFiglia et al., 1995; Caviston and Holzbaur, 2009).

Neuropathologically, HD is primarily characterized by loss of MSSNs (medium-sized spiny projection neurons) in the striatum (caudate nucleus and putamen) and pyramidal neurons in the cerebral cortex (Vonsattel et al., 1985). Striatal and cortical interneurons are relatively spared (Vonsattel and DiFiglia, 1998). Cell loss leads to substantial atrophy of the striatum, enlarged lateral ventricles, and thinning of the cortical mantle (Rosas et al., 2005). Within the striatum, MSSNs that project to the external globus pallidus (indirect pathway) are the most vulnerable (Reiner et al., 1988; Albin et al., 1992). These neurons express enk (enkephalin) and DA (dopamine) D2 receptors. In contrast, MSSNs that project to the substantia nigra pars reticulata (direct pathway), express SP (substance P) and DA D1 receptors (Gerfen et al., 1990), and become affected later in the course of the disorder.

Another pathological landmark of HD is the presence of aggregated forms of mutant htt in neurons. These aggregates comprise intranuclear [NII (neuronal intranuclear inclusion)] and cytoplasmic inclusions, as well as microaggregates. The

¹To whom correspondence should be addressed [email: ccepeda@mednet.ucla.edu].

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; BAC, bacterial artificial chromosome; BDNF, brain-derived neurotrophic factor; DA, dopamine; enk, enkephalin; EPSC, excitatory postsynaptic current; GABA, γ-aminobutyric acid; HD, Huntington’s disease; htt, huntingtin; IPSC, inhibitory postsynaptic current; IR-DIC, infrared differential interference contrast; MSSN, medium-sized spiny projection neuron; NII, neuronal intranuclear inclusion; NMDA, N-methyl-D-aspartate; WT, wild-type; YAC, yeast artificial chromosome.

© 2010 The Author(s) This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial Licence (http://creativecommons.org/licenses/by-nc/2.5/) which permits unrestricted non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.
role of inclusions in cell death is controversial as there is evidence for both deleterious and protective effects (Ho et al., 2001; Arrasate et al., 2004; Reiner et al., 2007). Alterations in the hypothalamus and the endocrine system (e.g. loss of orexin-containing cells and increased cortisol levels), also play an important role in the manifestation of HD symptoms (Petersen et al., 2005; Bjorkqvist et al., 2006; Aziz et al., 2009; Petersen et al., 2009). Dysfunction in these systems lead to sleep and metabolic disturbances. Finally, widespread pathology in peripheral tissues including skeletal muscle, heart, bone and testis, are beginning to be recognized. These changes are independent of brain dysfunction and appear to be related to the expression of mutant htt in peripheral tissues (van der Burg et al., 2009).

EARLY ANIMAL MODELS OF HD

In the late 1970s, several lines of investigation converged to generate animal models of HD (Coyle, 1979). First, glutamate was shown to be the main excitatory amino acid in the brain [reviewed in (Watkins and Jane, 2006)]. Secondly, glutamate also was shown to be the transmitter of the corticostriatal projection providing the major excitatory input to the striatum (McGeer et al., 1977; Fonnum et al., 1981). Finally, specific glutamate analogues were shown to produce selective, axon-sparing lesions in the brain (Coyle et al., 1978). As striatal cell loss is the primary neuropathological landmark in HD, one of the first rodent models used the excitotoxin kainic acid to selectively destroy striatal MSSNs (Coyle and Schwarz, 1976; Schwarz and Coyle, 1977). Later, quinolinic acid [a selective NMDA (N-methyl-D-aspartate) receptor agonist] was used as it better replicated the neuropathology seen in HD (Schwarz et al., 1983). Thus the roles of glutamate transmission and postsynaptic NMDA receptors became important and generated the core of the excitotoxicity hypothesis of HD which posits that striatal neurons degenerate in HD because of enhanced glutamate neurotransmission.

As deficits in energy metabolism also occur in HD, other models that targeted mitochondrial function were developed. Inhibition of complex II with 3-nitropropionic acid became a useful model of HD because it produced lesions in the striatum that were similar to the cell loss in HD (Beal et al., 1993; Damiano et al., 2009). The major advantage of both the excitotoxic and the 3-nitropropionic acid models was that the neuropathology was replicated in non-human primates (Brouillet et al., 1995).

Although toxic models were instrumental in the understanding of some of the mechanisms involved in cell death (DiFiglia, 1990), they were limited because it was not possible to study the progression of the disease or to replicate the widespread neuropathology observed in the human condition. This fact is important as, although it was generally believed that the progression of symptoms in HD was due to neurodegeneration of MSSNs, studies in genetic animal models have demonstrated that severe neuronal dysfunction precedes degeneration and is probably the major cause of many symptoms (Levine et al., 2004). The discovery of the HD gene in 1993 led to the creation of genetic models of the disease and opened the doors for mechanistic studies.

GENETIC MOUSE MODELS

Genetic mouse models of HD permit examination of the progression of the disease in detail. The first mouse model of HD was created in the laboratory of Gillian Bates (Mangiarini et al., 1996). Since then, numerous genetic mouse models have been generated. These models include transgenic (with truncated or full-length human mutant genes), knock-in and conditional models. We would like to point out that the models we describe in this review do not represent an exhaustive or complete list. Only those models deemed relevant for our major points are included. We apologize in advance for not citing other important models that also have added to our understanding of HD mechanisms.

FRAGMENT MODELS

The R6 line of transgenic mice (Mangiarini et al., 1996) remains one of the most widely used models, not only because it was the first genetic mouse model generated, but because it offers many advantages. In particular, R6/2 mice (with approx. 150 CAG repeats) manifest a very aggressive, rapidly progressing form of HD, similar to the juvenile form in humans. R6/2 mice display overt behavioural symptoms as early as 4–5 weeks of age, show hindlimb clasping and weight loss and die at approx. 15 weeks. Alterations include the formation of NIIs (Davies et al., 1997), which were later also shown to be present in human HD brains (DiFiglia et al., 1997). NIIs can be observed very early, in the presymptomatic stage (Morton et al., 2000). There are also changes in neurotransmitter receptor expression (Carter et al., 1999) and altered signalling mechanisms (Bibb et al., 2000; Luthi-Carter et al., 2000; Menalled et al., 2000). Many of these alterations are correlated with motor (Carter et al., 1999) and learning impairments on a number of cognitive tasks (Lione et al., 1999), as well as deficits in synaptic plasticity at hippocampal CA1 (cornu ammonis 1) synapses before an overt phenotype appears (Murphy et al., 2000).

Another line, the R6/1 (with approx. 110 CAG repeats and decreased mutant htt expression compared with the R6/2), presents with similar phenotypic alterations as the R6/2, but in a more protracted form (Mangiarini et al., 1996). Weight
loss and clamping can be observed at 19–23 weeks and become more pronounced with age. In addition, aberrant synaptic plasticity, which occurs prior to the formation of nuclear aggregates, has been described in these mice (Cummings et al., 2006; Milnerwood et al., 2006).

