HHS Public Access

Author manuscript

*Prog Brain Res*. Author manuscript; available in PMC 2015 April 24.

Published in final edited form as:

*Prog Brain Res*. 2014 ; 211: 235–254. doi:10.1016/B978-0-444-63425-2.00010-6.

# The Role of Dopamine in Huntington's Disease

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## Abstract

Alterations in dopamine (DA) neurotransmission in Parkinson's disease are well-known and widely studied. Much less is known about DA changes that accompany and underlie some of the symptoms of Huntington's disease (HD), a dominant inherited neurodegenerative disorder characterized by chorea, cognitive deficits and psychiatric disturbances. The cause is an expansion in CAG (glutamine) repeats in the *HTT* gene. The principal histopathology of HD is the loss of medium-sized spiny neurons (MSNs) and, to a lesser degree, neuronal loss in cerebral cortex, thalamus, hippocampus and hypothalamus. Neurochemical, electrophysiological and behavioral studies in HD patients and genetic mouse models suggest biphasic changes in DA neurotransmission. In the early stages DA neurotransmission is increased leading to hyperkinetic movements that can be alleviated by depleting DA stores. In contrast, in the late stages DA deficits produce hypokinesia that can be treated by increasing DA function. Alterations in DA neurotransmission affect glutamate receptor modulation and could contribute to excitotoxicity. The mechanisms of DA dysfunction, in particular the increased DA tone in the early stages of the disease, are presently unknown but may include initial upregulation of DA neuron activity caused by the genetic mutation, reduced inhibition resulting from striatal MSN loss, increased excitation from cortical inputs, and DA autoreceptor dysfunction. Targeting both DA and glutamate receptor dysfunction could be the best strategy to treat HD symptoms.

### Keywords

Huntington's disease; dopamine; neurotransmission; receptors; glutamate; medium-sized spiny neurons

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## Introduction

Huntington's disease (HD) is a fatal, slowly progressing neurodegenerative disease caused by a mutation in the *HTT* gene. The symptoms of HD include chorea (uncontrollable dance-like movements), cognitive deficits and mood changes. Histopathologically, there is massive loss of striatal medium-sized spiny neurons (MSNs) and, to a lesser degree, cortical pyramidal neurons. The mechanisms of cell loss remain unclear but may involve excess glutamate release from cortical and thalamic terminals, increased sensitivity of glutamate receptors, and increased activation of pro-apoptotic extrasynaptic N-methyl-D-aspartate (NMDA) receptors. Alterations in dopamine (DA) function and neurotransmission have a significant role in the motor and cognitive symptoms of HD since it is well-known that glutamate receptor function is modulated by activation of DA receptors. In this chapter we discuss changes in DA neurotransmission that may underlie some of the electrophysiological, neuropathological, behavioral and cognitive alterations in HD. Based on clinical and experimental data we propose that the modulatory function of DA is disrupted early in disease progression, leading to aberrant glutamate transmission and consequent excitotoxic cascades. We also discuss possible mechanisms of altered DA modulation and the search for rational therapies based on these findings.

## Striatal DA Innervation in the HD Postmortem Brain

Neuropathological alterations that characterize HD are widespread but predominantly affect the striatum and the cerebral cortex. The massive atrophy of the striatum is the major pathological hallmark (Vonsattel et al., 1985) and is largely caused by the loss of MSNs, the interneurons being relatively well preserved (Graveland et al., 1985; Ferrante et al., 1987; Kowall et al., 1987; Massouh et al., 2008; Vonsattel et al., 2008a), except for parvalbumin interneurons (Reiner et al., 2013). These changes contribute to the expression of HD symptoms that include hyperkinesia and choreiform involuntary movements in the early stages, as well as rigidity, hypokinesia and debilitating psychiatric symptoms in the later stages (Phillips et al., 2008).

