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REVIEW

FUNCTIONAL INTERACTIONS WITHIN STRIATAL MICROCIRCUIT IN ANIMAL MODELS OF HUNTINGTON'S DISEASE

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Abstract—Mutant huntingtin (mhtt) causes loss of synaptic plasticity and selective degeneration of striatal medium spiny neurons (MSNs), a core pathological feature of Huntington's disease (HD). However, projecting neurons become dysfunctional in the very early stages, long before death and this dysfunctional state may contribute to disease. Interneurons appear to be more resistant to the effects of mhtt and play important roles in supporting the activity of projecting neurons. Therefore, early modifications in the plasticity or in the pattern of cortical and striatal interneuronal activity may also be a factor in the alteration of the corticostriatal pathway in HD. While new models of HD provide information on the onset of complex behavioral changes, the mechanisms underlying alterations of the striatal microcircuit and their role in HD pathogenesis are still unclear. As a consequence, despite the development of new compounds, no adequate treatment is so far available to stop or reverse HD. Electrophysiological studies provide crucial information on neuronal dysfunction and circuit changes that underlie or precede symptoms. Here we review recent papers in which HD models have been used to study various aspects of neuronal physiology of corticostriatal pathway. We will also discuss advantages and limitations of rodent models compared to primate models and current challenges of therapies aimed at rescuing striatal function in HD.

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Key words: striatum, neurodegenerative disorders, interneurons, HD animal models, synaptic changes, corticostriatal pathway.

Contents

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Abbreviations: A2a, adenosine receptor; ACh, acetylcholine; BDNF, brain-derived neurotrophic factor; cAMP, cyclic AMP; CB1, cannabinoid receptor type 1; ChAT, choline acetyl transferase; DA, dopamine; D2R, D2 receptor; FSI, fast-spiking interneuron; HD, Huntington's disease; htt, huntingtin; IPSC, inhibitory postsynaptic current; LAI, large aspiny cholinergic interneuron; LTD, long-term depression; LTP, long-term potentiation; MSN, medium spiny neuron; NMDA, N-methyl-D-aspartate glutamate; NMDAR, NMDA receptor; PV, parvalbumin; TH, tyrosine hydroxylase; TrkB, tropomyosin-related kinase B; YAC, yeast artificial chromosomes; 3NP, 3-nitropropionic acid.

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by psychiatric disturbances and progressive cognitive decline associated to development of involuntary choreic movements. The cause of HD is a mutation that leads to polyglutamine (CAG) expansion in the coding region of the huntingtin (htt) gene (The Huntington's Disease Collaborative Research Group, 1993). In unaffected humans, there are typically 10–29 (median 18) repetitions of the CAG triplet at 5′ end of htt gene, which, upon translation, result in polyglutamine stretch; in contrast, HD patients have a significantly expanded number—36–121 (median 44)—of trinucleotide repeats. The length of the CAG/polyglutamine repeat is inversely correlated with the age of disease onset and severity of symptoms: the higher number of expanded trinucleotide repeats results in an earlier onset of the disease, and a lower number in a later onset.

ROLE OF HUNTINGTIN

Although the function of normal htt is still not completely clarified, it is expressed very early in development and several lines of evidence suggest that it has a role in vesicular trafficking, exocytosis, and endocytosis (DiFiglia et al., 1995; Nasir et al., 1995; Caviston and Holzbaur, 2009). Accordingly, disruption of htt gene results in embryolethality (Nasir et al., 1995) and its mutant form (mhtt) interacts with a number of important pre- and postsynaptic proteins involved in vesicle transport, receptors internal-

ization, and control of synaptic structure (Li et al., 2003; Borrell-Pages et al., 2006; Truant et al., 2006), promoting cellular alterations by changing htt–protein interaction patterns. Such action is made possible because CAG expansion does not result in complete loss of normal function of htt gene, but rather it confers a novel gain-of-function independent of the physiological role of the protein (White et al., 1997). Indeed mhtt is able to alter cell signaling and induce neuronal disfunction also by altering transcriptional pathways and several gene expression patterns (Cha, 2000; Luthi-Carter et al., 2003) causing molecular changes able to modify structure and function of synapses.

It has been reported that axon terminals in mice with advanced HD contain fewer synaptic vesicles than wild-type mice and that mhtt binds more tightly to synaptic vesicles than wild-type htt culminating in a global reduction of glutamate release *in vitro* that produces specific impairment of exocytosis and endocytosis (Li et al., 2003). These features may account for the early synaptic and cellular dysfunctions in HD brains, which occur years prior to cell death or appearance of overt neurological symptoms and seem to be related to initial psychiatric and cognitive deficits (Orth et al., 2010; Paulsen et al., 2008; Schippling et al., 2009).

SELECTIVITY OF STRIATAL LESION

HD is characterized by early selective loss of GABAergic striatal medium spiny neurons (MSNs) accompanied by degeneration of neurons in the cortex and in other brain areas (Vonsattel and DiFiglia, 1998). The selective vulnerability of specific neuronal subtypes is one of the most interesting aspects of HD pathophysiology. In fact, despite its ubiquitous expression throughout the central nervous system (Strong et al., 1993; Bhide et al., 1996), mhtt produces an altered protein particularly harmful to the GABAergic projecting neurons of striatum, a nucleus in which htt levels are even lower than in other unaffected areas. Several hypotheses have been made to explain such specific neurodegenerative effect and many are the aspects to take into account as various complex interactions take place within the striatal microcircuit.

THE STRIATAL MICROCIRCUIT

Topographically organized sensory and motor areas of the neocortex project to the dorsal striatum through glutamatergic corticostriatal projections (McGeorge and Faull, 1987, 1989). These excitatory cortical signals overlap with glutamatergic inputs from midline thalamic nuclei and dopaminergic projections from the pars compacta of the substantia nigra (Gerfen et al., 1987) providing for the convergence of sensory inputs with information on movement sequences (Brown, 1992; Flaherty and Graybiel, 1994; Graybiel et al., 1994). The functional interplay of these converging pathways occurs in the MSNs, providing a correct information processing that is essential for striatal control of motor learning and habit formation (Calabresi et al., 2007).

Similar to other areas in which synaptic plasticity has been observed, in the striatum such complex integration of signals requires a finely tuned crosstalk within and between cell assemblies to be flexible. In fact, the critical filtering role played by striatum in the basal ganglia network relies also on the close interactions between MSNs and several subtypes of interneurons. This heterogeneous neuronal population includes a group of large aspiny cholinergic interneurons (LAIs) and different subtypes of GABAergic neurons: one coexpresses parvalbumin, one calretinin, and one nitric oxide synthase (Kawaguchi et al., 1995). Another class of interneurons is represented by local tyrosine hydroxylase (TH)-positive cells that produce both GABA and dopamine (DA) (Tepper et al., 2010). All of them receive powerful excitatory inputs from cortex and thalamus and exert a modulatory action on striatal synaptic transmission through pre- and postsynaptic mechanisms, affecting the function of corticostriatal glutamatergic system (Brown and Arbuthnott, 1983; Kerkerian et al., 1987; Garcia-Munoz et al., 1991; Cepeda et al., 1993; Calabresi et al., 2000; Centonze et al., 2001). For these reasons, although representing a minority of total striatal neuronal population (Kawaguchi et al., 1995), interneurons play a crucial role in the modulation of striatal function, contributing to the correct processing of corticostriatal information.

This aspect has been particularly studied in LAIs, the class of interneurons that represents the main source of acetylcholine (Ach) within the striatum (Suzuki et al., 2001). Striatal LAIs receive excitatory glutamatergic inputs from cortical and thalamic regions (Lapper and Bolam, 1992; Thomas et al., 2000) and their axons develop intense arborization that forms synaptic contacts with virtually all portions of MSNs. This anatomical organization allows LAIs to play a major integrative role and exert a modulatory influence upon vast populations of striatal projection neurons (Izzo and Bolam, 1988) regulating their excitability and, consequently, the corticostriatal information processing. In particular, endogenous cholinergic tone is required for corticostriatal synaptic plasticity (Calabresi et al., 2000, 2007) suggesting that cholinergic interneuronal activity contributes to striatal-dependent learning and motor habit formation. Hence, long-lasting changes in synaptic efficacy have been also observed at glutamatergic synapses on LAIs (Pisani et al., 2000, 2001; Bonsi et al., 2004; Fino et al., 2008) and most recently it has been reported that LAIs are important sites of interaction among DA, adenosine, and endocannabinoid receptor signaling systems (Tozzi et al., 2011).

