Journal of Huntington's Disease 5 (2016) 303–331
DOI 10.3233/JHD-160221
IOS Press

Review

Dysregulation of Corticostriatal Connectivity in Huntington's Disease: A Role for Dopamine Modulation

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Abstract. Aberrant communication between striatum, the main information processing unit of the basal ganglia, and cerebral cortex plays a critical role in the emergence of Huntington's disease (HD), a fatal monogenetic condition that typically strikes in the prime of life. Although both striatum and cortex undergo substantial cell loss over the course of HD, corticostriatal circuits become dysfunctional long before neurons die. Understanding the dysfunction is key to developing effective strategies for treating a progressively worsening triad of motor, cognitive, and psychiatric symptoms. Cortical output neurons drive striatal activity through the release of glutamate, an excitatory amino acid. Striatal outputs, in turn, release γ-amino butyric acid (GABA) and exert inhibitory control over downstream basal ganglia targets. Ample evidence from transgenic rodent models points to dysregulation of corticostriatal glutamate transmission along with corresponding changes in striatal GABA release as underlying factors in the HD behavioral phenotype. Another contributor is dysregulation of dopamine (DA), a modulator of both glutamate and GABA transmission. In fact, pharmacological manipulation of DA is the only currently available treatment for HD symptoms. Here, we review data from animal models and human patients to evaluate the role of DA in HD, including DA interactions with glutamate and GABA within the context of dysfunctional corticostriatal circuitry.

Keywords: Huntington's disease, corticostriatal pathway, basal ganglia, cerebral cortex, striatum, dopamine, glutamate, GABA

INTRODUCTION

Huntington's disease (HD) is a fatal monogenetic neurodegenerative disorder that affects approximately 10–12 individuals per 100,000 of European ancestry [1]. Clinical manifestations include progressively deteriorating motor, cognitive, and psychiatric symptoms [2]. The motor phenotype normally begins with gait disturbances and a lack of coordination followed by chorea and jerky body movements [3, 4]. In late stages of HD, the motor alterations switch to bradykinesia and dystonia [5]. Although the motor signs are typically the trigger for seeking medical attention, cognitive symptoms often develop first. Early-stage cognitive decline is characterized by difficulties in decision-making, planning, and cognitive inflexibility [6, 7] followed in late stages by dementia [8]. Psychiatric signs also can emerge in HD and are frequently reported as "changes of personality" with symptoms such as impulsivity, irritability, aggression, and altered mood regulation, which lead progressively to apathy and depression [9]. Symptoms generally begin in the prime of life between

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35–45 years of age and progressively worsen until death; survival after motor onset is approximately 15–20 years [10].

Although the etiology of HD has been broadly identified, its underlying neural mechanisms have been difficult to establish. The most prominent neural change is a massive loss of neurons in the striatum, which receives information from all areas of cerebral cortex and processes it for behavioral output via downstream loops that converge back onto cortex, especially motor regions [11, 12]. Cortical neurons also degenerate in HD, creating a widespread pattern of corticostriatal neuropathology [13, 14].

Long before cortical and striatal neurons die, however, they become dysfunctional, setting the stage for the emergence of the HD behavioral phenotype. In this review, we discuss corticostriatal connectivity and its dysfunction in HD, including alterations in downstream information flow through the circuitry of the basal ganglia (BG). The two most prominent transmitters in these circuits – glutamate, the excitatory amino acid released by corticostriatal neurons, and γ-amino butyric acid (GABA), the inhibitory amino acid released by striatal output neurons – are closely tied to HD neuropathology and have been discussed extensively [15–22]. We review both transmitters here to provide context for a more detailed discussion of dopamine (DA), a key modulator of corticostriatal information flow, along with evidence for its emerging role in HD.

Clinical overview

HD is an autosomal dominant neurodegenerative disorder caused by a trinucleotide repeat expansion within the huntingtin gene (*HTT*). The repeat involves the CAG codon, which translates into a long poly-glutamine (polyQ) sequence insertion in the mutant huntingtin protein (mHTT). Abnormal aggregates of mHTT have been proposed to cause cellular dysfunction and ultimately neuronal death [23–25]. Clinical manifestations are fully penetrant when the CAG repeat number exceeds 39. The number of repeats in the mutant gene *(mHTT)* roughly corresponds to an inverse association with HD onset such that the greater the number, the earlier the onset [26, 27]. A less common form of HD begins in childhood or adolescence and is known as juvenile HD. In this case, symptoms occur before the age of 20 years and usually include changes in handwriting along with learning disabilities, motor problems (such as slowness, rigidity, tremor, and muscular twitching), and, most commonly, epileptic seizures [28, 29].

Medium spiny neurons (MSNs), which account for more than 90% of the striatal neuronal population, are particularly vulnerable. Also known as striatal projection neurons (SPNs), their progressive degeneration is the main feature of HD [30]. Because mHTT is expressed throughout the body [31], the role of mHTT aggregates in causing the relatively selective loss of MSNs in striatum is unclear, but ample evidence shows that mHTT underlies MSN dysfunction as well as abnormal communication between cortical and striatal neurons [32–37]. In fact, data obtained from transgenic animal models of HD indicate that dysfunction of corticostriatal circuitry precedes frank degeneration and likely plays a key role in symptom onset [19, 38–40].

Rodent models

The generation of transgenic mice and rats has greatly advanced understanding of HD pathology by identifying potential mechanisms underlying HD progression [2]. Transgenic rodent models can be classified into three groups: truncated models (expressing only the first exon of the mutant gene), full-length models (expressing the complete mutant gene), and knock-in (KI) models (with direct insertion or "knock-in" of the CAG repeat expansion into the *HTT* gene).

Truncated models

Two of the most widely used truncated models belong to the R6 mouse line and are designated as R6/1 and R6/2. R6/1 mice contain about 115 CAG repeats, display symptoms from 4-5 months of age and live approximately 10–14 months. Robust motor symptoms do not occur until approximately 5–7 months of age [41]. In contrast, R6/2 mice, which can carry upwards of 150 CAG repeats, display a very early onset (4-5 weeks of age) and rapid progression of neurological signs leading to death by 15 weeks of age [41, 42]. Although the behavioral phenotype is robust and easy to characterize, the short lifespan limits the usefulness of this model for identifying the pre-symptomatic triggers of HD onset and the gradual progression of HD through adulthood. Like HD patients with a high number of CAG repeats, the R6/2 model appears to recapitulate juvenile HD [43, 44].

A truncated rat model, the tgHD51, carries a truncated *mHTT* cDNA fragment with 51 CAG

repeats [45]. This model exhibits a high degree of similarity to the late-onset form of HD due to the relatively small number of CAG repeats. These animals survive up to 24 months and exhibit a slow cognitive decline and relatively mild motor deficits [46, 47].