FULL-LENGTH MODELS

The most widely studied full-length model uses YAC (yeast artificial chromosomes) expressing normal (YAC18) and mutant (YAC46 and YAC72, and YAC128) htt (Hodgson et al., 1999; Slow et al., 2003). YAC72 mice display abnormal behaviour around 7 months of age, as well as selective degeneration of MSSNs in the lateral striatum by 12 months. Subsequent experiments in these mice showed that the formation of aggregates may not be essential to initiate neuronal death (Hodgson et al., 1999). An increase in CAG repeat length led to a more severe phenotype, arguing in favour of a gene–dose effect. YAC128 mice display alterations similar to YAC72 mice, but these alterations are more severe and occur earlier (Slow et al., 2003). YAC128 mice exhibit increased open-field activity at approx. 3 months, followed by rotarod abnormalities at 6 months. By 12 months, open-field activity is diminished significantly compared with controls. In addition, atrophy and neuronal loss (approx. 10%) occur in the striatum and cortex of YAC128 mice (Van Raamsdonk et al., 2005).

A recently described full-length model of HD uses a BAC (bacterial artificial chromosome)-expressing mutant htt with 97 glutamine repeats (Gray et al., 2008b). These mice exhibit progressive motor deficits, neuronal synaptic dysfunction and late-onset selective neuropathology in both the striatum and cortex. Interestingly, studies in BACHD mice revealed that the pathogenic process can occur without early and diffuse nuclear accumulation of aggregated mutant htt (Gray et al., 2008b). BAC models also have been instrumental in demonstrating an important role of cell–cell interactions, compared with cell autonomous processes, in HD pathogenesis (Gu et al., 2005, 2007; Gray et al., 2008a). However, cell autonomous processes also occur. In a different HD model (N171-98Q), striatal expression of mutant htt was sufficient to produce NIs and motor impairment, which the investigators attributed to cell-autonomous transcriptional dysregulation (Brown et al., 2008).

KNOCK-IN MODELS

Knock-in models also contributed to our understanding of HD. The major advantage of these models is that they express full-length htt in its native genomic context. Several models that differ mainly in the number of CAG repeats (from 48 to 200) have been generated (White et al., 1997; Levine et al., 1999; Shelbourne et al., 1999; Wheeler et al., 2000; Lin et al., 2001; Heng et al., 2007). Although overt behavioural changes are often subtle in knock-in mice, sensitive and careful testing demonstrates abnormalities as early as 1–2 months of age (Menalled et al., 2002, 2003). Furthermore, a consistent feature 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, NIs are observed only in older mice (10–18 months) (Menalled et al., 2002), and loss of MSSNs occurs at approx. 2 years (Hickey et al., 2008). Two additional knock-in models, the HdhQ150 and HdhQ200, display a behavioural phenotype that is CAG-length dependent, with motor abnormalities appearing at 50 or 100 weeks of age and reduced DA receptors in heterozygotes (Heng et al., 2007, 2009). The HdhQ200 mice also show regional-selective pathology in the striatum and cortex, including NIs and gliosis, and display age-dependent weight loss beginning at approx. 70 weeks (Heng et al., 2009).

CONDITIONAL MODELS

An important step in the understanding of HD pathology was the creation of conditional mouse models of the disease. Taking advantage of the tetracycline-regulatable system, mutated htt can be ‘turned off’ after being expressed in the brain (Yamamoto et al., 2000). One contribution of this model was the demonstration of a close relationship between the HD phenotype and the presence of NIs. Interrupting the expression of mutant htt led to inclusion clearance and a reversal of motor symptoms. Thus a continuous influx of mutant htt seems to be required to support inclusions and symptoms. Autophagy, via acetylation, appears to play a critical role in this effect (Jeong et al., 2009).

USING MOUSE MODELS TO UNDERSTAND MECHANISMS

As pointed out above, HD mouse models provide a way to follow the progression of the disorder especially before overt symptoms are present. Since each model is unique, similar phenotypic changes in different models provide a way to validate alterations and to make sure such changes are not due to idiosyncratic effects of variables relating to a particular mouse model. However, no mouse model recapitulates the human condition in its entirety, nor displays the degree of neurodegeneration that occurs in humans (Levine et al., 2004). Regardless, each model provides relevant information for the understanding of HD mechanisms.
It has been argued that knock-in models are more faithful in terms of genetic context and in recapitulating the late onset, slow natural progression and neuropathology of HD (Heng et al., 2008). However, in these models the symptoms are generally mild and normal aging may be a confounding factor. The R6/2 model has been criticized for the rapid onset and aggressive development of the phenotype, as well as early and widespread presence of NIs. This has raised questions about its validity for drug screening (Heng et al., 2008), even though it has been standardly used in many screening experiments (Gil and Rego, 2009), and whether or not it recapitulates adult-onset HD since many of the phenotypic properties of the model are similar to juvenile HD (Cummings et al., 2009). The conclusion from a careful and systematic comparison of fragment and full-length knock-in models of HD was that, when strain background and CAG repeat length are controlled for, fragment and knock-in models develop comparable phenotypes (Woodman et al., 2007). Full-length models, such as the BACHD and the YAC, display a more robust phenotype than knock-in models, but they also have shortcomings. In particular, these mice tend to be heavier than their WT (wild-type) littermates. In human HD and in other genetic mouse models, weight loss is the common denominator. The increased body weight in these models has been associated with overexpression of htt (Van Raamsdonk et al., 2006). Interestingly, in contrast with R6/2 and some of the knock-in mice where there are considerable alterations in receptor expression, alterations in YAC128 mice appear limited to glutamate receptors, as DA, GABA (\(\gamma\)-aminobutyric acid) and adenosine receptor binding remained unchanged (Benn et al., 2007).

**NEURONAL MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS**

As in the human disease, most mouse models of HD display significant reductions in brain volume. However, in mice this is probably not the result of a decrease in the number of neurons. Instead, reduced somatic size and loss or thinning of dendrites and spines are the main contributors (Klapstein et al., 2001). The lack of cell loss should not be surprising and could be related to the resiliency of neurons in mouse compared with the human brain. For example, most genetic mouse models of Parkinson’s disease have been unable to reproduce significant loss of DA cells even though functional changes occur (Goldberg et al., 2003; Itier et al., 2003; Kitada et al., 2009; Watson et al., 2009; Wu et al., 2009). Similarly, it is probable that the majority of symptoms in mice can be attributed to functional rather than structural alterations. In particular, changes in voltage- and ligand-gated ion-channel function and alterations in synaptic activity occur and become more pronounced with disease progression (Cepeda et al., 2007).

At this point it remains unknown whether morphological changes are produced by initial functional alterations or if these alterations are the consequence of gene-induced structural abnormalities.