A proper internal control of striatal function relies on the interactions between MSNs and a subtype of GABAergic cells that express parvalbumin (PV), which are called fast-spiking interneurons (FSIs) on the basis of their electrophysiological characteristics (Kawaguchi et al., 1995). Striatal PV-containing FSIs receive unique combinations of inputs from cortex and exert a strong feed-forward inhibition over MSNs, their predominant synaptic target (Kawaguchi et al., 1995; Koos and Tepper, 1999; Mallet et al., 2005). Synapses between striatal FSIs and MSNs exhibit extremely low failure rates and effective temporal summation, and are powerful enough to delay or completely block

spiking in postsynaptic MSNs (Koos and Tepper, 1999). Thus, neuronal activity of FSIs is able to influence the fine timing of MSNs spiking (Pennartz et al., 2009) and provide the major synaptic inhibitory control within the striatum (Ramanathan et al., 2002).

Although the glutamatergic inputs to striatal PV-positive cells have long been considered invariable (Nissen et al., 2010), it has been recently demonstrated that both LAIs and FSIs respond earlier than MSNs to cortical stimulation, depending on the specific temporal sequence of activation, to modulate MSNs excitability. In particular, using pairing stimulations of corticostriatal neurons and target cells, it is possible to observe that when presynaptic (corticostriatal) neurons are activated earlier than postsynaptic neurons (either MSNs or interneurons), the stimulation pairing leads to an increase of the GABAergic inhibition exerted by interneurons on MSNs, while synaptic strength of MSNs and cholinergic interneurons decreases. Conversely, if activation of presynaptic neurons follows stimulation of MSNs and interneurons, the stimulation induces a reduction of GABAergic inhibition from FSIs while reinforcing the synaptic efficacy of MSNs and LAIs (Fino and Venance, 2011; Fino et al., 2008).

Because the striatal functions in learning and memory processes require the cooperation of these neuronal populations, the capability of striatal interneurons to develop activity-dependent long-term synaptic efficacy changes in physiological condition (Suzuki et al., 2001; Bonsi et al., 2004; Fino et al., 2008) has important functional consequences and its dependence on several neurotransmitter systems is becoming a focus of intense study.

At corticostriatal synapses, repetitive cortical activation can generate either long-term depression (LTD) or long-term potentiation (LTP) depending on the subtype of ionotropic glutamate receptor activated during the induction phase of these forms of synaptic plasticity (Calabresi et al., 1992; Wang et al., 2006) and the interneuronal subtypes involved (Calabresi et al., 2007). Unique characteristic of striatal neurons is that DA critically regulates both the induction and the maintenance of neuroplasticity at corticostriatal synapses via DA D1-like and D2-like receptors activation as full DA denervation abolishes the physiological corticostriatal plasticity by producing biochemical and morphological changes within the striatum (Calabresi et al., 2007) and partial DA depletion alters maintenance of LTP (Paille et al., 2010). A third form of striatal synaptic plasticity, distinct from LTD and defined synaptic depotentiation, results from the reversal of an established LTP by the application of a low-frequency stimulation of corticostriatal fibers (O'Dell and Kandel, 1994; Picconi et al., 2003). This form of plasticity critically relies on glutamatergic N-metyl-D-aspartate receptor (NMDAR) activation and Ach striatal tone (Gardoni et al., 2006; Picconi et al., 2006). At the molecular level, the fact that the NMDAR complex is a dynamic structure involved in the regulation of corticostriatal long-term synaptic changes (Menegoz et al., 1995; Calabresi et al., 1996; Ulas and Cotman, 1996; Dunah et al., 2000; Hallett et al., 2005) makes the concurrent involvement of glutamatergic and dopaminergic pathways a characteristic of striatal synaptic plasticity. Activity-dependent plasticity of glutamatergic MSNs synapses is also modulated by endocannabinoids (presynaptically) and metabotropic glutamate (pre- and postsynaptic) receptors (Shen et al., 2008). In particular, cannabinoid CB1 receptors are expressed at MSNs but also at interneuronal level where they exert important modulatory function on the control of movement. CB1 receptors are also present presynaptically in glutamatergic neurons within the basal ganglia circuits, including the afferences to the striatum coming from cortical structures (Kofalvi et al., 2005; Uchigashima et al., 2007).

Interestingly, modulatory actions exerted through DA receptors synergistically interact with effects of intracellular second messengers activation triggered by Ach and GABA to determine whether corticostriatal LTP or LTD is triggered in MSNs in response to repetitive synaptic stimulation. Moreover, stimulation of DA D2 receptors (D2Rs) located on LAIs, inhibits Ach release and then removes the Ach-dependent activation of muscarinic M1 receptors located on MSNs, facilitating the induction of LTD (see Fig. 1). On the other hand, DA D1/D5R stimulation favouring Ach release from LAIs promotes the induction of LTP in MSNs (Calabresi et al., 2007).

Thus, the integrative action exerted by striatal projection neurons on the converging information arising from the cortex, nigral DA neurons, and interneurons, shapes the activity of neurons throughout the entire basal ganglia circuitry.

NEUROPHYSIOLOGICAL ALTERATIONS IN HD PATIENTS' BRAIN

As previously mentioned htt mutation consists of CAG pathological expansion, which generates several conformational changes causing protein misfolding, abnormal protein aggregation and subsequent transcriptional dysregulation, mitochondrial complex II deficiencies, and excitotoxicity. This pattern of oxidative damage affects firstly striatal MSNs projecting to the globus pallidus (i.e. enkephalin/GABA-containing neurons), (Reiner et al., 1988; Albin et al., 1992) originating a biphasic profile of motor abnormalities that starts with an early hyperkinetic phase, manifested as chorea and ballism (Albin et al., 1989) to a late akinetic and more disabling phase (Albin and Young, 1988; Albin et al., 1990). Accordingly, in early HD patients, markers for striatopallidal neurons are decreased, including D2RS, adenosine A2a receptors, and enkephalin, whereas in later stages, both populations of striatal projection neurons are affected, with concomitant loss of markers of the striatonigral pathway as DA D1Rs and substance P (Reiner et al., 1988; Richfield et al., 1991). Other symptoms include affective disorders, depression, anxiety, irritability or aggressive behavior, and apathy that typically precede the onset of motor abnormalities by many years and can be more devastating than movement disturbances (Bonelli and Hofmann, 2007).

Further symptoms are observed in early stages as impaired sustained attention, difficult problem solving, and