Full-length models

Compared to truncated models, full-length models display a slower disease progression. In this group, two types of mice have been generated: the yeast artificial chromosome (YAC) mouse and the bacterial artificial chromosome (BAC) mouse. Three YAC models are available based on different CAG repeat lengths: YAC46, YAC72, and YAC128. The most commonly used is the YAC128 model. Although behavioral changes occur at approximately 7 months of age, YAC128 mice show some aspects of the human motor phenotype, such as hyperkinesia followed by bradykinesia [48, 49], but the overall symptom profile is relatively mild and the animals typically survive for more than 18 months. A BAC HD model carries 97 repeats and exhibits similarly late-onset motor deficits [50, 51]. Both YAC and BAC models display evidence of corticostriatal degeneration [49, 50].

KI models

Widely varying CAG repeat lengths, ranging from Q71 and Q94 to Q140 and Q175, characterize currently available KI models [52–54]. Although the inverse correlation between age of onset and number of CAG repeats (see above) would suggest a robust and early phenotype similar to the R6 line, KI mice more closely resemble the full-length rather than the truncated model. Heterozygous Q175 KIs, for example, exhibit first motor signs at 3-4 months of age and survive well past 18 months [55, 54]. An extensive evaluation of these mice reported subtle but significant cognitive and motor impairments along with alterations in the level of intracellular proteins involved in synaptic function and axonal transport [35]. These molecular changes may correspond to common HD neuropathological features such as striatal atrophy, cortical thinning, degeneration of MSNs, and dense mHTT inclusions [33].

Dysfunctional neuronal activity also has been found in KI models. The Q140 mouse shows many of the same neurological abnormalities in striatum and cortex as the R6/2 model [56, 57]. In addition, reduced synaptic transmission in the striatum has been correlated with hypokinetic symptoms in homozygous Q175 mice [58]. Although Q175s display slow disease progression and relatively subtle behavioral changes, this animal model contains the human *mHTT* allele with the expanded CAG repeat within the native mouse *HTT* gene.

CORTICOSTRIATAL CONNECTIVITY AND DYSFUNCTION

Alterations in the flow of information from cerebral cortex to striatum play a key role in the onset and progression of HD. Virtually all areas of cerebral cortex have the ability to activate striatal neurons through a massive topographically organized projection system. Cortical input to striatum is driven by glutamate. The corticostriatal system, however, is tightly regulated by dopamine (DA), a monoamine modulator, and γ-amino butyric acid (GABA), an amino acid synthesized from glutamate that exerts a strong inhibitory influence. Together, DA and GABA provide a critical counterbalance to the glutamate-induced excitation of striatal neurons, which in turn modulates the activity of downstream targets in the BG. Thus, DA- and GABA-mediated control of the activation of striatal neurons by glutamate allow for the motor and cognitive responses that define healthy BG function. HD disrupts all three transmitter systems, creating a slowly progressing motor and cognitive phenotype that ends in death. To gain some perspective on this disruption, it is important to understand the basic organization of cortico-BG circuits.

According to the classical model proposed more than 25 years ago [59, 60], cortical pyramidal neurons (CPNs) activate the striatum where they target interneurons as well as MSNs, which project to other BG targets. Without excitatory input, MSNs, because of a relatively high potassium conductance at rest, are in a hyperpolarized or "down" state. Glutamate input is required to move MSNs into a depolarized or "up" state where they are readily excitable by additional glutamate input. But even under excitatory drive from cortex, MSNs typically discharge at a relatively slow rate (<15 spikes/s). GABA may account for some of this inhibitory influence since MSNs receive input from GABA-releasing interneurons that typically discharge at a fast rate (see below). Moreover, MSNs, which also release GABA, send axon collaterals within the striatum. Thus, even though MSNs receive direct glutamate input from cortex, there are sufficient constraints on their activity to ensure that they are not chronically hyperactive.

MSNs send their GABA projections to two segments of the globus pallidus, forming the so-called direct and indirect pathways. Direct-pathway MSNs send axons to the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNpr). This pathway is considered direct because the GPi/SNpr is the output nuclei of the BG circuit, and thus these MSNs exert a direct influence on BG output. In contrast, indirect-pathway MSNs sends axons to the external segment of the globus pallidus (GPe). The GPe sends axons to the subthalamic nucleus (STN), which in turn projects to the GPi/SNpr. Thus, multiple synapses intervene before striatal information traveling via the indirect pathway reaches BG output.

Direct- and indirect-projecting MSNs can be distinguished by the peptides they contain. MSNs that stain positively for dynorphin (DYN) and substance-P (SP) project directly to the GPi/SNpr, whereas a positive stain for enkephalin (ENK) identifies indirect-projecting MSNs [61–63].

Interestingly, all these neuronal projections are GABAergic except for the STN projection to GPi/SNpr, which releases glutamate. As shown in Fig. 1, activation of the direct pathway inhibits BG output, and the opposite occurs when the indirect pathway is activated. Accordingly, these pathways can be considered to have opposite effects on behavior because the GPi/SNpr sends inhibitory GABA projections to thalamus, which in turn activates motor cortex via glutamate. Thus, based on the classical model of BG circuits, the direct pathway disinhibits movement by suppressing inhibitory input to thalamus, whereas the indirect pathway has the opposite effect on the GPi/SNpr and suppresses movement. Recent studies using optogenetic technology, however, have proposed that both pathways are necessary for the initiation of movement because both have been found to be simultaneously active during the performance of motor sequences [64, 65]. In addition, both pathways are required not only for the initiation of sequential movements, but also for the performance of learned action sequences [66]. Importantly, despite concurrent activation of the two pathways, their motor contribution is not identical. Direct pathway inactivation has been shown to slow initiation of movement but indirect pathway activation terminated it, whereas activation of the direct but not indirect pathway prolonged action sequences, suggesting that both pathways trigger movements by acting in concert rather than in opposition [66]. Together, this evidence suggests that BG circuitry is more complex than activation or inactivation of direct and indirect pathways in the control of movement. In fact, it has