In a pioneering neuropathological study, Bernheimer and colleagues reported no significant cell loss in the substantia nigra of HD patients (Bernheimer et al., 1973). However, by using more appropriate stereological procedures that accounted for substantia nigra atrophy occurring in this neurodegenerative disease (Gibb, 1991; Vonsattel et al., 2008b), other investigators reported a significant decrease in the number of substantia nigra neurons in HD brains (Oyanagi et al., 1989; Richardson, 1990). Interestingly, recent evidence has suggested that changes in chemical content of monoaminergic neurons might occur in the dorsal raphe nucleus, leading to an increase of DA neurons at the expense of serotonin neurons (Jahanshahi et al., 2013). Such a phenotypic shift has to be taken into account to understand the neuropathological and neuroadaptive mechanisms in HD.

Post-mortem studies of HD brains and age-matched controls reveal a significant decrease of tyrosine hydroxylase (TH) immunoreactivity accompanied by a diminution in the density of TH axon terminals throughout the entire extent of the striatum in advanced HD patients (Bedard et al., 2011). This change appears to be more significant in the caudate nucleus,

followed by the putamen and the nucleus accumbens. It is believed that the reported striatal DA innervation decrease might significantly contribute to the rigidity and akinesia displayed by advanced HD patients, a motor impairment that strikingly resembles Parkinson's disease. These post-mortem observations are in keeping with other preliminary studies suggesting nigrostriatal DA system impairment in advanced HD (Ferrante and Kowall, 1987; Ginovart et al., 1997; Bohnen et al., 2000; Suzuki et al., 2001; Yohrling et al., 2003).

Besides the overall decrease of TH immunoreactivity in the striatum of HD brains (Bedard et al., 2011), an intense and well-delineated TH-immunoreactive zone lying along the ventricular border of the caudate nucleus has recently been described (Bedard et al., 2010; Parent et al., 2013). The small and densely packed DA axons found in this restricted striatal area overlap the deep layers of the subventricular zone, one of the rare brain areas that has retained the possibility to generate new neurons throughout life. The marked increase in the size of the subventricular zone reported in HD (Curtis et al., 2007) contrasts strikingly with the severe cell loss and atrophy that occurs in the adjoining portion of the striatum. Indeed, the close proximity of the subventricular zone with the striatum makes it a potential source of endogenous neurons that could be engaged in brain repair strategies for this neurodegenerative disease. The dense DA innervation of the subventricular zone observed in HD brains indicates that this monoamine, known to exert a robust excitatory influence upon adult neurogenesis (Baker et al., 2004; Hoglinger et al., 2004; Van Kampen et al., 2004; Lao et al., 2013), might significantly contribute to cell proliferation in HD and could have a crucial role in intrinsic mechanisms involved in attempts to produce new neurons in order to compensate for the massive striatal neuronal losses that occur. It could also play a role in striatal gliogenesis that takes place in such a pathological condition (Sapp et al., 2001).

Evidence for the presence of DA neurons intrinsic to the striatum was obtained in various species, including humans (Porritt et al., 2000; Prensa et al., 2000; Cossette et al., 2004; Cossette et al., 2005b; Cossette et al., 2005a; Huot and Parent, 2007). Immunhistochemical studies indicate that the vast majority of TH positive striatal interneurons also express the enzyme glutamic acid decarboxylase (GAD) suggesting that they might represent a particular subtype of GABA producing neurons (Cossette et al., 2005a). In healthy brains, these neurons were reported to be more abundant in the ventral striatum and occurred in larger number in the putamen than in the caudate nucleus (Cossette et al., 2005b; Huot and Parent, 2007). In the striatum of HD brains, very few of these TH interneurons were observed compared to age-matched controls (Huot et al., 2007). Whether this specific type of striatal interneuron degenerates, as it is the case for parvalbumin interneurons (Reiner et al., 2013), or undergoes a phenotypic shift is presently unknown. Although they have been shown to act through fast GABAergic synaptic transmission in transgenic mice (Ibanez-Sandoval et al., 2010), these TH positive interneurons might also play a significant role in impairments in DA transmission reported in HD.