**NMDA RECEPTOR-MEDIATED RESPONSES IN HD MOUSE MODELS**

As pointed out above, the excitotoxicity hypothesis, based on the acute toxicity models, was the initial underlying hypothesis used to explain neurodegeneration in HD. Accordingly, increased glutamate release and sensitivity of NMDA receptors caused striatal cell death. Thus initial studies in mouse models were aimed at verifying or refuting this hypothesis. The two most vulnerable areas in HD are the striatum, especially the MSSNs, and the cerebral cortex. The R6/2 line has been particularly useful to verify the excitotoxicity hypothesis. The rapid progression of the disease allows electrophysiological studies in brain slices which require visualization of individual neurons with infrared videomicroscopy and IR-DIC (infrared differential interference contrast) optics, a technique better suited for younger animals. Our laboratory performed one of the first studies examining NMDA receptor function in genetic mouse models of HD. Long-lasting bath application of NMDA induces cell swelling, an index of excitotoxicity that can be visualized using IR-DIC microscopy (Dodd et al., 1993; Colwell and Levine, 1996). In striatal slices from symptomatic R6/2 mice and CAG94 (but not CAG72) knock-in mice, NMDA-induced cell swelling was enhanced compared with slices from control mice (Levine et al., 1999), thus providing evidence for the excitotoxicity hypothesis. In contrast, in vivo studies from another laboratory using R6/1 mice showed that injections of quinolinic acid produced less damage in HD mice (Hansson et al., 1999). Initially, these differences were difficult to explain. However, it is well-known that, in vivo, excitotoxic lesions require the integrity of the glutamatergic corticostriatal pathway (McGeer et al., 1978). Subsequently we showed that the corticostriatal connection is compromised in the R6 mice as well as in other mouse models which then reduces the excitotoxic response in these models. Interestingly, in other models [e.g. the CAG100 (Laforet et al., 2001)], in vivo neuroprotection to quinolinic acid did not occur (Petersen et al., 2002) and in the YAC72 model neurotoxicity was enhanced (Zeron et al., 2002). Increased NMDA receptor function was also verified using electrophysiological recordings and calcium imaging showing that a population of MSSNs had increased responses to NMDA (Cepeda et al., 2001). Similar findings have been obtained in YAC72 (Hodgson et al., 1999) and 128 (Graham et al., 2009) mice.

Another significant alteration in striatal NMDA receptor function is the early and persistent reduction of Mg\(^{2+}\) sensitivity (Table 1). When the cell membrane is hyperpolar-
The disease. Biphasic changes in spontaneous EPSCs are evident in MSSNs from HD mice in which increased activity occurs early, but is followed by reduced activity in overtly symptomatic mice. A similar pattern occurs with IPSC activity in cortical pyramidal neurons from HD mice. NMDA receptor activity (as measured by current amplitude and density) and Mg²⁺ sensitivity differ between cell types. RMP, resting membrane potential; VG, voltage-gated; VGCC, voltage-gated calcium channels.

### Table 1 Intrinsic and synaptic alterations in cortical and striatal neurons from mouse models of HD

| Properties                      | Cortical pyramidal neurons | MSSNs |
|---------------------------------|----------------------------|-------|
| Membrane capacitance            | Reduced cell capacitance (L) (Cummings et al., 2006, 2009) | Reduced cell capacitance (E, L) (Klapstein et al., 2001; Cepeda et al., 2003) |
| Input resistance                | Increased membrane input resistance (L) (Cummings et al., 2006, 2009) | Increased membrane input resistance (E, L) (Klapstein et al., 2001; Cepeda et al., 2003) |
| RMP                             | Depolarized resting membrane potentials (L) (Cummings et al., 2006, 2009) | Depolarized resting membrane potentials (L) (Klapstein et al., 2001) |
| VG channel activity             | Increased VGCC currents (L) (André et al., 2006) | Decreased VGCC currents (E) (Cepeda et al., 2001) |
| K⁺ channels                     | Decreased K⁺ channel inward rectification (E, L) (Ariano et al., 2001; Klapstein et al., 2001) | Decreased K⁺ channel inward rectification (E, L) (Ariano et al., 2001; Klapstein et al., 2001) |
| Synaptic activity               | Increased spontaneous EPSC frequency (L) (Cummings et al., 2009) | Decreased spontaneous EPSC frequency (L) (Cepeda et al., 2003) |
|是我的 | Increased evoked EPSCs (L) (Cummings et al., 2009) | Large-amplitude spontaneous EPSCs (E) (Cepeda et al., 2003) |
| IPSCs                           | Increased spontaneous IPSC frequency (E) (Cummings et al., 2009) | Increased evoked EPSCs (E) (Joshi et al., 2009) |
|                                 | Decreased spontaneous IPSC frequency (L) (Cummings et al., 2009) | Decreased evoked EPSCs (L) (Joshi et al., 2009) |
| Action potentials               | Increased firing rate (E) (Walker et al., 2008) | Increased firing rate (E) (Rebec et al., 2006; Miller et al., 2008) |
| Frequency                       | Decreased synchrony between neuronal pairs (E) (Walker et al., 2008) | Decreased correlated firing (E) (Rebec et al., 2006; Miller et al., 2008) |
| Correlated Activity             | Increased NMDA receptor currents (E) (André et al., 2006) | Increased NMDAR currents (E, L) (Cepeda et al., 2001; Starling et al., 2005; Zeron et al., 2002; Graham et al., 2009) |
| Receptors                       | Increased NMDAR Mg²⁺ sensitivity (E) (André et al., 2006) | Decreased NMDAR Mg²⁺ sensitivity (E, L) (Cepeda et al., 2001; Starling et al., 2005) |

RESTING MEMBRANE POTENTIALS AND IONIC CONDUCTANCE ALTERATIONS

In the striatum, other signs of functional pathology seen in MSSNs of HD mice are increases in cell membrane input resistance and depolarized resting membrane potentials (Levine et al., 1999; Klapstein et al., 2001; see Table 1). Determinants of these biophysical parameters are cell size and K⁺ conductances, in particular those dependent on leak and inwardly rectifying K⁺ channels. Cell size is decreased in HD mice (Levine et al., 1999; Klapstein et al., 2001) and K⁺ conductances are reduced (Ariano et al., 2005). We examined changes in inward rectification in R6/2 mice and found a significant reduction concomitant to the onset of overt behavioural symptoms. In addition, correlative immunofluorescence studies demonstrated decreases in the expression of K⁺ channel subunit proteins, Kir2.1 and Kir2.3 (Ariano et al., 2005).
2005). One of the consequences of increases in membrane input resistance is an enhancement of cell excitability which, coupled with depolarized membrane potentials, could lead to amplification of synaptic inputs and increased action potential firing in MSSNs. Consistent with this idea, in vivo recordings of striatal neurons demonstrated that cell firing is elevated in R6/2 transgenic relative to WT mice at 6–9 weeks of age (Rebec et al., 2006). Not only the frequency, but also the burst activity and correlated firing patterns were altered in HD mice (Miller et al., 2008). Thus correlated firing and coincident bursts between pairs of MSSNs were prominent in cells from WT animals, but reduced in R6/2 and knock-in models, suggesting that information processing at both the single-neuron and population level is compromised in the striatum of symptomatic HD mice (Miller et al., 2008). Similar changes were also observed in cortical pyramidal neurons (Walker et al., 2008).