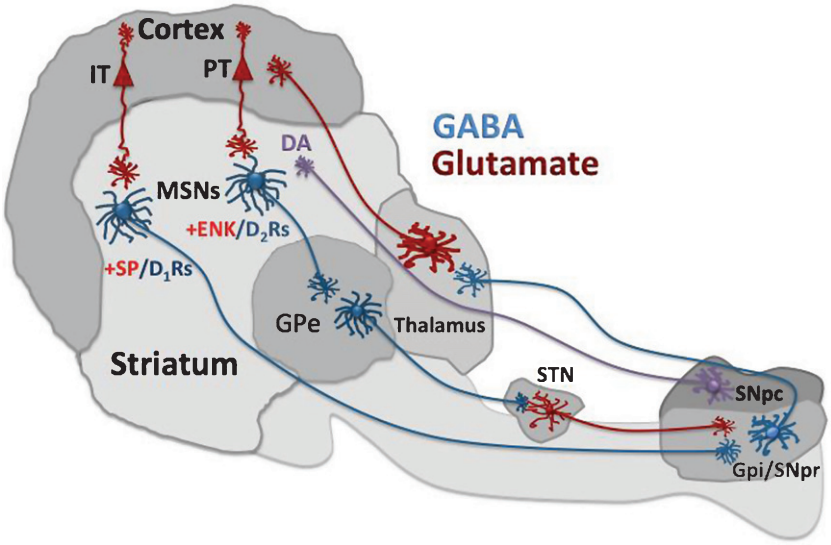

Fig. 1. Schematic illustration of basal ganglia circuitry. Striatal medium spiny neurons (MSNs) receive excitatory corticostriatal input from IT and PT pyramidal neurons in cerebral cortex. Intra-telencephalic (IT) neurons preferentially activate substance P/D_1 receptor (SP/D_1R) MSNs that project to the internal globus pallidus and sustantia nigra pars reticulata (GPi/SNpr) forming the direct pathway. Pyramidal tract (PT) neurons activate enkephalin/D_2 receptor (ENK/D_2R) MSNs that form the indirect pathway and send projections to the external globus pallidus (GPe). GPe neurons in turn send axons to the subthalamic nucleus (STN), which projects to GPi/SNpr. GPi/SNpr is the basal ganglia output system that integrates direct and indirect pathway information and sends it back to cortex via thalamus.

been reported that activation of the direct pathway can evoke both excitatory and inhibitory actions in different cell populations within the GPi/SNpr [67]. Thus, the BG output nuclei appear to integrate information from these two pathways by acting as a gate that can be opened or closed to release coordinated movement [67].

In HD, the indirect pathway seems to deteriorate first as denoted by the preferential loss of striatal ENK neurons [68], and decreased ENK immunoreactivity in GPe [69]. This loss, according to the canonical model of BG connectivity, would bias the system toward activation of the direct pathway and thus induce chorea [70]. The model is further supported by evidence that cortical input to the indirect pathway is higher than that for the direct pathway [71], which may contribute to the vulnerability of the indirect pathway in HD since glutamate in high concentrations can be neurotoxic [72]. But in addition to the neuropathology of the indirect pathway, it is likely that direct pathway MSNs can be dysfunctional even though they may not show early-stage deterioration. Recent *in vitro* evidence, for example, indicates that selective activation of the direct pathway in either YAC128 or R6/2 mice results in a decreased SNpr response relative to healthy wild-type controls [73]. Thus, both striatal projections are likely to make important contributions to the HD behavioral phenotype.

Glutamatergic cortical pyramidal neurons

Despite the topographic organization of cortical pyramidal neurons (CPNs) and their striatal projections, the potential influence of these projections on striatal activity is complex [71, 74–78]. This section highlights important characteristics of the control that corticostriatal connectivity exerts over the direct and indirect BG pathways.

The CPN projection to the striatum can be divided into two main types: the intra-encephalic tract (IT) and the pyramidal tract (PT). Each type has distinct connectivity with the striatum and involvement in motor control. For example, IT neurons from the motor cortex but not from sensorimotor cortex project both contralaterally and ipsilaterally, whereas PT neurons only project to the ipsilateral striatum [77]. The distribution of IT and PT neurons in cortical layer 5, which is highly involved in voluntary movement, is about 65% for IT and 90% for PT [74–77, 79]. In an elegant series of studies, Reiner and colleagues [77] demonstrated that these two types of neurons show very distinct and preferential synaptic contact onto striatal MSNs. These researchers found that 50.9% of IT-type corticostriatal neurons project to DYN/SP MSNs that form the direct pathway and only 12.6% to the indirect pathway. While 50.5% of PT-type corticostriatal neurons target ENK MSNs, which form the indirect pathway, only 21.3% project to the direct pathway [71, 77, 79]. In addition, PT neurons show complex firing activity during movement, while IT neurons fire during motor planning before movement occurs [80, 81]. These different electrophysiological properties also correspond to differences in glutamate release. For example, PT neurons that target the indirect pathway have a higher probability of glutamate release than IT neurons that target the direct pathway [82, 83]. This difference may make indirect pathway MSNs more susceptible to degeneration and death [68, 70, 84]. Nevertheless, dysregulated corticostriatal activity seems to be critical in the neuropathology of HD [40, 57, 85, 86].

Although the specific involvement of IT and PT corticostriatal connectivity has not been associated with the pathological features of HD, several studies have noted cortical alterations in HD patients and animal models. Both show evidence of cortical deterioration such as atrophy, demyelination, and decreased size of soma and dendritic field [35, 87–90]. Moreover, GABA transmission is decreased in HD patients [91] and in BACHD mice [92], suggesting a reduction of inhibitory tone. In HD mice, increased calcium currents were reported for CPNs [93], which also have hyperexcitable membranes [51]. Consistent with increased excitability of CPNs is evidence of altered firing patterns *in vivo*, including a decrease in synchronized activity among simultaneously recorded neurons [57]. Furthermore, preventing the expression of *mHTT* in cortical efferents improved striatal neuronal activity [36, 94], suggesting that *mHTT* alters striatal activity via dysregulated cortical input.

GABAergic medium spiny neurons

The neuronal population of the striatum is divided into two groups: projection neurons and interneurons. Projection neurons account for more than 90% of the neuronal population and include all MSNs [95, 96], while the remaining includes GABA- and acetylcholine (ACh)-containing interneurons [97, 98].

The projection system is an integral part of the cortico-BG-thalamo-cortical loop (see above). Striatal MSNs are activated by glutamate input from

IT and PT cortical neurons, and information flows through the direct and indirect pathways to the BG output nuclei, the thalamus, and back to cortex (Fig. 1). Importantly, a separate region of thalamus, the intralaminar nuclei, also sends glutamate input to both direct and indirect MSNs as well as striatal interneurons [99–101]. Thalamostriatal axon terminals have a higher probability of glutamate release than corticostriatal axon terminals [102, 103]. Interestingly, the thalamic projection to striatum also shows signs of neuropathology in HD and is a likely contributor to the motor phenotype [104], much as the thalamostriatal projection also contributes to the motor signs of Parkinson's disease [105]. In fact, using *in vitro* co-cultured thalamostriatal axons from YAC128 mice, investigators reported that functional synapses on MSNs are significantly altered. For example, thalamostriatal afferents showed decreased membrane capacitance and increased membrane resistance compared to corticostriatal afferents, suggesting that thalamostriatal axons are affected earlier [103]. Thus, thalamostriatal involvement in HD deserves further investigation.