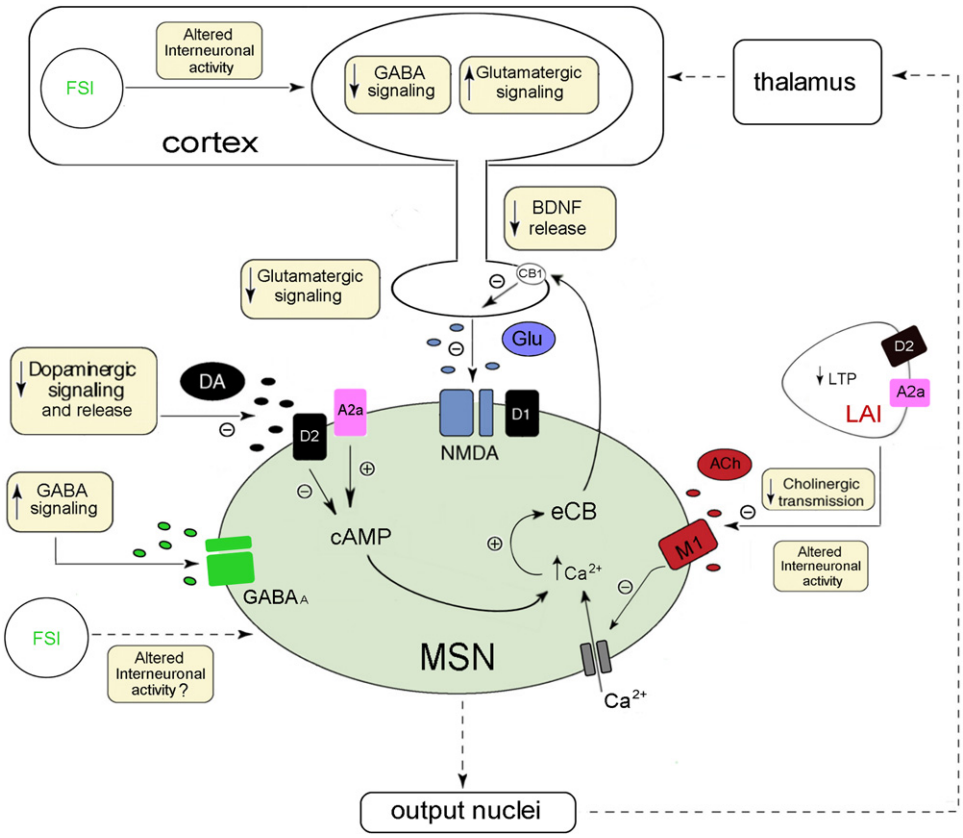

Fig. 1. Alterations of neurotransmitter systems in the striatal and cortical circuits during HD. In both patients and experimental models of the disease, multiple alterations in neurotransmitters at presynaptic and postsynaptic sites have been described at striatal medium spiny neurons and cholinergic interneurons as well as at cortical pyramidal neurons and interneurons. Dopamine, acetylcholine, GABA, endocannabinoid, and glutamate signaling systems, which in control conditions operate a synergistic control over striatal projecting neurons activity, have been demonstrated (solid lines) to be severely altered at various levels (i.e. release, uptake, neurotransmitter-mediated synaptic events). Moreover, the ability of striatal cholinergic interneurons to undergo synaptic plasticity is suppressed and alterations of interneuronal activity were also demonstrated in the cortex of HD mice (solid lines). We hypothesize (dotted lines) that unbalanced functions within the striatum may also involve other striatal interneuronal subtypes, leading to temporally distinct alterations in both direct and indirect pathways that would cause dysregulation of basal ganglia output nuclei. As a consequence, uncontrolled activity of thalamic nuclei that project back to the cortex would generate characteristic fluctuations in HD symptoms. A2a, adenosine receptor; ACh, acetylcholine; BDNF, brain-derived neurotrophic factor; cAMP, cyclic AMP; CB1, cannabinoid receptor type 1; D1 and D2, dopamine receptor types 1 and 2; DA, dopamine; eCB, endocannabinoids; FSI, fast-spiking PV-positive GABAergic interneuron; Glu, glutamate; LAI, large aspiny cholinergic interneuron; LTP, long-term potentiation; M1 muscarinic ACh receptor type 1 MSN, medium spiny neuron; NMDA, N-methyl-D-aspartate glutamate receptor.

poor verbal fluency along with memory deterioration over time (Caine et al., 1978; Brandt et al., 1984).

It is during presymptomatic phases that first alterations in the synaptic machinery can be detected. In fact, brain imaging studies indicated that neuronal alterations are present before the appearance of clinical symptoms (Mazziotta et al., 1987; Grafton et al., 1990; Aylward et al., 1994, 1996, 2000, 2004; Antonini et al., 1996; Andrews et al., 1999).

Glutamate

Research reports focusing on glutamate signaling system in humans with HD have revealed a variety of alterations, accounting for controversial data (Andre et al., 2010). Unchanged striatal and cortical levels of expression of amino acid receptors (Dure et al., 1991) were not confirmed by other studies showing reduction of NMDA and AMPA receptors expression (Young et al., 1988; Wagster et al., 1994) and decreased glutamate uptake in the prefrontal cortex of HD patients (Hassel et al., 2008). The fact that polyglutamine-expanded proteins alter glutamate transport is in agreement with previous works showing that in membrane preparations of HD postmortem brains, binding of D-[^{3}H] aspartic acid to high-affinity binding sites is reduced (Cross et al., 1986), and that diminished mRNA of the GLT-1 transporter subtype has also been observed (Arzberger et al., 1997).

Moreover, studies in HD patients using MRI spectroscopy demonstrated increased levels of striatal glutamate/glutamine and lactate suggesting that glutamatergic function and abnormalities in energy metabolism may contribute to the pathology of HD (Koroshetz et al., 1997).

Dopamine

It is well-established that an intact nigrostriatal pathway is critical for the proper regulation of motor control. Conse-

quently, it is likely that abnormal release of nigrostriatal DA has a key role in HD pathophysiology. Thus, it has been hypothesized that uncontrolled presynaptic activation of the nigrostriatal dopaminergic pathway induces chorea, while loss of DA inputs induces akinesia in patients with HD (Bird et al., 1980). Accordingly, initial studies found that DA levels and activity of TH, its biosynthetic enzyme, were increased in the striatum of postmortem HD brains compared with controls (Spokes, 1979, 1980; Bird, 1980; Bird et al., 1980). However, binding for the presynaptic DA transporter was reduced in the caudate of HD patients (Backman et al., 1997; Ginovart et al., 1997) suggesting that alterations of nigrostriatal DA transmission would lead to uncontrolled increase of DA synaptic levels and to choreic movements (Bird et al., 1980). The neurochemical basis for this suggestion is based on the observations that antagonists of DA receptors and DA-depleting agents reduce chorea, and that L-DOPA exacerbates chorea in HD. Moreover, it has been reported that TH-positive interneurons, as striatal local source of DA, are virtually absent from the striatum of HD patients (Huot et al., 2007), while in DA-denervated conditions this interneuronal population is significantly increased compared to controls (Betarbet et al., 1997; Bezard and Gross, 1998; Porritt et al., 2000). Accordingly, imaging studies have provided evidence in support of a reduced DA function in HD patients. In presymptomatic patients, which still show reduced cell loss, both striatal D1 and D2 receptor levels were decreased by 45–50% and their loss progressed by 3–5% per year (Andrews et al., 1999; van Oostrom et al., 2009).

GABA

In the complex balance that keeps the striatal microcircuit efficient, besides DA and glutamate, GABA plays a crucial role but its involvement in HD pathophysiology deserves to be explored more extensively. While inhibitory synapses have been studied in several HD models, mechanisms of dynamic alterations of GABA signaling in humans are still far from being elucidated. In the striatum there is a heterogeneous population of GABAergic interneurons represented by at least four distinct subpopulations each eliciting different inhibitory and/or modulatory control of MSNs activity (Tepper et al., 2010) and that are differentially affected by mhtt. As GABA content is decreased in the striatum of HD patients (Spokes, 1980; Spokes et al., 1980), reduced inhibitory function within the striatum is likely to reflect degeneration of projection neurons. This reduction in GABA levels was initially considered secondary to the loss of MSNs. However, a recent study reported that GABA receptors are increased in the internal globus pallidus, a basal ganglia output nucleus, at all stages of the disease in HD patients, suggesting compensatory mechanisms for the loss of striatopallidal/striatonigral GABA terminals (Allen et al., 2009). On this view the variety of GABAergic interneurons, which exert a strong inhibitory control of MSNs activity, may either contribute to early pathological changes that take place within the striatal microcircuit or exert a neuroprotective role, thus becoming a new interesting target for therapeutic interventions.

Postmortem studies revealed that in HD brains nitric oxide syntase (NOS)-positive interneurons are more resistant to mhtt effects (Dawbarn et al., 1985; Ferrante et al., 1985, 1987b; Beal et al., 1986), calretinin-positive are spared or increased in number (Cicchetti et al., 1996; Cicchetti and Parent, 1996; Massouh et al., 2008), while the group of striatal TH-positive cells, whose vast majority in both human and non-human primates appear to be GABAergic interneurons (Betarbet et al., 1997; Tepper et al., 2010), are significantly decreased in HD patients compared to control, as a compensatory response (Huot et al., 2007).

Acetylcholine

Although in the first studies cholinergic interneurons appeared to be spared (Ferrante et al., 1987a,b), the occurrence of cognitive deficits in patients prompted investigators to explore the possibility that cholinergic system was altered in HD brain. In line with this idea, the first neurochemistry investigations indicated a marked decrease of choline acetyl transferase activity (ChAT), the biosyntetic enzyme of Ach, which reflects lower levels of Ach (Bird and Iversen, 1974; Aquilonius et al., 1975; Spokes, 1980; Reynolds et al., 1990; Suzuki et al., 2001). These results are in line with the decrease in ligand binding of vesicular Ach transporter (Suzuki et al., 2001) and a diminution of its protein expression (Smith et al., 2006) observed in postmortem HD striata. A recent study has clarified that the decrease in the number of ChAT-positive neurons in HD does not appear to result from a degeneration of these interneurons, but rather from a marked diminution of their ChAT immunostaining (Massouh et al., 2008), according to the ability of mhtt to interfere with transcriptional process and gene expression.