GLUTAMATE AND GABA SYNAPTIC ACTIVITY IN STRIATUM AND CORTEX

In neurons the htt protein 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. Mutant htt produces specific impairment of exocytosis and endocytosis, potentially causing abnormal synaptic transmission, thus leading to the proposal that HD is a synaptopathology (Li et al., 2003). Using genetic mouse models we were able to examine the progression of synaptic alterations along the corticostriatal pathway in HD. Since cortical neurons are affected, we also examined synaptic changes in pyramidal neurons. Our results showed that changes in synaptic transmission are time- and region-dependent.

In R6/2 and YAC128 HD mice, alterations in glutamatergic function along the corticostriatal pathway change dynamically in a biphasic manner (Table 1). Although a progressive reduction in spontaneous and evoked glutamatergic synaptic activity, coinciding with the appearance of overt behavioural alterations, is the most noticeable change in R6/2 mice (Klapstein et al., 2001; Cepeda et al., 2003), dysregulation of glutamatergic input occurs early and is manifested by the presence of large-amplitude and complex synaptic events that peak at approx. 5–7 weeks of age (Cepeda et al., 2003). These large events could reflect increased cortical excitability and a possible reduction in presynaptic receptor function, including NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) receptor-mediated synaptic currents evoked by cortical stimulation were increased. At 7 and 12 months, after the development of the behavioural phenotype, glutamate release and AMPA synaptic currents were significantly reduced (Joshi et al., 2009). These effects were due to combined pre- and postsynaptic alterations.

The susceptibility to excitotoxic stress in YAC128 mice also changes in a biphasic manner (Graham et al., 2009). At 1 month, before phenotypic changes occur, mice display increased sensitivity to NMDA and quinolinic acid. In contrast, at 7–10 months symptomatic mice are resistant to quinolinic acid neurotoxicity. These changes are paralleled by increased NMDA receptor-mediated synaptic currents in slices and increased postsynaptic currents in acutely isolated MSSNs from presymptomatic, followed by reduced currents in symptomatic, YAC128 mice (Graham et al., 2009).

Multiple alterations in corticostriatal synaptic function also depend on the pathogenicity of mutant htt (Milnerwood and Raymond, 2007). Presynaptic dysfunction and a propensity towards synaptic depression in YAC72 and YAC128 compared with YAC18 mice occurs at 1 month. In YAC128 mice, reduced AMPA responses evoked by intrastriatal stimulation were also
observed. In contrast, when normalized to evoked AMPA currents, postsynaptic NMDA currents were enhanced in all three pathologic HD YAC variants (Mingerwood and Raymond, 2007).

One of the outcomes of excitatory activity in the corticostriatal pathway is the concomitant release of BDNF (brain-derived neurotrophic factor), a trophic factor essential for postsynaptic neuronal support that is reduced in HD (Zuccato and Cattaneo, 2007). Thus the progressive reduction in glutamate synaptic activity will also reduce the release of this important factor and potentially facilitate cellular dysfunction and subsequent degeneration.

**DIFFERENTIAL VULNERABILITY OF MSSNs**

One of the enigmas of HD is the particular vulnerability of MSSNs forming the indirect pathway. Decreased enk expression is one of the earliest molecular markers of neuropathology in HD mice (Menalled et al., 2000). What makes these neurons more susceptible to degeneration? The EGFP (enhanced green fluorescent protein) gene has been used as a reporter to identify DA D1 (direct pathway) and D2 (indirect pathway) receptor-expressing striatal cells. Several studies in MSSNs from intact mice have shown that dendritic elaboration and cell capacitance are reduced in D2 cells (Gertler et al., 2008). We have examined and compared electrophysiology in D1 and D2 receptor-expressing MSSNs. D2 receptor-expressing MSSNs are more excitable and appear to be better connected to the cerebral cortex than D1 cells. For example, cortical disinhibition using GABA<sub>A</sub> receptor blockers leads to the occurrence of membrane depolarizations and bursts in D2 receptor-expressing, but not in D1 receptor-expressing, MSSNs (Cepeda et al., 2008), confirming previous studies showing selective activation of enk-containing neurons using expression of immediate-early gene proteins, Fos and Jun B, after cortical disinhibition (Berretta et al., 1997; Parthasarathy and Graybiel, 1997). The size of corticostriatal glutamatergic boutons synapsing on to D2 receptor-expressing MSSNs is larger than those contacting D1 receptor-expressing MSSNs, as shown by electron microscopy (Reiner et al., 2003). This finding implies that D2 receptor-expressing MSSNs are subjected to increased glutamate release at the synapse. Perhaps these differences in glutamate release make striatal D2 cells more susceptible to degeneration in HD.

**MECHANISMS OF NEURONAL DEGENERATION IN HD**

How do the electrophysiological findings reviewed here contribute to our understanding of neuronal dysfunction and degeneration in HD? The findings from studies of mouse models permit the generation of a model of neuronal dysfunction and degeneration that may be applicable to the human disease (Figure 1). The starting point is dysregulation of glutamate release along the corticostriatal pathway and altered modulation by presynaptic receptors, followed by a series of physiological, compensatory mechanisms that attempt to counter the change in glutamate release. Compensatory mechanisms are effective initially but, eventually, they can have deleterious effects. It is worth mentioning that a similar mechanism, i.e. calcium-dependent increase in neurotransmitter release as the root of neuronal degeneration, was also postulated in a *Drosophila* model of HD (Romero et al., 2008).

The function of normal htt is not well understood, but convergent evidence points to this protein having a role in vesicular trafficking, exocytosis and endocytosis (DiFiglia et al., 1995; Caviston and Holzbaur, 2009). Elongation of the CAG tract leads to alterations in the synaptic machinery producing initial increases in glutamate release reflected by enhanced synaptic responses and large amplitude spontaneous synaptic events. Excess glutamate release causes the collapse of spines on postsynaptic MSSNs, which in turn increases membrane input resistance, reduces K<sup>+</sup> conductances, and further amplifies synaptic signals. Dysregulation of glutamate release is compounded by loss of DA D2, CB<sub>1</sub>, mGluR<sub>B2</sub> and other presynaptic receptors regulating glutamate release at corticostriatal terminals. A compensatory mechanism might be the increase of GABA<sub>A</sub>ergic synaptic activity that occurs within the striatum. Increasing GABA<sub>A</sub>ergic synaptic transmission could aid in preventing further neuronal damage by reducing glutamate release, by activation of presynaptic GABA<sub>A</sub> receptors, and/or inducing postsynaptic alterations by shunting excitatory inputs to MSSNs, via GABA<sub>A</sub> receptors.

The period of increased glutamate release in the striatum will be followed by a period of reduced synaptic input. Another adverse effect of reduced corticostriatal communication is the reduced release of BDNF. Lack of this trophic factor will negatively impact MSSNs. During this time, K<sup>+</sup> conductances are also reduced, and the resting membrane potential is depolarized, leading to an increased propensity for MSSNs to produce action potentials. Although these cells will fire more frequently, their firing patterns are now disorganized.