Striatal MSN activity is often linked to movement. For instance, the motor-activating effects of psychomotor stimulants as well as spontaneous episodes of rearing or stepping excite many MSN populations, although some MSNs fail to respond to movement or are inhibited [106–109]. Moreover, after intra-striatal infusion of amphetamine, a widely studied stimulant, the activity of motor-related MSNs increases prior to behavioral activation, suggesting that MSN activity is not secondary to movement [110]. In addition, MSN motor-responsiveness is region-specific with dorsal and especially dorso-lateral striatum most sensitive to motor activation [106]. Thus, striatal activity can be key in cases of motor dysfunction.

In HD mouse models, one of the most consistent electrophysiological alterations in MSNs is a change in membrane properties. For example, in R6/2 mice, MSNs have a depolarized resting membrane potential and reduced membrane capacitance [88, 111], consistent with a significantly elevated firing rate during behavior relative to wild-type controls [112]. MSN calcium conductance is also increased, but at late stages, when R6/2s become hypokinetic, calcium conductance decreases [113]. Notably, these electrophysiological changes occur in conjunction with such morphological changes as decreased number of dendrites, loss of spines, decreased soma size, and decreased dendritic spread [22, 35, 88, 111]. Thus, MSNs undergo both functional and morphological changes over the course of HD.

MSN activity also is regulated by interneurons, and interestingly, the relationship is not reciprocal: interneurons innervate MSNs but not vice versa [20, 97, 114, 115]. Despite their small numbers, striatal interneurons exert a large influence on MSN activity owing to their extensive pattern of axonal branching. Thus, the interneuron population, which also receives glutamate input from cortex and thalamus, is another important factor in MSN dysfunction in HD.

Striatal interneurons

There are two main types of striatal interneurons: ACh and GABA. Early reports suggested that the interneuron population remained morphologically intact in HD [43, 116], but further assessments have found that degeneration of striatal GABA interneurons might be associated with dystonia [117].

GABA interneurons are classified according to the type of co-localized protein, peptide, or enzyme, which would include calcium-binding proteins (e.g., parvalbumin or calretinin), tyrosine hydroxylase (TH), neuropeptide Y, somatostatin, nitric oxide synthase and NADPH diaphorase [98, 118–120]. The best characterized is the parvalbumin-positive or fast-spiking interneuron (FSI), which accounts for approximately 20% of the total interneuron population [95]. FSIs show an increased expression gradient from medial to lateral dorsal striatum [121], which parallels input from motor and sensorimotor cortical regions [122], suggesting a selective role in motor integration. An important feature of FSIs is that they connect with other interneuron dendrites by gap junctions, which may provide strong control of striatal activity forming a large meshwork of interneuron-interneuron communication [123, 124]. In fact, data from electrophysiological studies suggest that FSIs participate in MSN spike initiation [125]. For instance, FSIs make synaptic contact with hundreds of MSNs, and many of these contacts are onto the somatic region. In contrast, MSN-to-MSN synaptic contacts occur distal to the cell body [126]. FSIs exhibit a brief action potential and a significantly higher firing rate than MSNs [115]. FSI activity, characterized by irregular, high frequency bursting, is believed to induce gamma oscillations in local field potentials (LFPs) [97, 127, 128], which sample pre- and postsynaptic activity within a relatively large area surrounding the recording electrode (see below). FSI burst firing may be important for the synchronous

recruitment of MSNs throughout the sensoriomotor striatum causing LFP high-voltage spindles (HVSs), which have been reported to occur when there is no motivation to act or move [129].

Gap junctions seem to play an important role in spindle synchronization [130]. Because of the inhibitory influence of FSIs on MSNs [97, 115] hypofunction or loss of FSIs is associated dystonia [131, 132]. In fact, FSIs are lost in HD, suggesting a mechanism for dystonia onset [117].

Another striatal neuron type is the TH-positive interneuron. This cell type, named after TH, the rate-limiting step in DA synthesis, appears to play an important role in the pattern of striatal activity by making synaptic contact with MSNs [119, 120]. Although these interneurons are not DAergic, they have the unique capability of producing widespread and effective inhibition of both direct and indirect pathway MSNs [133]. Interestingly, it has been shown that DA enhances the ability of TH-positive interneurons to generate long-lasting depolarizing potentials [134]. Few studies have targeted TH-positive interneurons for analysis in HD, but available evidence from HD patients suggests that they are decreased in number [135]. As data accumulates on this particular class of interneurons, further studies of their role in HD, including the behavioral phenotype of HD mice, are needed.

ACh-containing interneurons appear to correspond to the group of tonically active neurons (TANs) identified in striatal electrophysiological recordings [136]. Unlike FSIs, TANs have a very long-duration action potential [137]. They receive prominent glutamate input from intralaminar thalamus [99, 101], and seem to control MSN activity through the release of ACh and consequent activation of postsynaptic muscarinic receptors, which increase MSN excitability [138, 139].

The activity of choline acetyl transferase, the enzyme that synthetizes ACh, is significantly decreased in HD patients [91] along with decreased binding and expression of the ACh vesicular transporter [140, 141]. In addition, HD patients treated with inhibitors of acetyl cholinesterase, to elevate Ach levels, showed some improvement in both cognitive function and motor performance [142]. Recent evidence also showed that deficient thalamic input to the dendrites of ACh interneurons occurs early in the lifespan of Q140 mice [143]. Collectively, these data suggest that altered ACh interneuron activity may play a role in the emergence of the HD behavioral phenotype.

DOPAMINE MODULATION

Because DA plays an important role in the modulation of excitatory and inhibitory signaling in both cortex and striatum to control the flow of information through cortico-BG circuits, DA dysfunction deserves attention as another potential mechanism underlying HD neuropathology. DA and its receptors have been broadly studied in the neuropathology of Parkinson's disease, a progressive neurodegenerative disorder characterized by motor disturbances. Although DA system alterations in HD remain elusive, neurochemical findings have shown important changes in DA transmission that emerge at early stages of the disease and might be related to motor impairments, cognitive dysfunction, and psychiatric symptoms.

Dopamine overview

Two major DA pathways innervate cortical and striatal areas: nigrostriatal and mesocorticolimbic. The nigrostriatal pathway, which modulates the activity of striatal neurons in the control of movement [144], is defined by the projection of DA neurons from the substantia nigra pars compacta (SNpc) to dorsal striatum (Fig. 2). The degeneration of this pathway in Parkinson's disease is the primary mechanism underlying the slowness of movement and shuffling gait of Parkinsonian patients. This pathway also has been implicated in cognitive function. Striatal regions with high DA innervation play an important role in cognitive tasks and cognitive flexibility [145, 146].

Psychiatric symptoms, which can also emerge in HD, are associated primarily with mesocorticolimbic dysfunction, although nigrostriatal abnormalities are likely to contribute [147–149]. The mesocorticolimbic pathway originates from DA cell bodies in the ventral tegmental area (VTA) with axons ascending to the nucleus accumbens or ventral striatum as well as large areas of frontal cortex, including the prelimbic and infralimbic areas of prefrontal cortex [144]. In the target areas of both pathways, DA modulates the influence of glutamate by adjusting the strength of the glutamate signal relative to background activity [150].