Since early observation of an altered cholinergic system, research effort has been focusing on attempts to restore the cholinergic tone in the brain of HD patients using inhibitors of acetylcholinesterase, the enzyme that degrades endogenous Ach. However, very few studies reported significant clinical outcomes. While some studies reported a therapeutic effect of acetylcholinesterase inhibitors on either cognitive functions (Rot et al., 2002; de Tommaso et al., 2004), or motor performance (de Tommaso et al., 2007), another report failed to demonstrate any beneficial outcome of the treatment (Cubo et al., 2006). Interestingly, however, positive effects on cognitive performances support the role of Ach in striatal-dependent forms of learning, and the reduction of motor disabilities confirms the role of cholinergic striatal neurones in the control of voluntary movements.

Brain-derived neurotrophic factor (BDNF)

Another adverse effect of reduced corticostriatal communication in HD is the reduced release of BDNF. Corticostriatal neurons deliver BDNF via activity-dependent release into the striatum where it preferentially binds to its high-affinity receptor, the tyrosine kinase tropomyosin-related kinase B (TrkB) receptor, leading to the activation of various intracellular pathways that control neurite growth,

synaptic plasticity, proliferation, and survival. Notably, decreased BDNF levels have been found in the brains of HD patients (Zuccato and Cattaneo, 2007). Moreover, studies have demonstrated that transcription of BDNF is increased by htt and reduced by mhtt (Zuccato et al., 2001, 2003) and that reduced BDNF expression is observed in presymptomatic HD mice (Zuccato et al., 2001).

Interactions between neurotransmitter systems

Although few clinical studies have been focused on the role of modulatory neurotransmitters in HD, an aspect that is recently attracting increasing attention from researchers in the field of neurodegeneration is the derangement of the interactions between distinct neurotransmitter systems. An example is given by the cross-talk existing between DA D1 and NMDARs. It has been shown that D1R activation increases the surface levels of NR2B-containing NMDARs and their synaptic localization in striatal cells (Hallett et al., 2006) leading to augmented glutamate toxicity in HD models (Tang et al., 2007). However, the nature of this relationship is complicated by the observation that D1 activation may also suppress NMDAR-mediated currents and reduce NMDAR-mediated toxicity through NR1 and NR2AC-terminal interactions with D1Rs (Lee et al., 2002). Further investigations of DAergic modulation of NMDAR subunits localization, toxicity, and activity in HD models should prove informative and provide new insights into the role of these two important players in the functioning of glutamatergic synapse. These data indicate that striatal synaptic plasticity could be affected also by changes in modulatory neurotransmission in HD. Activation of D1-expressing cells is positively coupled to cAMP (Shen et al., 2008), whereas MSNs mostly expressing DA D2R, whose activation inhibits cAMP, coexpress adenosine receptors, which are positively coupled to cAMP (Shen et al., 2008). This involvement of adenosine might be important because cAMP levels are reduced early in HD mice (Gines et al., 2003). The importance of A2a adenosine receptors in HD pathogenesis relies also on the fact that they are highly expressed in the striatum in which they operate a strong control of DA-modulatory actions, particularly in the striatopallidal neurons that are affected earlier in HD. Several lines of evidence indicate that A2a receptors are also strongly involved in the regulation of both BDNF function and levels in the brain (Tebano et al., 2010; Potenza et al., 2007). Interestingly, it has been observed that concomitant activation of DA D2Rs and blockade of A2a adenosine receptors is able to decrease striatal glutamatergic transmission (Tozzi et al., 2007). This interaction is made possible by a retrograde action of endocannabinoids released by postsynaptic MSNs and acting on CB1 cannabinoid receptors located on glutamatergic terminals (Tozzi et al., 2011).

Therefore, it is not surprising that both adenosine and endocannabinoids receptors have been implicated in early HD pathogenesis (Tang et al., 2005; Cha, 2007; Zhang et al., 2008). In fact, alterations in A2a receptor expression and signaling have been observed and A2a antagonists have protective effects in several experimental models of HD (Kumar et al., 2010). Moreover, one of the first neurochemical changes observed in HD patients is the loss of cannabinoid receptor binding in the basal ganglia, an alteration that significantly precedes the development of identifiable striatal neuropathology as documented in postmortem samples of HD patients at very early stages of the disease (Richfield and Herkenham, 1994; Glass et al., 2000). Such loss of CB1 receptors becomes much more marked when striatal degeneration emerges as seen in postmortem samples collected from HD patients at intermediate and advanced phases of the disease (Richfield and Herkenham, 1994; Glass et al., 2000). In symptomatic stages, CB1 agonists are in fact successfully used to reduce hyperkinesia suggesting that the cannabinoid signaling system, and particularly that acting through CB1 receptor, would become hypoactive in the basal ganglia of HD patients and of patients suffering from other hyperkinetic disorders. This hypothesis has been confirmed in numerous studies in which different endocannabinoid elements have been analyzed in patients, in particular the CB1 receptor type (Glass et al., 1993, 2000; Richfield and Herkenham, 1994; Lastres-Becker et al., 2001; Battista et al., 2007).

MODELS OF HD

Excitotoxic models

As striatal cell loss appears to be the primary neuropathological hallmark in HD, the first rodent models developed to mimick HD features used excitotoxins to selectively destroy striatal MSNs (Coyle and Schwarcz, 1976; Schwarcz and Coyle, 1977; Brouillet et al., 1999; Wang and Qin, 2006), leading to the generation of the excitotoxic hypothesis as possible first explanation of striatal selective vulnerability in HD.

The most studied excitotoxic model is perhaps the rat intoxicated with the NMDAR agonist quinolinic acid (Roberts et al., 1993), an endogenous excitotoxin which is found elevated in the brain of HD patients. The principal advantage of this model is represented by the selective neurodegeneration of GABAergic neurons exerted by quinolinic acid administration, with relative sparing of LAIs. Another interesting aspect consists in the observation that rats intoxicated with quinolinic acid show an age-dependent decrease in enkephalin neuron vulnerability in contrast to substance P-positive striatal neurons. This result supports the idea that a differential age-related decline in the sensitivity of striatal projection neuron types to this process may contribute to the more uniform striatal neuron loss observed in juvenile-onset compared to the more differential loss in adult-onset HD (Sun et al., 2003).

Mitochondrial toxicity models

Other models were generated starting from the observation that deficits in energy metabolism also occur in HD. To selectively target mitochondrial function various mitochondrial toxins were used, such as rotenone (Greenamyre et al., 1992), 1-methyl-4-phenylpyridinium (MPP) (Storey et al., 1992), malonate (Beal et al., 1993a), 3-acetylpyridine

(Schulz et al., 1994), and 3-nitropropionic acid (3-NP); (Beal et al., 1993b; Brouillet et al., 1993). In rodents and non-human primates, systemic or intracerebral administration of 3-NP or malonate were able to block the mitochondrial respiratory complex II by inhibiting the activity of the membrane-bound mitochondrial enzyme succinate dehydrogenase (Alston et al., 1977; Coles et al., 1979). Irreversible inhibition of this mitochondrial enzyme by 3-NP induces depletion of intracellular ATP in neurons, leading to impairment of cation exchange pumps and progressive membrane depolarization due to intracellular sodium overload (Brouillet et al., 1999) with a selective striatal lesion similar to the pattern of cell loss observed in HD (Damiano et al., 2010; Beal et al., 1993b; Brouillet et al., 1995). These lesions correlate in an age-dependent fashion to a number of motor and neuropathological symptoms observed in HD patients and result in differential sparing of striatal interneurons with a significant loss of GABAergic neurons. Moreover, as the degeneration is prevented by prior decortication, this model provided the first evidence that intact corticostriatal glutamatergic innervation plays an important role in striatal degeneration produced by systemic administration of 3-NP.

Genetic models

Although toxic models greatly contributed to the understanding of principal mechanisms underlying cell death in HD, advanced studies on the progression of the disease have been made possible after the discovery of htt gene in 1993 and the generation of genetic models (Cepeda et al., 2010; Kumar et al., 2010; Heng et al., 2008; Menalled et al., 2009). The possibility to reproduce htt mutation and create more faithful paradigms of the disease allows the dissection of early events in neuronal degeneration introducing the idea that motor symptoms and cell death might be preceded by neuronal dysfunctions in the affected brain areas (Levine et al., 2004).