## Neurochemistry

The idea that aberrant DA signaling underlies behavioral abnormalities in HD was first proposed as a predictive test when asymptomatic offspring of affected individuals developed dyskinesias in response to levodopa (L-DOPA) administration (Klawans et al., 1970). The

hypothesis was that stimulation of DA receptors was involved in the production of dyskinesias as a basic mechanism of chorea. In support, studies in HD patients demonstrated that increased DA release induces chorea while a reduction in DA leads to akinesia (Bird, 1980). Other studies indicating an involvement of the DA nigrostriatal pathway in HD demonstrated increased levels of DA in postmortem brains of HD patients and showed that DA-depleting agents, such as tetrabenazine (TBZ), can be used with therapeutic benefit (Bird, 1980).

Early post-mortem biochemical measurements of DA concentrations in HD patients yielded inconsistent results. The first biochemical attempts to determine the level of DA markers in autopsied HD brains led to the conclusion that it was unchanged (Bernheimer et al., 1973; Bird and Iversen, 1974; McGeer and McGeer, 1976) or increased (Bird et al., 1980; Spokes, 1980) in the striatum. However, later neurochemical studies of HD patients suggested that increased DA occurs in the early stages of the disease (Garrett and Soares-da-Silva, 1992) while postmortem studies of late-stage HD patients showed reduced levels of caudate DA and homovanillic acid, the principal DA metabolite (Kish et al., 1987). Thus, it was thought that DA levels in HD may show biphasic, time-dependent changes, with early increases followed by late decreases associated with biphasic movement symptoms of early (chorea) and late (akinesia) HD.

The impairment of the nigrostriatal DA system in advanced HD was supported by PET studies in which various DA markers can be imaged in the brains of living patients. These studies indicated a significant decrease in the binding of the DA transporter (DAT) (Ginovart et al., 1997) and vesicular monoamine transporter 2 (VMAT2) (Bohnen et al., 2000) in the striatum. These findings can be interpreted as indications of a loss of DA striatal innervation in HD, which appears to be particularly severe in patients suffering from the rigid-akinetic variant (Bohnen et al., 2000). More direct proofs of striatal losses of DAT and VMAT2 could be obtained by means of autoradiographic binding studies in autopsied HD brains (Suzuki et al., 2001).

## DA Receptors

Studies using positron emission tomography, autoradiography, and markers for pre- and postsynaptic markers demonstrated reduced striatal DA D1 and D2 receptor density, even in asymptomatic HD patients, further indicating that DA signaling is disrupted early in HD (Richfield et al., 1991; van Oostrom et al., 2009). These observations were confirmed by imaging studies, which reported reduced striatal D1 and D2 receptors in both HD patients and asymptomatic HD mutation carriers (Weeks et al., 1996). Striatal and cortical loss of DA receptors in presymptomatic and early stage HD patients has been correlated with early cognitive decline, which may reflect altered synaptic plasticity and lead to deficits in cognitive processes such as attention, executive function, learning, and memory (Backman and Farde, 2001).

## DA in Genetic Animal Models of HD

The generation of genetic rodent models of HD has permitted examination of mechanisms during disease progression. The most widely used mouse model of HD is the R6/2 line, a

fragment transgenic mouse expressing exon 1 of *HTT* with ~150 CAG repeats (Mangiarini et al., 1996). R6/2 mice display a very rapidly progressing phenotype, similar to the juvenile form of HD in humans. In these mice, overt symptoms begin to appear at 5–7 weeks of age and become fully manifest after 8 weeks. HD mouse models with full-length mutant *HTT* include the yeast artificial chromosome model with 128 CAG repeats (YAC128) and the bacterial artificial chromosome model with 97 CAG repeats (BACHD) (Slow et al., 2003; Gray et al., 2008). These models show a longer development of the HD phenotype and thus are generally studied at both an early (1.5–2 months of age) and late stage (12 months of age), corresponding roughly to periods of hyperkinesia and hypokinesia, respectively. A transgenic rat model of HD (tgHD) carries a truncated huntingtin cDNA fragment with 51 CAG repeats (von Horsten et al., 2003).