Several steps are involved in DA transmission as outlined in Fig. 2. Multiple pharmacological approaches have been developed to modulate each of these steps.

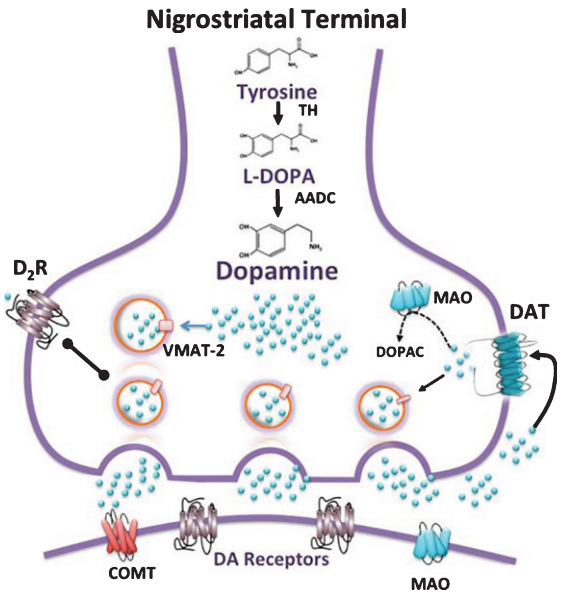

Fig. 2. DA synthesis, vesicular loading, and release. DA is synthetized from tyrosine, which is converted to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase. Decarboxylation of L-DOPA by the L-amino acid decarboxylase (AADC) produces DA. Newly synthesized DA is incorporated into vesicles by vesicular monoamine transporter-2 (VMAT-2). Action potential activity allows the vesicles to fuse with the plasma membrane and release their contents into the synaptic cleft. Extracellular DA can activate postsynaptic receptors and be transported back to the terminal by the DA transporter (DAT). Remaining extracellular DA is metabolized by catechol-O-methyltransferase (COMT) or by monoamine oxidase (MAO). Presynaptic D_2 receptors play an important role in the feedback regulation of DA release.

Dopamine in HD

In postmortem studies, HD patients lose more than 40% of DA neurons in SNpc relative to controls [151, 152] along with a significant decrease in DA terminals in the striatum [140]. This evidence is consistent with a significant decrease in immunoreactivity for TH in the SNpc and striatum [153, 154] and a significant decrease in striatal vesicular monoamine transporter-2 (VMAT-2), which transports newly synthesized DA into presynaptic vesicles [140]. Similarly, the DA transporter (DAT), located on DA axon terminals and removes extracellular DA after its release, shows a 50% reduction in HD postmortem specimens [140, 155] and in binding studies of HD striatum [156]. In line with this evidence, DA uptake is reduced in striatal tissue of HD patients relative to controls, and the volume of the HD substantia nigra is also decreased [157].

Evidence for altered DA transmission also appears in HD models. For example, decreased neuronal size in the SNpc of R6/1 mice correlates with an increase in mHTT aggregates [158]. In addition, an expansion of CAG repeats in SNpc is associated with decreased DA content [159]. Evoked DA release in brain slices also is decreased in R6/1 [160] and R6/2 mice relative to controls [161]. Microdialysis studies, moreover, indicate a 70% reduction in striatal extracellular DA content [158]. Interestingly, however, although decreased DA was found in symptomatic R6/1s relative to control mice, the opposite effect was reported for pre-symptomatic mice [159], suggesting that nigrostriatal DA transmission is differentially affected over the course of HD progression. In support of this view, TH activity relative to control was increased at 4 weeks of age in R6/2 mice with no changes in TH expression, but a decrease of both protein and activity occurred at 12 weeks of age [154]. In the same animal model, DAT was significantly reduced at late but not at early stages, although no DAT change was found in BACHD mice [162]. Interestingly, a decrease in striatal DA content was correlated with a reduction in total locomotor activity in both R6/2 and YAC128 mice [163]. Gait disturbances in tgHD rats also were also associated with decreased DA release from 12 to 15 months of age as measured by fast scan cyclic voltammetry [160].

Curiously, however, studies of the Q175 mouse model fail to present a consistent DA picture. In heterozygous Q175s, for example, hypokinesia is not accompanied by decreased DA content; in fact, the alteration in DA did not occur until the mice reached 12 months of age, and no changes in DA fibers were found [35]. In contrast, homozygous Q175s show decreased DA release in striatum accompanied by reduced TH immunoreactivity and VMAT-2 expression along with hypokinetic symptoms [58]. Furthermore, evidence of decreased DA content in the heterozygous nucleus accumbens is believed to contribute to cognitive neurological signs [164]. It appears that additional research is needed to clarify DA changes in the KI-Q175 model and to determine the extent to which the DA changes in this model parallel the changes in truncated and full-length HD models.

DA metabolism also is altered in animal models, but again with some inconsistency. For example, a significant decrease in the DA metabolite homovanillic acid was found in Q175, R6/2 and YAC128 mice [35, 165, 166], while DOPAC was found to be decreased in R6/2 and YAC128 mice [163] but increased in KI-Q175 at 6 months with no change at 12 or 16 months [35]. Collectively, these animal