Why should changes occur earlier and/or be more evident in MSSNs of the indirect pathway? One possible reason is that these cells appear to be more connected to cortical pyramidal neurons, and reduced corticostriatal communication will first affect this subpopulation of cells. Enk expression is tightly regulated by cortical inputs (Uhl et al., 1988) and decreased cortical communication will reduce enk expression in these MSSNs.

Reductions in spine density and synaptic markers cause a redistribution of postsynaptic glutamate receptors that is also deleterious in neurons. Synaptic NMDA receptors activate a
pro-survival cascade and BDNF transcription. In contrast, extrasynaptic NMDA receptors (rich in NR2B subunits) activate a pro-apoptotic cascade (Papadia and Hardingham, 2007). In the striatum of HD mice, there is evidence of increased extrasynaptic NMDA receptor expression and signalling (Milnerwood et al., 2010). Thus the balance between synaptic and extrasynaptic activity determines neuronal survival (Okamoto et al., 2009; Levine et al., 2010). Interestingly, synaptic activity is required for inclusion formation which, in turn, is believed to be neuroprotective (Okamoto et al., 2009).

**FUTURE DIRECTIONS**

Many unanswered questions still remain. A major one concerns the role of brain regions other than the striatum and cortex in HD manifestations. In humans with HD there is evidence of significant cell loss within the thalamus (Heinsen et al., 1996) and hypothalamus (Kremer et al., 1990). The thalamus, particularly the centromedian and parafascicular nuclei, is the origin of a second major glutamatergic input to the striatum (Smith et al., 2004). The nature of these inputs is just beginning to be unravelled in slice preparations that preserve both cortico- and thalamo-striatal inputs (Ding et al., 2008; Smeal et al., 2008). It will be important to determine whether this pathway also plays a role in the alterations of excitatory synaptic activity that are observed in HD mouse models.

Another area that has not been extensively investigated is the function of glial cells and glio-neuronal interactions in HD. How are astrocytes and glutamate transporters changed in HD and how do they modulate neuronal degeneration? Initial evidence points to an important role of mutant htt in astrocytes, which might lead to decreased levels of glutamate transporters (Lievens et al., 2001; Shin et al., 2005; Estrada-Sanchez et al., 2009). The contribution of glial cells to disease progression further supports a non-cell autonomous process in HD (Lobsiger and Cleveland, 2007).

**CONCLUSIONS**

Genetic mouse models of HD have become important tools for examining the natural evolution of the disease and understanding its mechanisms. Convergent evidence supports cell-autonomous and non-cell autonomous processes in neuronal dysfunction and subsequent degeneration. In particular, striatal neuronal dysfunction seems to depend on both intrinsic changes in NMDA receptor sensitivity, as
well as altered cortical input. Synaptic alterations occur early, before overt symptoms emerge, and are biphasic in nature, with age-dependent increases followed by decreases in excitatory transmission along the corticostriatal pathway. In terms of therapeutics, structural and functional changes are time- and region-dependent. In consequence, treatments should be tailored to different stages of the disease and be specific to different brain areas.

**FUNDING**

Work in the author's laboratory is supported by the United States Public Health Service (USPHS) [grant number NS41574]; and contracts from CHDI, Incorporated and the Hereditary Disease Foundation.

**REFERENCES**

Albin RL, Reiner A, Anderson KD, Dure 4th LS, Handelin B, Balfour R, Whetsell Jr WO, Penney JB, Young AB (1992) Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. Ann Neurol 31:425–430.

Andr e VM, Cepeda C, Venegas A, Gomez Y, Levine MS (2006) Altered cortical glutamate receptor function in the R6/2 model of Huntington's disease. J Neurophysiol 95:2108–2119.

Ariano MA, Aronin N, Difiglia M, Tagle DA, Sibley DR, Leavitt BR, Hayden MR, Levine MS (2002) Striatal neurochemical changes in transgenic models of Huntington's disease. J Neurosci Res 68:716–729.

Ariano MA, Cepeda C, Calvert CR, Flores-Hernandez J, Hernandez-Echegaray E, Klapstein GJ, Chandler SH, Aronin N, Difiglia M, Levine MS (2005) Striatal potassium channel dysfunction in Huntington's disease transgenic mice. J Neurophysiol 93:2565–2574.

Arrasate M, Mitra S, Schweitzer ES, Segal MR, Schweitzer ES, Finkbeiner S (2004) Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 431:805–810.

Aziz NA, Pijl H, Frolich M, van der Graaf AW, Roelfsema F, Roos RA (2009) Increased hypothalamic-pituitary-adrenal axis activity in Huntington's disease. J Clín Endocrinol Metab 94:1223–1228.

Beal MF, Brouillet E, Jenkins BG, Ferrante RJ, Kowall NW, Miller JM, Storey E, Srivastava R, Rosen BR, Hyman BT (1993) Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. J Neurosci 13:4181–4192.

Benn CL, Slow EJ, Farrell IA, Graham R, Deng Y, Hayden MR, Cha JH (2007) Glutamate receptor abnormalities in the YAC128 transgenic mouse model of Huntington's disease. Neuroscience 147:354–372.

Berretta S, Parthasarathy HR, Graybiel AM (1997) Local release of GABAergic inhibition in the motor cortex induces immediate-early gene expression in indirect pathway neurons of the striatum. J Neurosci 17:4752–4763.

Bibb JA, Yan Z, Svenningsson P, Snyder GL, Pieribone VA, Horikuchi A, Nairn AC, Meser A, Greengard P (2000) Severe deficiencies in dopamine signaling in presymptomatic Huntington's disease mice. Proc Natl Acad Sci USA 97:6809–6814.

Björkvist M, Peterson A, Bacos K, Isaacs J, Norlen P, Gil J, Popovic N, Sundler F, Bates GP, Tabrizi SJ, Brundin P, Mulder H (2006) Progressive alterations in the hypothalamic-pituitary-adrenal axis in the R6/2 transgenic mouse model of Huntington's disease. Hum Mol Genet 15:1713–1723.

Brouillet E, Hantraye P, Ferrante RJ, Dolan R, Leray-Willing A, Kowall NW, Beal MF (1995) Chronic mitochondrial energy impairment produces selective striatal degeneration and abnormal choreiform movements in primates. Prog Natl Acad Sci USA 92:7105–7109.

Brown TB, Bogush AI, Ehrlich ME (2008) Neocortical expression of mutant huntingtin is not required for alterations in striatal gene expression or motor dysfunction in a transgenic mouse. Hum Mol Genet 17:3085–3104.

Carter RJ, Lione LA, Humby T, Mangiarini L, Mahal A, Bates GP, Dunnett SB, Morton AJ (1999) Characterization of progressive motor defects in mice transgenic for the human Huntington's disease mutation. J Neurosci 19:3248–3257.

Cavitton JP, Holzhaebel EL (2009) Huntington as an essential integrator of intracellular vesicular trafficking. Trends Cell Biol 19:147–155.