In agreement with analyses of HD patients, striatal D1 and D2 receptors also are affected in HD mouse models. Striatal D1 and D2 receptor binding is reduced early, with deficits in DA signaling seen in R6/2 mice (Cha et al., 1998; Bibb et al., 2000; Ariano et al., 2002). Significant reductions also are observed in mRNA levels of striatal D1 and D2 receptors in late stage YAC128 mice, but not in BACHD mice (Pouladi et al., 2012). It is unclear why these differences occur between the two full-length models.

There is evidence that DA release is reduced in transgenic mouse models in the late stages of the disease, consistent with what is proposed to occur in human HD. In R6/2 and R6/1 mice, there is a progressive reduction in striatal DA release beginning at 6 weeks of age (Hickey et al., 2002; Petersen et al., 2002; Johnson et al., 2006; Callahan and Abercrombie, 2011), as well as a reduction in homovanillic acid in symptomatic stages concomitant with motor abnormalities (Mochel et al., 2011). Deficits in DA levels and/or release have been attributed to either impaired vesicle loading or a reduction in DA reserve pool vesicles available for mobilization (Ortiz et al., 2010). The tgHD rat model displays an increase in striatal DA levels and DA neurons at the early symptomatic stage in two main sources of telencephalic DA input, the substantia nigra pars compacta and ventral tegmental area (Jahanshahi et al., 2010). However, these rats also show impaired DA release dynamics, as demonstrated by a reduction in evoked release of DA (Ortiz et al., 2012). Since these results from animal models are not entirely consistent, future studies of DA release dynamics in HD will be necessary to determine the changes in DA levels that occur in the early and late disease stages.

## Synaptic Electrophysiology in HD Models

Electrophysiological studies in genetic mouse models have suggested biphasic changes in glutamate release along the corticostriatal pathway with early increases followed by significant decreases (Cepeda et al., 2003; Joshi et al., 2009) until, in the late stages, there is a major disconnection between cortex and striatum (Cepeda et al., 2007). Alterations in DA receptor modulation of glutamate release also have been demonstrated (Joshi et al., 2009). In particular, age-dependent alterations in corticostriatal activity are paralleled by a decrease in DA D2 receptor modulation at the presynaptic terminal (Joshi et al., 2009), which can be explained by reduced numbers of D2 receptors.

The use of enhanced green fluorescent protein to identify striatal direct and indirect pathway MSNs that express DA D1 and D2 receptors, respectively has allowed examination of differential changes in DA modulation of excitatory synaptic inputs to neurons originating these pathways during the course of HD. Studies indicate that, similar to changes in glutamate function, DA tone also follows a biphasic progression with early increases followed by decreases. For example, glutamatergic input to direct pathway MSNs is increased in the early stages of HD in the YAC128 and BACHD mouse models and this input is not modulated by DA. However, modulation is restored by TBZ, supporting an increased DA tone in early HD (André et al., 2011). Thus, contrary to the classic paradigm of basal ganglia function, these recent studies highlight the role of direct pathway neurons in the early symptoms of HD.