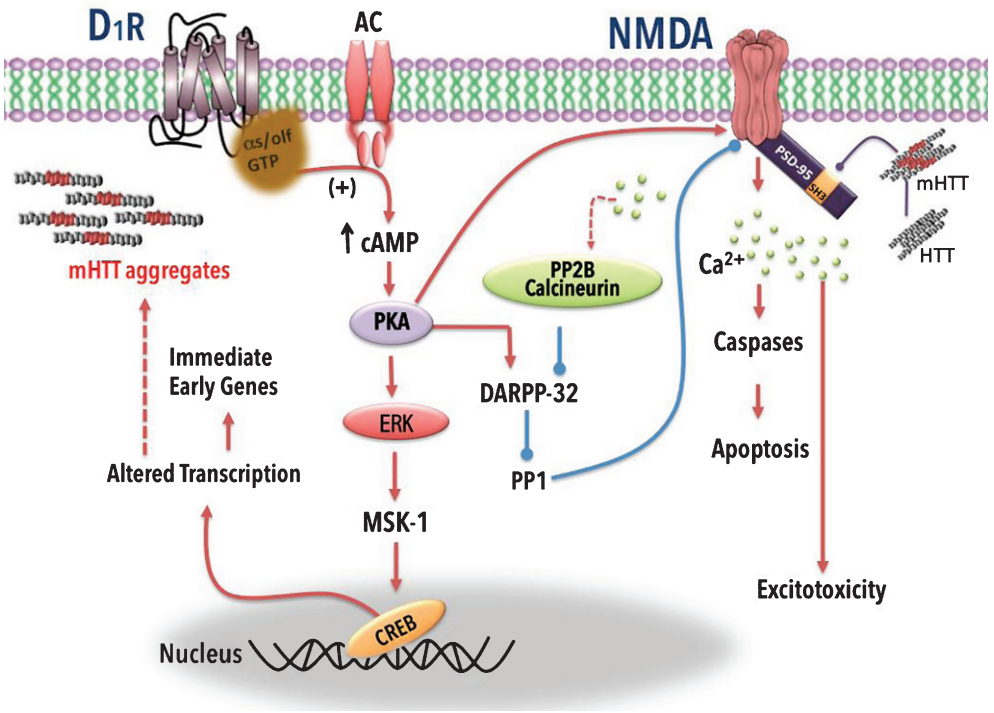

Fig. 3. D_1 and NMDA receptor signaling pathways and mHTT aggregates. The activation of D_1 receptors results in G protein αs/olf coupling and the stimulation of adenylyl cyclase (AC), which transforms adenosine triphosphate (ATP) into 3′-5′-cyclic adenosine monophosphate (cAMP). This messenger activates protein kinase dependent cAMP (PKA), which phosphorylates cAMP-regulated phosphoprotein-32 (DARPP-32) leading to inactivation of phosphatase-1 (PP1). PKA can also phosphorylate NMDA receptors enhancing its activity. Through the phosphorylation of extracellular regulated kinase (ERK) and subsequent phosphorylation of mitogen- and stress- protein kinase-1 (MSK-1), PKA may activate the cAMP response element-binding protein (CREB), which is involved in gene transcription processes. Activation of the D_1 receptor induces mHTT aggregations [202, 203], possibly by activating CREB. NMDA receptors interact with the postsynaptic density-95 (PSD-95) protein, which contains the domain Src homology 3 that interacts with HTT; mHTT prevents the interaction causing sensitization of NMDA receptors and promoting apoptosis. Stimulatory effects are indicated with arrows; inhibitory effects with a line ending in a circle. Broken lines indicate possible mechanism of action.

data suggest that DA transmission is altered in HD perhaps even at very early stages when no motor symptoms are apparent, but the lack of consistency across models suggests the data should be interpreted with caution.

Receptor expression and signaling

DA receptors belong to the large family of G-protein-coupled receptors. There are five types of mammalian DA receptors divided into two subfamilies according to their amino acid structure, homology, and biological response. The D1-like subfamily includes D_1 and D_5 receptors, while the D2-like subfamily consists of D_2, D_3 and D_4 receptors. D1-like receptors are positively coupled to adenylyl cyclase (AC); their activation induces the intracellular accumulation of cyclic 3,5 adenosine-monophosphate (cAMP), which in turn, activates protein-kinase dependent cAMP (PKA) (Fig. 3). PKA is an important intracellular kinase directly involved in the phosphorylation of ion channels and activation of phosphatases such as DA regulated phosphatase-32 (DARPP-32) that play an important role in the electrophysiological properties of the neuronal membrane [167]. D2-like receptors, in contrast, are negatively coupled to AC. As a result, their activation decreases cAMP accumulation and PKA activation (Fig. 4) [168–170]. Growing evidence has shown, however, that activation of DA receptors is not only restricted to modulation of AC but also other complex transduction signaling pathways, depending on the brain area and any ongoing physiological and pathological conditions [171].

Striatal MSNs that comprise the direct pathway (SP/DYN), preferentially expresses D1-like receptors [62, 172, 173]. When activated, these receptors increase MSN activity by increasing time spent in the "up" or depolarized state [174]. Because these

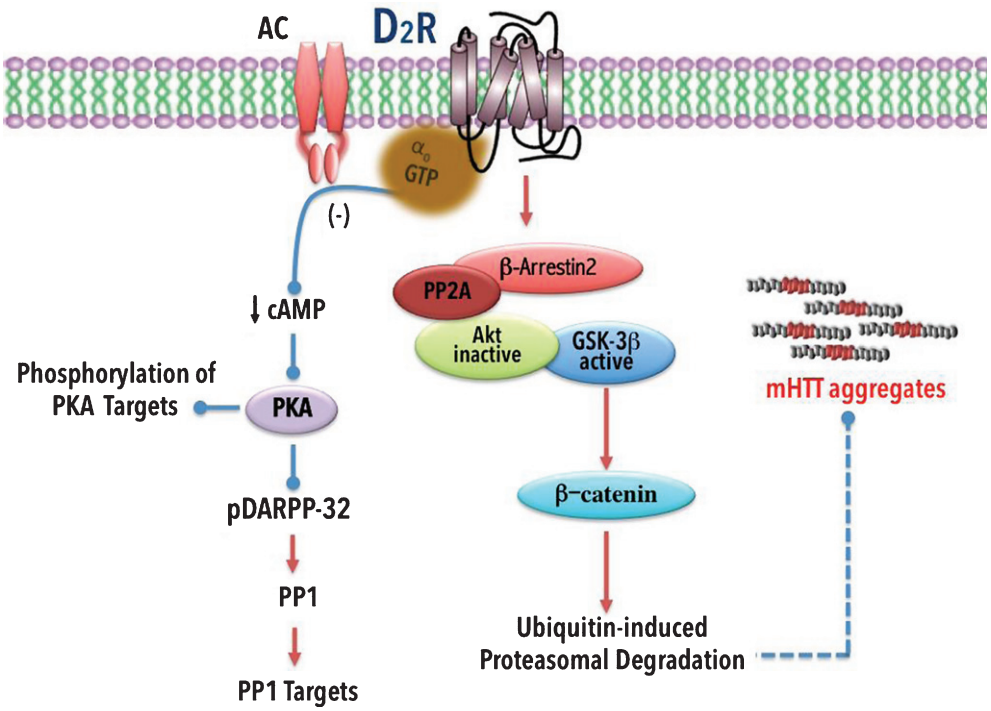

Fig. 4. Alteration of the D_2 receptor signaling pathway in HD. D_2 receptor activation decreases cAMP signaling. D_2 receptors can also activate β-arrestin2, which recruits phosphatase-2A (PP2A). PP2A in turn interacts with thymoma viral protoncogen (Akt). The PP2A-Akt complex promotes activation of glycogen synthase kinase-3 β (GSK-3β), which induces phosphorylation of β-catenin, a protein involved in the activation of the ubiquitin-induced proteasomal degradation system [209, 210]. Because GSK-3β expression is decreased in HD [90, 207] the decrease in phosphorylated β-catenin causes cellular toxicity [211]. Decreased activation of D_2 receptors may be involved in the reduced degradation of mHTT. Stimulatory effects are indicated with arrows; inhibitory effects with a line ending in a circle. Broken lines indicate possible mechanism of action.

receptors are also located presynaptically on striatonigral terminals, they also increase GABA release in the GPi/SNpr [175, 176, 177]. Thus, the end result of D1-like activation of striatal MSNs is GABA-mediated inhibition of BG outputs, which in turn disinhibits the thalamic projection to motor cortical areas and promotes movement.