Cepeda C, Ariano MA, Calvert CR, Flores-Hernandez J, Chandler SH, Leavitt BR, Hayden MR, Levine MS (2001) NMDA receptor function in mouse models of Huntington disease. J Neurosci Res 66:525–539.

Cepeda C, Hunt RS, Calvert CR, Hernandez-Echegaray E, Nguyen OK, Jocoy E, Christian LJ, Ariano MA, Levine MS (2003) Transient and progressive electrophysiological alterations in the corticostriatal pathway in a mouse model of Huntington's disease. J Neurosci 23:961–969.

Cepeda C, Starling AJ, Wu N, Nguyen OK, Uzgil B, Sada T, Andre VM, Ariano MA, Levine MS (2004) Increased GABAergic function in mouse models of Huntington's disease: reversal by BDNF. J Neurosci Res 78:855–867.

Cepeda C, Wu N, Andre VM, Cummings DM, Levine MS (2007) The corticostriatal pathway in Huntington's disease. Prog Neurobiol 81:253–271.

Cepeda C, Andre VM, Yamazaki I, Wu N, Kleinman-Weiner M, Levine MS (2008) Differential electrophysiological properties of dopamine D1 and D2 receptor-containing striatal medium-sized spiny neurors. Eur J Neurosci 27:671–682.

Cha JH, Kosinski CM, Kerner JA, Alsdorf SA, Mangiarini L, Davies SW, Penney JB, Bates GP, Young AB (1998) Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human Huntington disease gene. Proc Natl Acad Sci USA 95:6480–6485.

Colwell CS, Levine MS (1996) Glutamate receptor-induced toxicity in neostriatal cells. Brain Res 724:205–212.

Coye JT (1979) An animal model for Huntington's disease. Biol Psychiatry 14:251–276.

Coye JT, Schwarzc R (1976) Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. Nature 263:244–246.

Coye JT, Molliver ME, Kuhar MJ (1978) In situ injection of kainic acid: a new method for selectively lesioning neural cell bodies while sparing axons of passage. J Comp Neurol 180:301–323.

Cummings DM, Milnerwood AJ, Dallercas GM, Waight S, Brown YJ, Vatsavayal SC, Horst MC, Murphy KPSJ (2008) Aberrant cortical synaptic plasticity and dopaminergic dysfunction in a mouse model of Huntington's Disease. Hum Mol Genet 15:2856–2866.

Cummings DM, Cepeda C, Leavitt BR, Hayden MR, Zeitlin SQ, Levine MS (2007) Altered striatal glutamatergic and GABAergic neurotransmission are consistent across genetic mouse models of Huntington's disease. Abstract View/Itinerary Planner San Diego, CA: Society for Neuroscience Program No. 372.5.

Cummings DM, Andre VM, Uzgil BO, Gee SM, Fisher YE, Cepeda C, Levine MS (2009) Alterations in cortical excitation and inhibition in genetic mouse models of Huntington's disease. J Neurosci 29:10371–10386.

Damiano M, Galvan L, Deglon N, Brouillet E (2009) Mitochondria in Huntington's disease. Biochim Biophys Acta 1802:52–61.

Davies SW, Turmaine M, Cozens BA, Difiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE, Mangiarini L, Bates GP (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 90:537–548.

Difiglia M (1990) Excitotoxic injury of the neostriatum: a model for Huntington's disease. Trends Neurosci 13:286–289.

Difiglia M, Sapp E, Chase K, Schwarz C, Meloni A, Young C, Martin E, Vonsattel JP, Carraway R, Reeves SA et al. (1993) Huntington is a cytoplasmic protein associated with vesicles in human and rat brain neurons. Neuron 14:1075–1081.

Difiglia M, Sapp E, Chase KD, Davies SW, Bates GP, Vonsattel JP, Aronin N (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 277:1990–1993.

Ding J, Peterson JD, Surmeier DJ (2008) Corticostriatal and thalamostriatal synapses have distinctive properties. J Neurosci 28:84–96.

Dodd HU, Hager G, Ziegleransberger W (1993) Direct observation of neurotoxicity in brain slices with infrared videomicroscopy. J Neurosci Methods 50:165–172.

Estrada-Sanchez AM, Montiel T, Segovia J, Massieu L (2009) Glutamate toxicity in the striatum of the R6/2 Huntington's disease transgenic mice is age-dependent and correlates with decreased levels of glutamate transporters. Neurobiol Dis 34:78–86.

Fonnum F, Storm-Mathisen J, Divac I (1981) Biochemical evidence for glutamate as neurotransmitter in corticostriatal and corticothalamic fibres in rat brain. Neuroscience 6:863–873.
Gambardella A, Muglia M, Labate A, Magariello A, Gabriele AL, Mazzei R, Pirritano D, Conforti F, Palattucci A, Valentino P, Zappia M, Quattrone A (2001) Juvenile Huntington's disease presenting as progressive myoclonic epilepsy. Neurology 57:708–711.

Gerfen CR, Engber TM, Mahan LC, Susel B, Chase TN, Monnssa Jr FJ, Sibley DR (1990) D1 and D2 dopamine receptor-regulated gene expression of striatogranin and striatopallidal neurons. Science 250:1429–1432.

Gertler TS, Chan CS, Surmeier DJ (2008) Dichotomous anatomical properties of adult striatal medium spiny neurons. J Neurosci 28:10814–10824.

Gerrits MJ, Rego AB (2008) The R6 lines of transgenic mice: a model for screening new therapies for Huntington's disease. Brain Res Rev 59:410–431.

Goldberg MS, Fleming SM, Palacino JJ, Cepeda C, Lam HA, Bhatnagar A, Meloni EG, Wu N, Ackerson LC, Klappstein GJ, Gajendiran M, Roth BL, Chesselet MF, Maidment NT, Levine MS, Shen J (2003) Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons. J Biol Chem 278:43628–43635.

Graham RK, Pouladi MA, Joshi P, Lu G, Deng Y, Wu NP, Figueroa BE, Metzler M, Andre VM, Slow EJ, Raymond L, Friedlander R, Levine MS, Leavitt BR, Hayden MR (2009) Differential susceptibility to excitotoxic stress in YAC128 mouse models of Huntington disease between initiation and progression of disease. J Neurosci 29:2193–2204.

Gray M, Gu X, Shirasaki D, Cepeda C, Yamazaki I, Levine MS, Yang X (2008a) Cortical control of striatal pathogenesis in the CreLoxP conditional BAC transgenic mouse model of Huntington's Disease (BACHD). Abstract Viewer/Itinerary Planner Washington, DC: Society for Neuroscience Program No. 114.6.

Gray M, Shirasaki D, Cepeda C, Andre VM, Wilburn B, Lu KH, Tao J, Yamazaki J, Lu SH, Sun YE, Li XJ, Levine MS, Yang X (2008b) Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice. J Neurosci 28:6182–6195.

Gu X, Li C, Wei W, Lo V, Gong S, Li SH, Iwashita T, Itohara S, Li XJ, Mody I, Heintz N, Yang X (2005) Pathological cell-cell interactions elicited by a neuropathogenic form of mutant Huntington contribute to cortical pathogenesis in HD mice. Neon 46:433–444.