## DA and Synaptic Plasticity in HD

In humans, the symptoms of HD, which usually appear in the third to fifth decades of life often include impairment of cognitive function that can lead to dementia (Harper, 1996). The primary sites of neurodegeneration are the striatum (Vonsattel et al., 1985) and cerebral cortex (Vonsattel et al., 1985; Hedreen et al., 1991), and to a lesser extent the hippocampus (Spargo et al., 1993). Several studies have shown that cognitive impairment in both working memory and executive function can occur in gene carriers before the onset of classical symptoms (Foroud et al., 1995; Lawrence et al., 1998; Thiruvady et al., 2007). Post mortem studies (Vonsattel et al., 1985) reveal that the first symptoms (both motor and cognitive) appear in the absence of overt neuronal loss, suggesting that impaired cognition is caused by synaptic and neural dysfunction rather than a consequence of neuronal cell death. Higher cognitive processing involving changes in synaptic weighting in neural networks and alterations in hippocampal synaptic plasticity have been reported in several mouse models of HD (Hodgson et al., 1999; Usdin et al., 1999; Murphy et al., 2000; Gibson et al., 2005). In R6/2 mice, the ability to support long-term potentiation (LTP) at CA1 hippocampal synapses was reduced and this loss of plasticity was apparent prior to the onset of motor symptoms (Murphy et al., 2000), consistent with the view that cognitive disruption precedes motor decline. This view is further supported by the observation that spatial learning is also affected in R6/2 mice and precedes the onset of the motor phenotype (Murphy et al., 2000). The hippocampus is involved in spatial learning and the performance of R6/2 mice in the Morris water maze was found to be impaired; importantly, this behavioral cognitive deficit was also manifest before the onset of an overt motor phenotype (Murphy et al., 2000). The converse of LTP, long-term depression (LTD), is developmentally expressed at hippocampal synapses (Milner et al., 2004), such that it can only be experimentally induced in brain slices prepared from young animals. R6/2 mice exhibited full-blown LTD at all ages examined and failed to show a developmental down-regulation of this phenomenon (Murphy et al., 2000). Longer surviving R6/1 mice (mice with 116 CAG repeats), however, did exhibit a degree of developmental down-regulation, but this was transitory as the ability to support robust LTD re-emerged and persisted once the mice reached maturity (Milnerwood et al., 2006).

While hippocampal studies have been informative and demonstrated that changes in synaptic plasticity occur early in the murine disease phenotype, they do not address directly the cognitive abnormalities observed in human gene carriers nor the role of DA. One of the

key brain regions involved in the processing of working memory and executive function is the prefrontal cortex (Goldman-Rakic, 1995; Fuster, 2000). Local glutamatergic neuronal networks contribute to the temporary storage and dynamic control of information in this area. Alterations in the properties of these networks affect both working memory and executive function (Goldman-Rakic, 1995). EEG power spectra recorded in the cortex of HD patients are abnormal and the degree of abnormality is correlated with the severity of the cognitive impairment (Bylsma et al., 1994). A similar study examined EEG changes in preclinical gene carriers while performing a working memory task; EEG abnormalities were only apparent during the performance of the task (van der Hiele et al., 2007). Paradoxically, performance on the task was indistinguishable from that of controls, suggesting that alterations in neural network processing precede the development of symptoms. In R6/2 mice, the synchronicity of spike firing in the prefrontal cortex *in vivo* is reduced, indicating a population-level deficit in network processing (Walker et al., 2008). LTP has been examined in the prefrontal cortex of R6/1 mice *in vitro* and found to be abnormal. LTP was abolished in symptomatic mice and reduced in mice that were pre-symptomatic (Dallerac et al., 2011). The induction of LTP in the prefrontal cortex and the performance of working memory are both sensitive to the ambient concentration of cortical DA (Williams and Castner, 2006). The induction of LTP is dependent upon co-activation of D1 dopamine receptors and NMDA receptors (Gurden et al., 2000) and the impairment in synaptic plasticity seen in HD mice may be attributable to an alteration in the neuromodulatory properties of midbrain DA inputs that innervate the prefrontal cortex. There is additional evidence supporting the view that abnormal DA signaling may underlie deficits in synaptic function in the prefrontal cortex as a recent study showed that normal LTP can be restored in R6/1 mice in the presence of a D1 dopamine receptor agonist (Dallerac et al., 2011).