In contrast, D2-like receptors are found preferentially on striatal indirect pathway neurons [60], which project to the external segment of the globus pallidus (GPe). Activation of D_2 receptors has been reported to have an inhibitory effect on MSNs by preventing the transition to an "up" state [62, 66, 172, 178]. In striatopallidal terminals, the presynaptic activation of D_2 receptors will inhibit GABA release through the inhibition of PKA activity [179, 180, 181]. The inhibition of GABA release in GPe will activate the inhibitory GPe projection to the subthalamic nucleus (STN). Because the STN activates GPi/SNpr by releasing glutamate, inhibition of the STN ensures inhibition of BG outputs, and thus activates the thalamocortical system to promote movement. Without DA, however, cortical activation of indirect MSNs will tend to suppress movement by activating BG outputs.

Coordinated movement, therefore, depends on balanced DA transmission between D1- and D2-like receptors. In fact, recent evidence indicates that both pathways regulate movements by acting in a complementary manner [66]. In HD, a change in the D1- D2-receptor balance could trigger either excess of movement (chorea), an early-stage phenotype, or bradykinesia, which emerges later.

Transcriptional dysregulation of DA receptors has been found in HD patients. For instance, the mRNA for MSN D_2 receptors is significantly decreased and this effect is exacerbated in advanced stages of HD, whereas the mRNA for D_1 receptors showed an initial reduction and then a slight increase with HD progression [182]. Quantitative autoradiography has confirmed a loss of D_1 and D_2 receptors in striatum and also in corresponding terminal areas. A 55% loss of D_1 receptors in the GPi/SNpr was found in pathological grade 1 HD, but no further loss in grade 3,

while D_2 receptors in GPe showed a 30% decrease in grade 1 that jumped to 55% in grade 3 [183]. Similar stage-dependent D_2 receptor loss was found with positron emission tomography (PET) imaging such that the severity of neuropathological signs was strongly correlated with decreased expression of D_2 receptors [155, 184–186]. Moreover, in R6/1, R6/2, and YAC128 [187–189] but not BACHD mice [162, 189], the binding and mRNA expression of D_1 and D_2 receptors were decreased, and again, the changes were correlated with disease progression.

DA signaling also changes in HD. In pre-symptomatic R6/2 mice, for example, striatal D_1 receptor signaling is increased [113]; the same effect has been reported for pre-symptomatic Q175 mice [58]. In symptomatic R6/2 and YAC72 mice, D_1 receptor expression is decreased [188, 190], but both cAMP and the level of phosphorylation of DARPP-32 are increased [113, 188].

Under normal conditions, the activity of DARPP-32 would be inhibited by calcineurin (phosphatase-2B), but the expression of calcineurin is decreased by about 30% in pre-sympomatic R6/2s and Q175s but further downregulated when motor signs appear [191], suggesting that D_1 receptor signaling might be chronically activated. In support of this view, the expression of immediate early genes, which occurs after chronic activation of D_1 receptors [192], is elevated in R6/2 mice [190], indicating augmented neuronal activity in this model and confirmed by recording of striatal MSNs in behaviorally active R6/2s [112]. Because D_1 receptors are decreased but cAMP and DARPP-32 signaling are increased in HD models, one possibility is over-activation of AC (Fig. 3). Interestingly, increased AC activity has been found in other motor complications such as L-DOPA-induced dyskinesia [176, 177, 193, 194], autosomal dominant familiar dyskinesia, and myokymia [195].

Interestingly, D_1 receptor agonists activate extracellular regulated kinase (ERK), and in HD, ERK signaling is consistently altered in striatum but not cortex [196, 197]. The increased phosphorylation of ERK can phosphorylate cAMP response-element binding protein (CREB), which is an important regulator of D_1 receptor signaling [198, 199]. In fact, this pathway has been associated with movement disorders perhaps mediated by supersensitive D_1 receptors [63, 200]. Increased CREB phosphorylation has been found in striatum but not cortex in R6/2 mice at late stages of disease [196], suggesting that striatal postsynaptic signaling transduction pathways might be involved in transcriptional alterations. In line with this point of view, massive transcriptional dysregulation has been reported in HD (see review [201]).

D_1 receptors also could play a role in HD progression. Pharmacological activation of D_1 receptors, for example, accelerates the formation of mHTT nuclear aggregates, and again the effect is mediated by the activation of transcription factors [202]. Furthermore, the same result was found with forskolin, which directly activates AC, further implicating the D_1 receptor signal transduction pathway in the aggregation of mHTT (Fig. 3) [202, 203].

Altered D_2 receptor signaling also is a likely contributor to the neuropathology of HD. In addition to modulation of cAMP signaling, D_2 receptors can activate β-arrestin2, which recruits phosphatase-2A (PP2A), enhancing its interaction with thymoma viral protoncogen (Akt) (Fig. 4). This complex inactivates Akt, which in turn induces stimulation of the glycogen synthase kinase-3 β (GSK-3β) pathway [204–206]. Importantly, altered GSK-3β signaling is associated with HD neuropathology [90, 207]. Activation of GSK-3β induces phosphorylation of β-catenin, which can stimulate the ubiquitin-induced proteasomal degradation system [208]. Moreover, activation of this system induces disposal of mHTT, preventing its cellular aggregation (Fig. 4) [209, 210]. Interestingly, β-catenin phosphorylated levels were found to be decreased in HD cell lines, causing toxicity [211]. Recent studies using post-mortem HD specimens found a 50% reduction of GSK-3β in frontal cortex [90, 207]. In R6/2 mice, decreased GSK-3β protein levels and activity were found in cortex and striatum but not hippocampus, and this corticostriatal change contributes to brain atrophy, behavioral alterations, and learning deficits in early symptomatic and symptomatic but not in pre-symptomatic HD mice [90]. Restoring expression of GSK-3β resulted in amelioration of the behavioral phenotype [90]. In primary striatal neurons cultured from the Q111 KI mouse, Akt signaling contributed to mHTT localization and this occurred prior to cell death [212].

In conditions of decreased DA transmission, the lack of D_2 receptor activation would result in prolonged inactivation of GSK-3β and probably decreased ubiquitin-induced proteasomal degradation. To the best of our knowledge, the role of DA and its receptors in relation to GSK-3β signaling in HD has not been studied. Intriguingly, in conditions of DA depletion with subsequent chronic L-DOPA treatment, which is widely known to cause dyskinesia,

constitutive Akt signaling was found in striatum [213]. Given the likely biphasic change in DA transmission observed in HD, this receptor pathway may play a role in the formation of mHTT aggregates.