Gu X, Andre VM, Cepeda C, Li SH, Li XJ, Levine MS, Yang X (2007) Pathological cell-cell interactions are necessary for striatal pathogenesis in a conditional model mouse of Huntington's disease. Mol Neurodegener 2:8.

Hansson O, Petersen A, Leist M, Nicotera P, Castilho RF, Brundin P (1999) Enhanced sensitivity to N-methyl-D-aspartate receptor activation in transgenic and knockin mouse models of Huntington's disease. J Neurosci Res 58:515–532.

Heng MY, Cepeda Hickey MA, Levine MS, Chesselet MF (2004) Genetic mouse models of Huntington's and Parkinson's diseases: illuminating but imperfect. Trends Neurosci 27:691–697.

Henderson OB, peanut A, Leemont A, Drouin R, Frindel P (1999) Transgenic mice expressing a Huntington's disease mutation are resistant to quinolinic acid-induced striatal excitotoxicity. Proc Natl Acad Sci USA 96:4727–4732.

Harper PS (1996) New genes for old diseases: the molecular basis of myotonic dystrophy and Huntington's disease. The Lumleane Lecture 1995. J R Coll Physicians Lond 30:221–231.

Harper PS, Jones L (2002) Huntington's disease: Genetic and molecular studies. In: Huntington's Disease, Third Edition (Bates GP, Harper PS, eds), pp 113–158. Oxford: Oxford University Press.

Heinsen H, Rub U, Gangnus D, Jungkunz G, Bauer M, Ulmar G, Bethke B, Harper PS, Jones L, eds), pp 113–158. Oxford: Oxford University Press.

Kaplustin GJ, Fox R, Subha J, Timse J, Boyce F, Campbell M, Cadigan BA, Warzecki L, Tangle DA, Reddy PH, Cepeda C, Calvert CR, Jokel ES, Kapustin GJ, Ariano MA, Levine MS, D'Agliola M, Aronin N (2001) Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. J Neurosci 21:9112–9123.

Levine MS, Kapustin GJ, Koppel A, Gruen E, Cepeda C, Vargas ME, Jokel ES, Carpenter EM, Zanjani H, Hurst KS, Esfetrassis A, ZEITLIN S, Chesselet MF (1998) Enhanced sensitivity to N-methyl-D-aspartate receptor channel activation in transgenic and knockin mouse models of Huntington's disease. J Neurosci Res 58:515–532.

Li JY, Plompman M, Brundin P (2003) Huntington's disease: a synaptopathy? Trends Mol Med 9:414–420.

Lievesen JC, Woodman B, Mahal A, Spasic-Bosovic O, Samuel D, Kerkerian-Le Goff L, Bates GP (2001) Impaired glutamate uptake in the R6 Huntington's disease transgenic mouse. Neurobiol Dis 8:230–237.

Lin CH, Tallässén-Greene S, Chien WM, Cepeda C, Tomlinson C, Jackson WS, Cruse AB, Ren S, Li XJ, Albin RL, Detloff PJ (2001) Neurochemical abnormalities in a knock-in mouse model of Huntington's disease. Hum Mol Genet 10:137–144.

Liong LA, Carter RJ, Hunt MJ, Bates GP, Morton AJ, Dunnett SB (1999) Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. J Neurosci 19:10428–10437.

Lobsiger SR, Cleveland DW (2007) Glial cells as intrinsic components of non-cell-autonomous neurodegenerative disease. Nat Neurosci 10:1355–1360.

Luthi-Carter R, Strand A, Peters NL, Solano SM, Hollingsworth ZR, Menon AS, Frey AS, Spektor BS, Penney EB, Schilling G, Ross CA, Borchelt DR, Tapsco SJ, Young AB, Cha HJ, Olson JM (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Proc Natl Acad Sci USA 97:7025–7030.

Majumdar L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trottier Y, Lehrach H, Davies SW, Bates GP (1996) Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell 87:493–506.

McGeer PL, McGeer EG, Scherer U, Singh K (1977) A glutamatergic corticostriatal pathway? Brain Res 128:369–373.

Menalled LB, Sison JD, Wu Y, Olivieri M, Li XJ, Li H, Zeitlin S, Chesselet MF (2002) Early motor dysfunction and striatal distribution of huntingtin microaggregates in Huntington's disease knock-in mice. J Neurosci 22:8266–8276.
Mennally LB, Sison JD, Drapatis L, Zeitzin S, Chesnoff MF (2003) Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. J Comp Neurol 465:11–26.

Miller BR, Walker AG, Shah AS, Barton SJ, Rebec GV (2008) Dysregulated information processing by medium spiny neurons in striatum of freely behaving mouse models of Huntington's disease. J Neurophysiol 100:2205–2216.

Milenirov AJ, Raymond LA (2007) Corticostriatal synaptic function in mouse models of Huntington's disease: early effects of huntingtin repeat length and protein load. J Physiol 585:817–831.

Milenirov AJ, Cummings DM, Dallerac GM, Brown JY, Vatsavayai SC, Hirst MC, Rezaie P, Murphy KP (2006) Early development of aberrant synaptic plasticity in a mouse model of Huntington's disease. Hum Mol Genet 15:1690–1703.

Milenirov AJ, Gladdum CM, Poulaud MA, Kaufman AM, Hines RM, Boyd JD, Ko RW, Vasuta OC, Graham RK, Hayden MR, Murphy TH, Raymond LA (2010) Early increase in extrasynaptic NMDA receptor signaling and expression contributes to phenotype onset in Huntington's disease mice. Neuron 65:178–190.

Morton AJ, Lagan MA, Skepper JN, Dunnett SB (2000) Progressive formation of inclusions in the striatum and hippocampus of mice transgenic for the human Huntington's disease mutation. J Neurocytol 29:679–702.

Murphy KP, Caturegli RJ, Lione LA, Maryanoff BE, Mahal A, Bates GP, Dunnett SB, Morton AJ (2000) Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation. J Neurosci 20:5115–5126.

Nowak L, Bregestovsky P, Ascher P, Herbet A, Prochiantz A (1984) Magnesium gates glutamate-activated channels in mouse central neurones. Nature 307:462–463.

Okamoto S, Poulaud MA, Talatona M, Yao D, Xia P, Ehninger DE, Zaidi R, Clemente A, Kaul M, Graham RK, Zhang D, Vincent CN, HS, Tong G, Hayden MR, Lipton SA (2009) Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin. Nat Med 15:1407–1413.

Papadia S, Hardingham GE (2007) The dichotomy of NMDA receptor signaling. Neuronscientist 13:572–579.

Parthasarathy NB, Graybiel AM (1997) Cortically driven immediate-early gene expression reflects modular influence of sensorimotor cortex on identified striatal neurons in the squirrel monkey. J Neurosci 17:2477–2491.

Petersen A, Chase K, Puschban Z, DiFiglia M, Brundin P, Aronin N (2002) Maintenance of susceptibility to neurodegeneration following intrastriatal injections of quinolinic acid in a new transgenic mouse model of Huntington disease. Exp Neurol 175:287–300.