Reduced synaptic plasticity appears to be a common deficit in the cortex of HD patients and the neocortex of mouse models of HD. A recent human study, using trans-cranial magnetic stimulation of motor cortex to induce LTD-like changes in motor evoked potentials, showed that both pre-manifest and very early manifest HD patients exhibited a marked reduction in the magnitude of experimentally induced LTD compared with control participants (Orth et al., 2010), validating the predictive power of murine models of neurodegenerative disease. The role of DA in the induction of LTD has also been assessed *in vitro* in the perirhinal cortex of R6/1 mice (Cummings et al., 2006; Cummings et al., 2007). In these mice, the age- and phenotype-dependent expression of LTD is unusual in that it has a biphasic profile. In pre-symptomatic mice the magnitude of LTD is greater than that seen in age-matched controls whereas in symptomatic mice the ability to support LTD is absent (Cummings et al., 2006). The loss of LTD is also associated with a change in the paired-pulse profile. Instead of exhibiting paired-pulse depression, the profile is shifted to one of paired-pulse facilitation, suggesting a functional loss of neuromodulatory input. The addition of a D2 receptor agonist to the perfusate not only rescued the ability of perirhinal synapses to support LTD but also restored the normal paired-pulse profile (Cummings et al., 2006). DA deficits have also been implicated in the reduction of LTP expressed at corticostriatal synapses in R6/2 mice (Kung et al., 2007).

In summary, data from human studies show that changes in the properties of cortical neuronal networks are early events in the pathogenesis of HD and the rodent studies indicate, in part, that such network abnormalities are likely to be a consequence of altered DA function.

## DA and Excitotoxicity

Although DA exists in high concentrations in the striatum, studies also suggest a toxic role for DA in which cell death is accelerated through increases in free radical production (Jakel and Maragos, 2000). This has been demonstrated in striatal cultures derived from R6/2 mice, where MSNs undergo DA-mediated oxidative stress and apoptosis (Petersen et al., 2001). DA and glutamate signaling pathways can synergistically enhance MSN sensitivity to huntingtin toxicity. Studies demonstrate that this deleterious process occurs through D1 but not D2 receptor activation (Tang et al., 2007; Paoletti et al., 2008) and are in agreement with previous studies demonstrating that DA and D1 receptor agonists enhance excitotoxicity (Cepeda et al., 1998; McLaughlin et al., 1998).

D1 receptor-mediated potentiation of NMDA responses, which holds key functional consequences in HD, has been verified in the cortex and striatum (Cepeda et al., 1993; Wang and O'Donnell, 2001; Flores-Hernandez et al., 2002). For example, D1 receptor-induced cell death in MSNs of knock-in HD mice is increased by pretreatment with NMDA when compared with cells from wildtype mice (Paoletti et al., 2008). In neurons from YAC mice or Q111 knock-in mice, the convergence of DA and glutamate signaling pathways leads to $Ca^{2+}$ overload, resulting in excitotoxic processes such as induction of mitochondrial depolarization and caspase activation (Zeron et al., 2002; Tang et al., 2007; Paoletti et al., 2008).

While D1-NMDA receptor activation is thought to be neurotoxic, activation of D2 receptors reduces NMDA receptor responses and thus may be neuroprotective (Bozzi and Borrelli, 2006). For example, activation of D2 receptors by quinpirole reduces the toxicity of both NMDA and kainic acid in rat striatal neurons (Cepeda et al., 1998), as well as in mesencephalic and cortical neurons (Sawada et al., 1998; Kihara et al., 2002). However, an exclusive role for D1 receptor activation in mediating MSN degeneration is contradicted by evidence that blocking D2 receptor stimulation significantly reverses DA potentiation of mutant huntingtin-induced MSN cell death (Charvin et al., 2005). As cultured striatal neurons can be protected by antagonism of D1 and D2 receptors, it is possible that both D1 and D2 receptor activation might contribute to neurotoxicity (Davis et al., 2002; Bozzi and Borrelli, 2006).

## Mechanisms of DA Dysregulation

Several mechanisms can be invoked to explain alterations in DA neurotransmission. During the early phase of HD, neuropathological studies have shown that discrete islands of neuronal loss and astrocytosis appear in the striosomes almost exclusively, whereas in the late phase, cell loss increasingly occurs in the matrix compartment (Hedreen and Folstein, 1995). As MSNs from the striosomes project to the substantia nigra pars compacta, it may

be that early degeneration of these inhibitory neurons produces hyperactivity of the DA pathway, contributing to chorea and other early clinical manifestations of HD.