The different genetic mouse lines can be subdivided based on how the mhtt is incorporated into the mouse genome in: (a) transgenic mice that, besides expression of both alleles of murine wild-type htt, express also a fragment of the human htt gene containing polyglutamine mutations, like R6/2 and R6/1 mice (Mangiarini et al., 1996; Laforet et al., 2001); (b) knock-in mice with pathogenic CAG repeats inserted into the existing CAG expansion of wild-type murine htt (White et al., 1997; Shelbourne et al., 1999; Wheeler et al., 1999, 2000; Lin et al., 2001; Menalled et al., 2002; Heng et al., 2007); (c) mice that express the full-length human HD gene, like mice expressing mhtt through yeast artificial chromosomes (YAC) or bacterial artificial chromosome (BAC) (Reddy et al., 1998; Hodgson et al., 1999; Hersch and Ferrante, 2004); (d) mice in which mhtt can be turned on or off at a certain age, mimicking distinct phases of the disease and allowing to dissect narrow effects of htt mutation on specific molecular targets (Yamamoto et al., 2000; Gu et al., 2005).

Besides mouse models, transgenic rats have also been generated and are currently studied. In these rats, carrying truncated htt cDNA fragment with variable numbers of CAG repeats under control of the native htt promoter, it is possible to reproduce a wide range of adult-onset neurological phenotypes that more closely resemble the neuropathological characteristics of human HD (Heng et al., 2008). Other rodent models have been generated using rats in which mhtt is delivered through viral vectors coding for variable numbers of CAG repeats (Senut et al., 2000).

Although most of the studies reviewed here have been conducted in R6 line, many of the HD symptoms can be reproduced in the currently available rodent models. Among them, behavioral cognitive alterations and motor abnormalities are reliable common features whose level of expression is based on the impact of toxin administration and the degree of overexpression of the mutant protein. Changes in neuronal activity can be effectively studied in most of the models, although subtle early neuronal alterations in synaptic events can be better characterized in genetic models, which offer the advantage of a defined onset and a progressive development of disease symptoms. Since electrophysiological analyses provide crucial information on neuronal dysfunction and circuit changes that underlie or precede symptoms, we will review seminal and more recent papers that focus on various aspects of neuronal physiology of corticostriatal pathway.

NEUROPHYSIOLOGY OF HD IN ANIMAL MODELS

Similar to human HD mutation carriers, HD mice exhibit early deficits in cognition and behavior years prior to motor dysfunction (Murphy et al., 2000; Nithianantharajah et al., 2008). These initial alterations are often associated with aberrant neuronal network properties in the striatum and cortex with disruption of NMDAR-dependent LTP and LTD (Usdin et al., 1999; Milnerwood et al., 2006; Lynch et al., 2007). In particular, subtle changes are likely to begin in the cortex as suggested by experimental reports (Miller et al., 2008, 2010; Spampanato et al., 2008; Walker et al., 2008; Schippling et al., 2009) showing loss of coordinated firing patterns in different HD models.

Glutamate and GABA

Among the many neurotransmitters involved in HD pathophysiology, glutamate has been so far the most studied. In fact, the initial underlying hypothesis used to explain neurodegeneration in HD, the excitotoxicity hypothesis, prompted initial studies in genetic mouse models at verifying whether increased glutamate release and sensitivity of NMDARs could cause striatal cell death in HD.

As the majority of the studies have been focused on striatal alterations during symptomatic stages, decreases of both striatal glutamate receptors and release have been mainly associated to development of symptoms.

In fact, increased NMDAR function was verified in R6/2, YAC72, and YAC 128 mice, in electrophysiological recordings and calcium imaging studies showing that MSNs had increased responses to NMDA (Graham et al., 2009; Hodgson et al., 1999; Cepeda et al., 2001). However, the most interesting aspect in the electrophysiologi-

cal changes of cortical and striatal glutamatergic and GABAergic signaling systems is that, in HD, they follow a biphasic pattern of alteration as the disease progresses (Cepeda et al., 2010). Most of these studies were done in R6/2 and YAC128 HD mice. Although a progressive reduction in spontaneous and evoked glutamatergic synaptic activity, coinciding with the appearance of overt behavioral 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 approximately 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 DA D2, metabotropic glutamate (mGluR2/3), and endocannabinoid CB1 receptors (Cha et al., 1998; Luthi-Carter et al., 2000; Ariano et al., 2002). As striatal neuronal action potential generation is highly dependent on cortical inputs, the presence of large-amplitude synaptic events in the striatum of R6/2 mice at 5–7 weeks, during the early symptomatic phase, in conjunction with higher membrane input resistance, predicts transiently increased activity along the corticostriatal pathway in a subset of MSNs. Hyperexcitability in cortical networks was confirmed in the R6/2 and other mouse models. Examination of somatosensory cortical pyramidal neurons in slices from R6/2 mice revealed that spontaneous excitatory postsynaptic currents (EPSCs) occurred at a higher frequency in behaviorally phenotypic mice, whereas inhibitory postsynaptic currents (IPSCs) were initially increased in frequency and subsequently decreased at 80–90 days (Cummings et al., 2009). Decreased inhibition in cortical pyramidal neurons and altered synaptic and passive properties of PV interneurons was also observed in BACHD mice at 6 months, when motor dysfunction occurs (Spampanato et al., 2008).

Interestingly, in contrast with reduced IPSC frequency in the cortex of symptomatic animals, the frequency of inhibitory GABA receptor-mediated synaptic events is increased in the striatum of R6/2 and other models of HD (Cepeda et al., 2007; Cummings, 2007). This inhibition within the striatum leads to temporally distinct alterations in both direct and indirect pathways possibly causing dysregulation of inhibitory nigrothalamic and pallidothalamic pathways.

Consequently, thalamocortical and thalamostriatal neuronal activities are no more under GABAergic control of basal ganglia output nuclei and may generate the characteristic fluctuations in HD symptoms. Similar to R6/2 mice, YAC128 mice showed biphasic age-dependent changes in corticostriatal function. At 1 month, before the behavioral phenotype develops, striatal glutamate release and AMPA receptor-mediated synaptic currents evoked by cortical stimulation were increased. At 7 and 12 months, after the development of the behavioral phenotype, glutamate release and AMPA synaptic currents were significantly reduced (Joshi et al., 2009). These effects were due to combined pre- and postsynaptic alterations, as demonstrated by another study showing that NMDAR-mediated synaptic currents and postsynaptic currents are increased in slices and in acutely isolated MSNs from presymptomatic YAC128 mice followed by reduced currents in symptomatic stage (Graham et al., 2009).

However, studies in symptomatic animals show decreases of striatal NMDA mRNA in 8–12-week R6/2 mice and decreases of AMPA receptors in 12-week R6/2 mice (Cha et al., 1998, 1999). In these studies, there was a loss of cortical glutamate receptors that occurred later than in the striatum. Basal striatal glutamate levels were also reduced in R6/1 mice at 16 weeks (Nicniocaill et al., 2001) and axons containing mutant htt aggregates had fewer synaptic vesicles suggesting that mhtt binds tightly to synaptic vesicle membranes, inhibiting uptake and release of glutamate (Li et al., 2003).

In contrast to the striatum, cortical NMDA and AMPA receptor-induced currents were decreased in presymptomatic but unchanged in symptomatic R6/2 mice compared to controls (Cha et al., 1998; Andre et al., 2006). Decreased postsynaptic glutamate currents in pyramidal neurons could account for decreased vulnerability in cortical structures compared to the striatum. However, in symptomatic R6/2, YAC128, and CAG140 knock-in mice, glutamate synaptic neurotransmission was increased in the cortex and pyramidal neurons showed signs of hyperexcitability (Cummings et al., 2009). These observations suggest that cortical glutamate inputs are increased in models of HD, while striatal glutamate inputs appear to be decreased (Cepeda et al., 2003) probably because thalamic activity is no more under inhibitory control of GABAergic neurons of internal globus pallidus and substantia nigra pars reticulata, the two main output nuclei of human basal ganglia. The differential changes in glutamate currents observed in the striatum and cortex suggest that alterations induced by mhtt are not solely cell-dependent, but also depend on more complex interactions within the basal ganglia circuitry.

Prior to motor deficits in YAC 128 HD mice, striatal glutamate release is increased during trains of cortical and callosal stimulation (Joshi et al., 2009). Increased glutamate release could contribute to striatal neuronal stress, a notion supported by the reduction of phenotype severity by decortication as shown in R6/2 mice (Stack et al., 2007). However, other studies in young presymptomatic R6/2 mice show that evoked and spontaneous glutamate release is not elevated, based on AMPAR current frequencies and amplitudes and that spine density is not altered (Milnerwood et al., 2010; Cepeda et al., 2003; Milnerwood and Raymond, 2007), suggesting that augmented corticostriatal glutamate currents in HD mice may be due to more complex intra-cortical region-specific alterations rather than to an increased synapse number.