Petersen A, Gil J, Maat-Schietman ML, Bjorkqvist M, Tanila H, Araujo JM, Smith R, Popovic N, Wierup N, Lo Y, Roos RA, Sandler F, Mulder H, Brundin P (2005) ß-trexin loss in Huntington disease. Hum Mol Genet 14:39–47.

Rasmussen A, Macias R, Yescas P, Ochoa A, Davila G, Alonso E (2000) Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. Neurology 65:745–747.

Schwarz R, Coyle JT (1977) Striatal lesions with kainic acid: neurochemical characteristics. Brain Res 127:235–249.

Schwarz R, Whetzel Jr WO, Mangano RM (1983) Quinolinic acid: an endogenous metabolite that produces axon-sparing lesions in rat brain. Science 219:316–318.

Seo E, Fagnan D, Keyomori K, Lissens W, Haserts D, Debuplaa S, Desprechens B, Liebaers I, De Meireir L (2004) Early onset Huntington disease: a neuronal degeneration syndrome. Eur J Pediatr 163:717–721.

Shearbourne PF, Kileeone N, Heverin RF, Johnston HM, Tecott L, Lewandowski M, Innes M, Ramirez L, Li Z, Iannicola L, Littman DR, Myers RM (1999) A Huntington disease CAG expansion at the murine Hdh locus is unstable and associated with behavioural abnormalities in mice. Hum Mol Genet 8:763–774.

Shin YJ, Fang ZH, Yu ZX, Wang CE, Li SH, Li XJ (2005) Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. J Cell Biol 171:1001–1012.

Slow EJ, van Raamsdonk JM, Rogers D, Coleman SH, Graham RK, Deng Y, Oh R, Bixada N, Hosain SM, Yang YZ, Li XJ, Simpson EM, Gutkeunst CA, Leavitt BR, Hayden MR (2003) Selective striatal neuronal loss in the YAC128 mouse model of Huntington disease. Hum Mol Genet 12:1555–1567.

Smea RM, Keefe KA, Wilcox KS (2008) Differences in excitatory transmission between thalamic and cortical afferents to single spiny efferent neurons of rat dorsal striatum. J Eur Neurosci 28:2041–2052.

Smith Y, Raju DV, Pare JF, Sidibe M (2004) The thalamostriatal system: a highly specific network of the basal ganglia circuitry. Trends Neurosci 27:520–527.

Sampaolato J, Gu X, Yang XW, Mody I (2008) Progressive synaptic pathology of motor cortical neurons in a BAC transgenic mouse model of Huntington disease. Neuroscience 157:606–620.

Starling AJ, Andjel VM, Cepeda C, de Lima M, Chandler SH, Levine MS (2005) Alterations in N-methyl-D-aspartate receptor sensitivity and magnesium blockade occur early in development in the R6/2 mouse model of Huntington disease. J Neurosci Res 82:377–386.

The Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983.

Uh R, Navia B, Douglas J (1988) Differential expression of preprodynorphin and preprodynorphin mRNAs in striatal neurons: high levels of preprodynorphin expression depend on cerebral cortical afferents. J Neurosci 8:4755–4764.

van der Burg JM, Bjorkqvist M, Brundin P (2008) Beyond the brain: widespread pathology in Huntington's disease. Lancet Neurol 8:765–774.

van Dijk JG, van der Velde EA, Roos RA, Broy VM (1986) Juvenile Huntington disease. Hum Genet 73:235–239.

van Raamsdonk JM, Murphy Z, Slow EJ, Leavitt BR, Hayden MR (2005) Selective degeneration and nuclear localization of mutant huntingtin in the YAC128 mouse model of Huntington disease. Hum Mol Genet 14:3823–3835.

Van Raamsdonk JM, Glisson WT, Pearson J, Murphy Z, Lu G, Leavitt BR, Hayden MR (2006) Body weight is modulated by levels of full-length huntingtin. Hum Mol Genet 15:1513–1523.

Vonsattel JP, DiFiglia M (1998) Huntington disease. J Neurospharmacol Exp Neurl 57:369–384.

Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson Jr EP (1988) Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol 14:39–47.

Watkins JC, Van der Velde EA, Roos RA, Broy VM (1986) Juvenile Huntington disease. Hum Genet 73:235–239.

Watkinke JC, Jane DE (2006) The glutamate story. Br J Pharmacol 147 Suppl 1:614–1587.

Wheeler VC, White JK, Gutekunst CA, Vrbanac V, Weaver M, Li XJ, Yi H, Desprechins B, Liebaers I, De Meirleir L (2004) Early onset Huntington disease in children: genotype-phenotype correlation. Neuropediatrics 35:190–194.

Rebec GV, Conroy SK, Barton SJ (2006) Hyperactive striatal neurons in Huntington disease in children: subcellular localisation of huntingtin in human, mouse and rat brain. J Neurochem 8:763–774.

Wheeler VC, White JK, Gutekunst CA, Vrbanac V, Weaver M, Li XJ, Li SH, Yi H, Vonsattel JP, Gusella JF, Hensch S, Auerbach W, Joyner AL, MacDonald ME (2000) Long glutamine tracts cause nuclear localization of a novel form of huntingtin in median spinal cord motor neurons in HdhQ22 and HdhQ111 knock-in mice. Hum Mol Genet 9:503–513.

White JK, Auerbach W, Duyao MP, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME (1997) Huntington disease is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. Nat Genet 17:404–410.

Wood JD, MacMillan JC, Harper PS, Lowenstein PR, Jones AL (1996) Partial characterisation of murine huntingtin and apparent variations in the subcellular localisation of huntingtin in human, mouse and rat brain. Hum Mol Genet 5:481–487.

© 2010 The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (http://creativecommons.org/licenses/by-nc/2.5/), which permits unrestricted non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.
Woodman B, Butler R, Landles C, Lupton MK, Tse J, Hockly E, Moffitt H, Sathasivam K, Bates GP (2007) The Hdh(Q150/Q150) knock-in mouse model of HD and the R6/2 exon 1 model develop comparable and widespread molecular phenotypes. Brain Res Bull 72: 83–97.

Wu N, Joshi PR, Cepeda C, Masliah E, Levine MS (2009) Alpha-synuclein overexpression in mice alters synaptic communication in the corticostriatal pathway. J Neurosci Res: In Press.

Yamamoto A, Lucas JJ, Hen R (2000) Reversal of neuropathology and motor dysfunction in a conditional model of Huntington’s disease. Cell 101:57–66.

Zeron MM, Hansson O, Chen N, Wellington CL, Leavitt BR, Brundin P, Hayden MR, Raymond LA (2002) Increased sensitivity to N-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntington’s disease. Neuron 33:849–860.

Zuccato C, Cattaneo E (2007) Role of brain-derived neurotrophic factor in Huntington’s disease. Prog Neurobiol 81:294–330.

Received 15 December 2009/11 March 2010; accepted 16 March 2010
Published as Immediate Publication 16 March 2010, doi 10.1042/AN20090058