Stimulation of corticostriatal neurons has been shown to activate DA release in the striatum (Nieoullon et al., 1978). In addition, DA neurons that modulate glutamate release in the corticostriatal pathway are subject to afferent glutamate regulation, which is suggested by the presence of glutamate receptors on DA neurons (Meltzer et al., 1997). There is substantial evidence for a direct cortico-nigral projection (Afifi et al., 1974; Kornhuber et al., 1984) and work in rodents demonstrates that this pathway both directly and indirectly regulates the firing pattern of DA neurons (Maurice et al., 1999; Sesack and Carr, 2002). Other studies indicate that stimulation of glutamate receptors on DA neurons increases DA release in both the substantia nigra and in DA innervated areas (Kalivas et al., 1989; Murase et al., 1993). Thus, if DA neuron firing is regulated by frontal cortical neurons, the activity of which is upregulated in early HD, the biphasic trends of DA levels in early and late human HD may be correlated with the biphasic changes of glutamate release by cortical afferents.

## DA Agonists and Antagonists as Treatments for HD

Since the abnormalities in the DA system appear to underlie some of the behavioral symptoms of HD, DA agonists, antagonists, and/or stabilizers may provide potential treatment options. Conceptually, DA stabilizers (or partial agonists) increase or decrease DA receptor activity depending on the level of DA tone. HD patients treated with aripiprazole, a partial D2 receptor agonist, demonstrate improvements in chorea, but not cognitive function (Brusa et al., 2009). A recent phase 3 clinical trial of the DA stabilizer pridopidine demonstrated improvements in hand movements, gait, and balance of HD patients as defined by the unified HD rating scale (de Yebenes et al., 2011). Although these changes fell short of the primary efficacy threshold, the slight improvements in motor dysfunction without any deleterious side effects suggest that treatments targeted towards DA imbalance may have therapeutic benefits.

Current treatment options for HD are limited and confined to antidopaminergic agents for motor symptoms while there are virtually no therapeutics for cognitive deterioration (Venuto et al., 2012). Additionally, clinical results of these treatments seem contradictory, possibly reflecting the dynamic and time-dependent changes that occur in the DA system as the disease progresses (Mochel et al., 2011). For example, both D2 agonists and antagonists have demonstrated clinical benefits for improvement of HD motor symptoms (Tedroff et al., 1999; Haskins and Harrison, 2000; Brusa et al., 2009). Conventional antipsychotic drugs, such as the D2 antagonist haloperidol, are used in clinical practice, but they do not improve functional capacity (Bonelli and Wenning, 2006). Atypical antipsychotic drugs with D2 antagonist properties such as olanzapine, risperidone, quetiapine, and ziprasidone, can improve chorea and impact a larger range of behavioral disturbances with a reduced risk of side effects. D2 agonists also have demonstrated therapeutic potential in HD (Frattola et al., 1977; Caraceni et al., 1980).

As the early stages of HD may reflect a hyperdopaminergic condition, drugs that reduce DA tone can be beneficial during the choreic movement phase (Mochel et al., 2011). DA-depleting agents, such as TBZ, which inhibit VMAT-2 and decrease DA content in presynaptic vesicles, have been shown to reduce chorea (Huntington Study Group, 2006). Currently, TBZ is the only drug formally approved for treatment of Huntington's chorea by a regulatory agency (Chen et al., 2012; Mestre and Ferreira, 2012).