A possible explanation of the functional dichotomy of NMDAR signaling during the progression of the disease and the differences between striatum and cortex, has been suggested to depend on the subcellular site of NMDAR activation (Vanhoutte and Bading, 2003) since the stimulation of synaptic NMDARs is able to trigger pro-survival signaling pathways, whereas activation of

NMDARs at peri- and extra-synaptic sites has been reported to be neurotoxic. Accordingly, altered trafficking of NMDAR subunits and elevated extra-synaptic NMDAR activity has been recently demonstrated in YAC72 and 128 mice, providing a possible mechanism for early synaptic disfunctions in HD (Milnerwood et al., 2010; Fan et al., 2007).

In summary, initial changes are likely to begin in the cortex (Miller et al., 2008; Spampanato et al., 2008; Walker et al., 2008; Schippling et al., 2009) and produce initial increases in glutamate release from corticostriatal terminals, reflected by enhanced synaptic responses and large-amplitude spontaneous synaptic events. Excess glutamate release causes the collapse of spines on postsynaptic MSNs, which increases membrane input resistance, reduces potassium conductances, and further amplifies synaptic signals (Klapstein et al., 2001). Dysregulation of glutamate release is compounded by loss of DA D2, cannabinoid CB1, metabotropic glutamate mGluR2/3 receptors, and other presynaptic receptors regulating glutamate release at corticostriatal terminals. A compensatory mechanism is represented by the increase of GABAergic synaptic activity that occurs within the striatum. Increasing GABAergic synaptic transmission could aid in preventing further neuronal damage by reducing glutamate release, by activation of presynaptic $GABA_B$ receptors, and/or inducing postsynaptic alterations by shunting excitatory inputs to MSNs, via $GABA_A$ receptors (Andre et al., 2010).

Dopamine

Many seminal works have explored the correlation between DA signaling alteration and HD motor symptoms, but studies aimed at understanding how impairments in the release of nigrostriatal DA contribute to behavior in HD have recently gained new interest suggesting that changes in DA signaling have a profound impact on locomotor activity also in early stages. In line with this idea, decrease in DA- and cAMP-regulated phosphoprotein DARPP-32 expression can be observed in early symptomatic transgenic mice that do not present any obvious cell loss (Bibb et al., 2000; Luthi-Carter et al., 2000; Menalled et al., 2000; van Dellen et al., 2000). At 6 weeks, during early symptomatic stage, R6/2 mice display decreases in D1R and D2R binding (Mangiarini et al., 1996; Cha et al., 1998), and D1-dependent modulation of AMPA currents was also decreased (Bibb et al., 2000). By this age, DA-dependent corticostriatal LTP recorded intracellularly from MSNs is not altered (Picconi et al., 2006) but synaptic depotentiation is abolished and concomitantly interneuronal plasticity is defective. As the disease progresses, in symptomatic R6/2 mice, D1R-dependent striatal LTP of field potential amplitude also becomes reduced compared to wild type littermates (Kung et al., 2007). Microdialysis studies showed that DA release was progressively reduced in R6/2 mice between 6 and 14 weeks (Hickey et al., 2002). In the 3-NP model, striatal DA content was unchanged but evoked DA release was decreased (Kraft et al., 2009) with concomitant hyperkinesia occurring late in the disease development similar to the quinolinic acid model (Sanberg et al., 1989; Brouillet et al., 1995). Other studies showed that in young YAC128 mice (1 month), D2Rs are functional, but become much less effective at 12 months (Joshi et al., 2009). Although DA receptor density was unchanged in 12-month-old YAC128 mice (Benn et al., 2007), this may represent a compensatory mechanism for decreased DA availability because the number of striatal neurons is reduced by 15% in this age group (Slow et al., 2003). Interestingly, YAC128 mice exhibit initial hyperactivity, followed by the onset of motor deficit and then hypokinesia correlated with striatal neuronal loss (Slow et al., 2003).

It has been shown that R6/2 mice were less responsive to the stimulatory effects of cocaine and amphetamine compared to wild-type control mice (Hickey et al., 2002). Additionally, a voltammetry study has revealed that striatal DA release in R6/2 mice is impaired, and also that a blunted locomotor response to cocaine correlates with this impairment (Johnson et al., 2006). Although the number of TH-positive neurons was not reduced and nigrostriatal connectivity remained intact, DA release, measured in the striatum by microdialysis sampling (Petersen et al., 2002a,b), and locomotor function (Bolivar et al., 2004) have been found to be decreased also in R6/1 mice relative to wild-type controls. It has been reported that in 3-NP intoxicated rats, removal of the nigrostriatal dopaminergic input protects the striatum from neurodegeneration (Reynolds et al., 1998).

Moreover, in a recent study using 3-NP treated rats, although striatal DA content was unchanged, its release and uptake were decreased compared to sham control rats and accompanied by impairment of locomotor activity (Kraft et al., 2009). Accordingly D1R-dependent LTP in MSNs is also lost in presymptomatic 3-NP rats (Picconi et al., 2006). In an *in vitro* study, in which mhtt-expressing lentiviral vectors were injected in rat striatum, it has been demonstrated that DA accelerates aggregate formation and striatal neuronal death, two neuropathological hallmarks gradually induced by mhtt (Charvin et al., 2005). Accordingly, treatment with the D2 antagonist haloperidol beginning at an early stage, significantly reduces both mhtt-induced neuronal dysfunction and striatal aggregate formation providing evidence that D2R blockade can slow down initial striatal dysfunction in HD (Charvin et al., 2008).

BDNF and PV-positive interneurons

Lack of BDNF, a common phenotype of mouse models of HD, has been linked to the loss of wild-type htt function (Zuccato and Cattaneo, 2007) and it negatively impacts MSNs, in which an initial period of increased glutamate release is followed by a progressive reduction of synaptic input. Such reduction is associated to decreased potassium conductances, and depolarized resting membrane potential, leading to an increased propensity for MSNs to produce action potentials and to fire in disorganized manner (Cepeda et al., 2010). Interestingly, BDNF is specifically required for maturation of inhibitory GABAergic synapses (Marty et al., 1996; Bartrup et al., 1997; Yamada et al., 2002). Consistent with these observations, 6-month-old BACHD mice are reported to have significantly reduced levels of BDNF (Gray et al., 2008), while in HD knock-in

mice, in addition to presymptomatic reductions of BDNF, cAMP levels are low, as is phosphorylation and activation of the transcription factor CREB (cAMP response element binding protein) (Gines et al., 2003). Neuronal CREB-mediated transcription, driven by synaptic NMDARs, regulates synaptic plasticity, mitochondrial function, and cell survival. Interestingly, both BDNF and synaptic NMDAR signaling activate the MAPK (mitogen activated protein kinase) and ERK (extracellular signal-regulated kinase) pathways, converging upon Ras GTPases (Harjes and Wanker, 2003), thus suggesting that BDNF signaling influences intracellular machinery involved in long-term modifications of synaptic plasticity.

Relevant to both cortical and striatal microcircuits, in which interneurons shape neuronal activity of projection neurons, is the evidence that PV-positive GABAergic interneurons require BDNF for proper electrophysiological and anatomical maturation, such as extensive dendritic arborization and synapse maintenance (Gorski et al., 2003; Berghuis et al., 2006; Itami et al., 2007). Cell type-specific interactions are a common feature for neurotrophins. In fact, effectiveness of BDNF is critically influenced by neuronal activity, and synaptic potentiation induced by BDNF can be selective for highly active synapses. Consequently, BDNF exerts opposite effects on cortical pyramidal neurons and GABAergic interneurons, depending on the level of neuronal activity. In particular, lower cortical activity associated with reduced BDNF release promotes adjusting of synaptic strengths in order to increase excitation onto pyramidal neurons. On the other hand, when cortical activity is high and BDNF release increases, synaptic strengths are adjusted to promote excitation onto PV-positive GABAergic interneurons, which, in turn, recruit more inhibition onto pyramidal neurons. This suggests that BDNF plays a key role in the activity-dependent stabilization of cortical activity (Rutherford et al., 1998).

Several studies pointed out to the specific role of BDNF in the differentiation of GABAergic terminals (Bolton et al., 2000). Specifically, BDNF is implicated in the development and maturation of GABAergic PV-positive interneurons (Berghuis et al., 2004). Interestingly, it has been reported that PV-containing interneurons appear to be preserved early in the course of HD but degenerate with progression of this neurodegenerative disease (Fusco et al., 1999; Wu and Parent, 2000; Vonsattel and DiFiglia, 1998; Giampa et al., 2006, 2009).