*In vivo* and *in vitro* studies of animal models support a role for DA inhibitors in protecting HD MSNs from cell death. The rationale follows and agrees with experimental and clinical findings suggesting that DA tone is elevated during the early stages of the disease. In YAC128 mice, TBZ alleviates motor deficits and reduces striatal loss in both early and late stages (Tang et al., 2007). TBZ also rescues the increased stereotypies in 1–2 month old YAC128 and BACHD mice (André et al., 2011). The D1 receptor antagonist SCH23390 rescues the changes in excitatory synaptic transmission of direct pathway MSNs that occur in the early symptomatic phase in YAC128 and BACHD mice, suggesting that tonic activation of D1 receptors may underlie early dysfunction of D1 MSNs (André et al., 2011). Similarly, SCH23390 prevents DA/GLU-induced MSN death in YAC128 mice (Tang et al., 2007). In the tgHD rat model, striatal toxicity is reduced by early and chronic treatment with haloperidol (Charvin et al., 2008). However, this evidence is complicated by the fact that haloperidol, a putative D2 receptor antagonist, also modulates NMDA receptor function (Ilyin et al., 1996; Arvanov et al., 1997). Predictably, DA antagonists may be more beneficial when administered with other neuroprotective drugs such as memantine, a NMDA receptor antagonist, as a combination therapy (Wu et al., 2006).

HD mouse models have demonstrated the therapeutic potential of not only DA antagonists, but also DA agonists. For example, in fully symptomatic R6/2 mice, replacement of reduced DA levels by chronic treatment with L-DOPA yields short-term improvements in the HD behavioral phenotype whereas long-term treatment impairs survival and rotarod performance (Hickey et al., 2002). Additionally, as pointed out above the D1 receptor agonist SKF38393 rescues cortical LTP impairment and deficits in synaptic plasticity of R6/1 mice (Dallerac et al., 2011), suggesting that increasing DA levels could improve cognitive dysfunction. Since some treatments may only be suitable early in disease progression, effective therapies need to be temporally oriented to accommodate differential changes in DA function throughout the course of the disease.

## Conclusions and Future Directions

While much knowledge on the role of DA in HD has been gathered in the past few years, many questions remain unanswered and should be the focus of future endeavors. The traditional view that D2 MSNs are more vulnerable in HD is beginning to change due to emerging data from experimental animal models. Based on new evidence, it may be proposed that D1 MSNs should be more vulnerable to the HD mutation, i.e., they become dysfunctional in the early stage of HD and D1-NMDA receptor interactions enhance neurotoxicity. Therefore, the standing question should be reformulated to ask why D1 MSNs are less susceptible to dysfunction in HD. Do they have an intrinsic neuroprotective mechanism that D2 MSNs lack? Recent studies using mice in which D1 or D2 receptor-

expressing neurons can be identified point in that direction. For example, fluorescence-activated cell sorting array analyses showed that the transcription factor Zfp521, which is enriched in D1 MSNs, is anti-apoptotic (Lobo et al., 2008). Specifically, Zfp521 promotes proliferation, delays differentiation, and reduces apoptosis (Shen et al., 2011).

Another important issue concerns causes of early perturbations in DA release. Is it the loss of striosome MSN projections to the substantia nigra pars compacta, increased activity along the cortico-nigral projection, or dysregulation of DA release due to loss of D2 auto-receptors? On a similar note, since there are at least two splice variants for D2 receptors, a short D2S (mostly presynaptic) and a long D2L (mostly postsynaptic) form, which one is reduced in early HD? In the striatum, DA D2 auto-receptor function is mediated by synapsin III expression. In brains of R6/2 mice and HD patients, there is a progressive loss of complexins, synaptic proteins similar to syntaxin III that are involved in synaptogenesis and modulate neurotransmitter release (Freeman and Morton, 2004). A similar reduction in synapsin III could explain increased DA transmission in early HD. Thus far, it is unknown whether or not presynaptic D2 auto- or hetero-receptors are lost before postsynaptic receptors (Sandstrom et al., 2010). However, selective agonists of D2 auto-receptors produce long-lasting suppression of extracellular brain DA levels *in vivo* and could provide promising therapeutic benefits for HD (Pifl et al., 1988). Knowledge of the initial and causative mechanisms of DA receptor dysfunction in HD will certainly lead to better and more rational treatments.

## Acknowledgments

CC and MSL are supported by USPHS NS41574, NS78633, NS81335 and a contract from CHDI Inc.

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