On this line, an aspect not often taken into consideration in experimental settings is the occurrence of epileptic seizures in juvenile HD patients, which is replicated in R6/2 mice where increased epileptiform activity in cortical slices and seizure susceptibility were found (Cummings et al., 2009).

In normal condition low levels of BDNF specifically bind to TrkB receptors expressed by MSNs, activating different calcium-dependent intracellular pathways that result in accurate tuning of MSNs activity. Recent evidence, however, indicated that during epilepsy, interneuronal activity is markedly altered (Slaght et al., 2004; Mallet et al., 2005; Pakhotin and Bracci, 2007) and BDNF colocalizes more with GABAergic interneurons resulting in an alternative pattern of BDNF distribution that favors an enhancement of inhibitory control within the striatum as adaptive mechanism (Ghiglieri et al., 2010). Thus, striatal changes in BDNF signaling through its high-affinity receptor TrkB contribute to the reorganization of inhibitory system as adaptive response to seizures. Such adaptive response initially protects MSNs from excessive activity and preserve striatal functions and it is likely to represent an early alteration of GABAergic function within the striatum.

Consistent with these data and considering the complex regulation of GABAergic PV-positive interneurons activity by BDNF during development (Marty et al., 1996; Rutherford et al., 1998; Bolton et al., 2000; Berghuis et al., 2004; Grosse et al., 2005), it is possible that also in other areas particularly enriched in PV-positive interneurons, like hippocampus and cortex, cell type-specific alterations of BDNF signaling may occur. The subsequent creation of abnormal circuitry may then predispose those areas to recurrent seizure activity and this pathological pattern may be a common trait of neurodegenerative disorders characterized by seizure susceptibility.

The role of cholinergic interneurons

It has long been established that the cholinergic system plays a key role in acquisition and retention of new information (Wilson and Cook, 1994; McGaugh and Cahill, 1997; Newhouse and Kelton, 2000). Accordingly, selective ablation of cholinergic neurons in the striatum impairs procedural learning (Kitabatake et al., 2003). In R6/2 mouse model at early symptomatic stage (6 weeks), both MSNs and LAIs showed specific alterations of plasticity (Picconi et al., 2006) supporting the hypothesis that endogenous Ach, in concert with glutamate and DA, critically modulates synaptic scaling of MSNs. Therefore, focusing on LAIs may represent an initial step toward the exploration of the emerging dysregulation of cellular properties in the striatal microcircuit in HD. Moreover, since LAIs are highly enriched in both htt and BDNF in the normal brain and after excitotoxic lesions (Fusco et al., 2003), these neurons might play a critical role in the pathophysiology of HD in a way that involves BDNF.

In response to high-frequency stimulation of corticostriatal fibers, MSNs recorded in presymptomatic transgenic R6/2 mice and 3-NP-intoxicated rats at an early stage of disease, displayed an LTP whose amplitude and time course were similar to those measured in control animals (Picconi et al., 2006). In control condition, after the induction of LTP, it is possible to reverse the previously potentiated synapse to pre-LTP levels. This last form of synaptic plasticity, called depotentiation (Picconi et al., 2003), is necessary to organize memory processes and to allow new salient information to be selected and stored. This form of plasticity is lost early in MSNs of both R6/2 mice and 3-NP–treated rats and its disappearance is accompanied by loss of LTP in the LAIs and poor cognitive performances (Picconi et al., 2006), in line with the reports demonstrating that the cholinergic system is functionally impaired in this pathological condition (Ferrante et al.,

1987a,b; Suzuki et al., 2001; Vetter et al., 2003; Smith et al., 2006; Calabresi et al., 2007; Di Filippo et al., 2007). Interestingly, in HD patients, cognitive disturbances often appear before the typical motor symptoms, years prior to a significant striatal and cortical degeneration, suggesting that even modest alterations of the striatal cholinergic system may cause initial abnormalities in the physiology of striatal MSNs and contribute to early deficits in behavioral flexibility (Calabresi et al., 2007). On this view, the lack of bidirectional plasticity may have its origin in a dysfunctional interplay between glutamate, DA, and Ach, and represent a general cellular and synaptic substrate for most of the early behavioral abnormalities observed in HD subjects, such as the absence of cognitive flexibility and the emergence of perseverative behaviors. Such alteration of plasticity might lead to an overload of information that disrupt critical filtering functions of the striatum leading to the inability to acquire new relevant cortical information and preventing rapid adaptation to environmental changes. In line with this hypothesis is the evidence that HD mutation compromises the capacity of MSNs to process learning and task-related information, thus resulting in decreased procedural learning in R6/1 mice (Cayzac et al., 2011).

Pharmacological manipulation of cholinergic system provided a causal link between endogenous Ach and the induction of depotentiation confirming that, at least in the striatum, converging glutamatergic inputs from cortex and thalamus are integrated by cholinergic and dopaminergic signaling to induce bidirectional synaptic plasticity in the MSNs (Picconi et al., 2006).

Recently, it has been shown that cholinergic interneurons are also crucial site of interaction between DA and adenosine signaling as they, similar to MSNs, coexpress D2 and A2a receptors (Tozzi et al., 2011). Concomitant activation of D2Rs and blockade of A2a receptors reduces the firing rate of these interneurons. One of the final effects of this inhibition would be a reduction of the release of endogenous Ach and the consequent reduced activation of muscarinic receptors on MSNs. The established effect of M1 receptor inhibition would be the opening of L-type calcium channels (Wang et al., 2006). This latter event might, in turn, trigger postsynaptic effects on MSNs, leading to endocannabinoid release and reduction of glutamatergic transmission by the activation of presynaptic CB1 receptors (Fig. 1). Therefore, even subtle alterations of LAIs functions in HD would affect endocannabinoid system that in turn may generate defects in MSNs and interneuronal plasticity. Accordingly, similar to human condition, it has been observed that in different transgenic mouse models of HD (e.g. R6/1, R6/2), analyzed at presymptomatic age, downregulation of cannabinoid receptors also occurs (Blazquez et al., 2011; Denovan-Wright and Robertson, 2000; Lastres-Becker et al., 2002; Naver et al., 2003; McCaw et al., 2004; Centonze et al., 2005). Such dysregulation is also present in rats lesioned with 3-NP at stages before the development of neuronal degeneration (Denovan-Wright and Robertson, 2000). In particular, it has been shown that whereas in control animals activation of cannabinoid CB1 receptors results in a significant inhibition of both evoked and spontaneous GABA-mediated synaptic events by a presynaptic mechanism (Szabo et al., 1998; Centonze et al., 2004), in R6/2 HD mice at early symptomatic stage, this treatment fails to reduce GABAergic currents but causes, in contrast, an increase of spontaneous IPSCs (Centonze et al., 2005). This observation indicates that the loss of cannabinoid-mediated control of GABA synapses might contribute to the dysregulation of GABA transmission in the striatum. This HD-associated hyperactivity of GABA transmission, however, has been indicated to reflect more complex changes involving multiple transmitter systems, as suggested by the observation that the regulation of GABA synapses by BDNF is also abnormal in R6/2 striatal neurons (Cepeda et al., 2004).

LIMITATIONS OF MURINE MODELS

Although toxic models greatly contributed to the understanding of some of the mechanisms involved in cell death (DiFiglia, 1990), they are limited by the difficulty to study the progression of the disease or to replicate the widespread neuropathology observed in the human condition. In addition, specific problems may also emerge from distinct neurotoxic model influencing the investigation of several aspects of the disease.

For instance, systemic administration of 3-NP is not specific to the central nervous system as it also induces peripheral neurotoxicity and severe cardiotoxic effects. Moreover, enkephalin and substance P striatal neurons are equally affected by 3-NP, a finding that is inconsistent with those present in adult-onset HD (Ferrante, 2009).

Also genetic models present caveats that might critically hamper a more global interpretation of the pathological HD scenario. In fact, while full-length htt mutation models are genetically more accurate, in these models HD symptoms develop gradually over many months and may not have a sufficient expression of disease to use progressive morbidity and survival as endpoints. Moreover, there are also specific limits like peculiar patterns of neurochemical alterations as in YAC128 mice, in which reduced expression appear limited to glutamate receptors, while in other models also DA, GABA, and adenosine receptor binding are profoundly altered (Benn et al., 2007).

Similarly, knock-in models are considered faithful in terms of genetic context and in recapitulating the late onset, slow natural progression, and neuropathology of HD (Heng et al., 2008), but the symptoms are generally mild and normal aging may be a confounding factor. Also the most used fragment models, which have been standardly used in many screening experiments (Gil and Rego, 2009), have shortcomings as they present well-defined neurobehavioral and neuropathological findings, but a too rapidly coursing phenotype that brings to death between 3 and 4 months of age. For these reasons, fragment models have been suggested to replicate the more fulminant juvenile form of HD and not necessarily the adult-onset form of the disease.

Another limit of murine models is represented by the lack of correlation between neuronal intranuclear inclu-

sions, cell death, and the pattern of selective degeneration (Saudou et al., 1998; Fusco et al., 1999) with the result that the exact role of these aggregates in HD pathogenesis is still unclear. In addition, the lack of correlation between aggregate localization and neuronal vulnerability in HD suggests that selective neurodegeneration might result not only from the specific distribution of toxic htt products but also from intrinsic neuronal properties.

In fact, several lines of evidence indicate that in many mouse models nuclear inclusions generally occur after overt behavioral anomalies, which are thought to depend more on neurophysiological changes and to other mechanisms, such as excitotoxicity, mitochondrial dysfunction, and reduced trophic factors levels (Perez-Navarro et al., 2006). As mentioned before, htt expression in the striatum, the most affected area in HD, is less abundant than in other brain regions (Landwehrmeyer et al., 1995). Furthermore, double labeling of individual striatal neurons showed low to moderate htt immunoreactivity in GABAergic MSNs (Ferrante et al., 1997; Fusco et al., 1999), whereas striatal interneurons, which are spared in HD, showed high htt immunoreactivity (Fusco et al., 1999; Sapp et al., 1999) especially in LAIs (Kuemmerle et al., 1999). Consistent with the ability of interneurons to cope with mhtt-associated degeneration, several studies have also suggested that cellular aggregates might have a protective role as their formation promotes the clearance of mhtt by activating autophagy (Fusco et al., 1999; Ravikumar et al., 2004).

Further distinction between human and animal conditions is that in most HD mouse models, despite striatal volume might be reduced, neuronal death is modest, if not absent, and behavioral, cognitive, and neurological symptoms occur well before cell death is present (Tobin and Signer, 2000). For instance in R6/2 mice, neuronal loss occurs modestly and at very late stages of the disease (Turmaine et al., 2000), while the YAC72 and YAC128 models display the most selective degeneration of MSNs (Hodgson et al., 1999; Slow et al., 2003) and knockin mice do not show any evidence of cell death (Menalled et al., 2002). The gold standard would be a model showing a robust phenotype, moderate to rapid disease onset and progression, well-defined behavioral abnormalities that can be quantified, and neuropathological features, all of which accurately replicate human HD. Nevertheless, available models have still much to offer, as they would potentially provide more valid and useful experimental outcomes that can be used to achieve a greater understanding of the disease process in humans and especially in identifying potential therapeutic strategies (Ferrante, 2009).

PRIMATE MODELS

Compared to rodents, HD nonhuman primates show analogous neuropathology and typical clinical traits, such as rigidity, seizure, dystonia, bradykinesia, and chorea (Yang et al., 2008; Wang et al., 2008), which are hard to replicate in other animal models. Selective degeneration of specific neuronal populations as well as accumulation of neuropil aggregates observed in HD monkey brain strongly support the hypothesis that the distinctive neuropathogenic events seen in these models recapitulate HD in man much better than in any rodent model (Chang and Yang, 2009; Yang and Chan, 2011). Notwithstanding, nonhuman primate models may either fill the gap left by rodent data or provide an alternative point of view aimed at completing the pathological scenario of HD. For example, a group of striatal interneurons that are much more expressed in primates, including humans, than in rodents is the population of calretinin-positive interneurons. This neuronal population, which has been reported to be increased in HD patients' brain (Cicchetti and Parent, 1996), has been reported to be the most abundant interneurons in the human striatum that outnumber PV-positive interneurons by 3 or 4 to 1 (Wu and Parent, 2000). Therefore, studies on mice may not be informative on this neuronal subtype and research on their role in HD should be oriented on the use of primate models.

Another group of interneurons involved in HD is represented by distinct classes of TH-positive interneurons, whose fate in HD has been clarified by Huot and coworkers (Huot et al., 2007). Many controversies about their characteristic and classification have started to be resolved using genetically modified mice that express enhanced green fluorescent protein under the control of the endogenous TH regulatory sequences (Ibanez-Sandoval et al., 2010). Therefore, with the advent of new technologies it is now possible to focus on their functions also in rodent models and information on higher functions from primate models may integrate results of electrophysiological analysis done in mice.

Similarl to rodent models, administration of excitotoxic agents (e.g. quinolinic acid, kainic acid, ibotenic acid, and malonic acid) or mitochondrial disrupters (e.g. 3-NP) reproduces the progressive neurodegenerative symptoms of the disease in nonhuman primates. Researchers have used these methods to induce the disease in baboons (Hantraye et al., 1990), capuchin monkeys (Roitberg et al., 2002), cynomolgus monkeys (Beal et al., 1986), and rhesus monkeys (Ferrante et al., 1993; Burns et al., 1995). Roitberg and colleagues (2002) compared 3-NP-treated capuchin monkeys to animals treated with quinolinic acid and found that both types of lesioned animals had behavioral characteristics of HD, although the two toxins create the lesions in different ways. Generation of genetic nonhuman primate models has started more recently. Palfi and colleagues (Palfi et al., 2007) induced HD symptoms in cynomolgus monkeys by injecting lentiviral vectors carrying a short N-terminal fragment of the htt gene into the putamen. Another research group (Yang et al., 2008) injected lentiviruses carrying exon 1 of the human htt gene with 84 repeats and the green fluorescent protein gene directly into rhesus oocytes before *in vitro* fertilization (Gagliardi and Bunnell, 2009).

The latest development of transgenic HD primates, although difficult to assess, has opened a new era of animal modeling that better represents human genetic disorders such as HD, which will accelerate the development of diagnostic tools and identifying novel biomarkers through longitu-

dinal studies including gene expression, nanotechnology applications, and noninvasive imaging. Furthermore, novel treatments with predictable efficacy in human patients can be developed using HD monkeys because of their brain comparable dimensions and citoarchitecture complexity, besides neuropathology and clinical features in disease condition (Yang et al., 2008).

CONCLUSIONS

All the reviewed works own the great value of having contributed to the understanding of many important mechanisms underlying the variety of alterations associated to HD. Future challenge of the field would be, however, to overcome shortcomings that are intrinsic to the models but also to the current approach to pathology. The limitations that every model carries unavoidably set the restrictions in which research investigators can operate. However, also the consideration of distinct aspects of disease as separated entities, may hamper the possible uses of exsistent models. This approach needs to be revised before putting efforts in the generation of new models increasingly faithful to human conditions. Without establishing a precise scenario of the interactions between the neuronal populations affected by htt mutation, the risk would be to have reliable evidence of electrophysiological deficits that fails to correlate with morphological alterations of specific neuronal subtypes. The effect of such approach would bring to a larger amount of data but also to increasingly difficult interpretation of the mechanisms involved. For example, although it has been established that in R6 transgenic mice lines two classes of striatal interneurons, the PV-positive FSIs and the LAIs, are differentially affected by the expression of mhtt, neuroanatomical investigations have not been exhaustively followed by electrophysiological analysis of possible functional correlates. Another unexplored issue is the fact that cholinergic interneurons, being highly enriched in both htt and BDNF in the normal brain and after excitotoxic lesions (Fusco et al., 2003), may play a critical role in the pathophysiology of HD in a way that involves BDNF.

Multidisciplinary approaches allowing the concomitant study of single units and field potential neuronal activity during behavior give important information on the network changes. It has been recently suggested by Cayzac and coworkers that the change in the number of recruited MSNs, rather than the proportion of the recorded MSNs that are task-sensitive, can account for the delayed learning in R6/1 mice (Cayzac et al., 2011). More interestingly, these authors also demonstrated that striatal neuronal activity is altered in the gamma frequency range, which has been suggested to be regulated by the intrinsic inhibitory system through the synchronous activity of GABAergic interneurons (Tepper et al., 2010). In line with this, it has been recently demonstrated that MSNs from R6/2, knock-in mouse, and transgenic rat models, have drastically altered MSNs spontaneous firing patterns compared to WTs (Miller et al., 2008, 2010).

In order to be successful and functional to development of new therapies, ideal models should be based on a comprehensive characterization of the striatal and cortical circuits. In doing this, it is important to take into account all the molecular and cellular players involved in the complex machinery that guarantees a proper expression of the synaptic functions, independently from their role (modulatory vs. inhibitory and excitatory) and from their relative abundance in the affected brain areas (interneurons vs. projection neurons) (Fig. 1).

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