Collectively, these data suggest a broad spectrum of changes in the DA system ranging from synthesis to release to receptors. But changes in DA are closely tied to changes in glutamate, and the interaction of these two systems has been associated with several aspects of HD neuropathology.

Interaction with glutamate

Dysregulation of DA and glutamate in HD has been widely proposed [17, 214–218]. In corticostriatal circuitry, DA modulates the glutamate system by controlling glutamate release or by the direct regulation of glutamate receptors [219–222]. For example, early studies showed that D_1 receptors and N-methyl-D-aspartate (NMDA) receptors co-immunoprecipitate, suggesting a protein-protein interaction [223, 224]. This interaction prevents D_1 receptor internalization [225]. Furthermore, activation of D_1 receptors increased the expression of NMDA receptors at the membrane surface of corticostriatal axon terminals [226], as well as the membrane expression of both NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in striatum. D_1 receptors not only regulate NMDA surface expression, but the phosphorylated state of NMDA receptors through activation of PKA [222, 227], which can increase NMDA receptor ion currents [228]. In striatum, D_1 receptor activation enhanced the NMDA response, indicating an important functional interaction [229–231].

In an interesting contrast, D_2 receptor activation in striatum decreases the glutamate response evoked by AMPA [229]. D_2 receptor activation also decreased the glutamate-evoked NMDA response by presynaptic modulation of glutamate release [232].

Abnormal DA and glutamate transmission has been associated with dysfunction and loss of MSNs in HD [214, 233]. It has been shown, for example, that increased NMDA activity could promote HD neurodegeneration [234, 235]. Interestingly, DA and glutamate act synergistically to induce apoptosis in YAC128 MSNs [214].

An important consideration regarding this interaction is the location of NMDA receptors. They are composed of different subunits that confer different properties on their activity [215, 236]. In the synapse, for example, NMDA receptors are mainly composed of NR1 and NR2B subunits, while extra-synaptic locations results in NR1, NR2B, and NR2A subunits [237]. The differential expression of these subunits has implications for the activation of specific intracellular signaling pathways. Synaptic NMDA receptors, for example, appear to activate anti-apoptotic pathways, whereas extra-synaptic receptors are associated with mitochondrial dysfunction and cell death [238]. Accordingly, YAC128 mice have increased expression of extra-synaptic NMDA receptors [239]. Blockade of these receptors, moreover, resulted in amelioration of striatal synaptic dysfunction and cell death [240]. Thus, it is possible to assume that the differential expression of synaptic and extra-synaptic NMDA receptors determines the extent of neurotoxicity, suggesting that a sustained increase in extracellular glutamate is the sole mechanism underlying cell death. DA, however, has been found to differentially modulate synaptic and extra-synaptic receptors. For instance, D_1 receptor-mediated potentiation of NMDA responses is increased by genetic deletion of the NR2A subunit [236]. Moreover, NMDA receptors dominated by NR2A subunits are linked to glutamate responses in MSNs expressing D_1 receptors, while NR2B-dominated NMDA receptors are associated with MSNs expressing D_2 receptors [236]. This interplay is also important in neuronal morphological changes. Analysis of corticostriatal morphology after treatment with a D_1 receptor agonist revealed an increase in the width of spine heads, and co-treatment with a NR2A antagonist, further enhanced this effect [241], suggesting that NMDA receptors counterbalance DA effects.

Another line of evidence indicates that in striatum proteins involved with postsynaptic receptor stabilization are dysregulated in HD [35]. NMDA and AMPA receptors interact with the postsynaptic density-95 (PSD-95) protein, a scaffolding protein that recruits receptors and signaling molecules. The interaction of glutamate receptors with PSD-95 has neuroprotective implications for HD [242]. PSD-95 contains the domain Src homology 3 (SH3), which in normal conditions interacts with HTT. An important feature of HD is that mHTT fails to bind to PSD-95 (Fig. 3) and also prevents the interaction with non-mutant HTT causing sensitization of NMDA and promoting apoptosis [242]. In both YAC128 and YAC72 mice, there is evidence of increased NMDA interaction with PSD-95 mediated by mHTT with implications for increased neurotoxicity [243]. PDS-95 is also decreased in Q175 mice [35].

PSD-95 also interacts with D_1 receptors located in spines and prevents activation of D_1 receptor

signaling [244]. Moreover, PSD-95 forms ternary protein complexes with D_1 and NMDA receptors [225]. Both receptors are expressed in MSN spine heads, where the majority of corticostriatal glutamatergic synapses are found [245]. Thus, failure of PSD-95 function would over-activate both NMDA and D_1 receptors, resulting in dysfunctional corticostriatal communication. The modulation of DA by PSD-95 is still elusive, but evidence suggests that the genetic deletion of PSD-95 produces concomitant activation of D_1 and NMDA receptors, resulting in motor impairments and striatal degeneration [246]. In addition, signaling pathways associated with D_1 but not D_2 receptors induce cell-death mediated by mHTT [202, 215]. It is likely, therefore, that increased expression of mHTT triggered by D_1 receptors may prevent binding between NMDA-PSD-95 to promote sensitization of NMDA receptors.

In a further link to D_1 receptors, glutamate release onto D_1- but not D_2-receptor-expressing striatal neurons is increased early in YAC128 mice, but later switches to a decrease [217]. Moreover, although D_1 receptor expression may decrease, receptor signaling is increased as shown by enhanced cAMP and DARPP-32 phosphorylation [58, 113, 182, 183, 188], suggesting augmented PKA activation, which in turn will increase NMDA receptor phosphorylation [222, 227, 228, 247]. Increased NMDA receptor activity and the synergistic action of D_1 receptors on intracellular calcium could activate apoptosis [214, 234, 235]. The over-activation of D_1 receptor signaling may contribute to an increase in mHTT aggregates, which in turn could disrupt the binding of NMDA and PSD-95 causing further sensitization of NMDA receptors, increased calcium signaling, neurotoxicity, and overall dysregulation of neuronal activity [202, 214, 242, 243]. Apart from modulation of NMDA receptors, D_1 receptor activation in normal conditions increases L-type calcium channel currents [248, 249], decreases somatic K^+ currents [250], and decreases activation of currents evoked by N- and P/Q-type calcium channels [251]. These channels control the small conductance calcium-activated K^+ channels, which play an important role in slowing MSN spiking activity [252]. The end result is increased neuronal activity in the direct pathway [253].

DA in motor alterations

Early evidence for the contribution of DA dysfunction to the motor alterations of HD emerged from a report that L-DOPA, widely used to treat Parkinson's disease, caused dyskinesia in asymptomatic HD patients [254]. There also was evidence of extensive atrophy of the SNpc in HD patients [255] as much as a 40% decrease of DA neurons has been reported [151, 152]. Nevertheless, increased levels of DA were found in the nigrostriatal pathway of HD patients who showed chorea-like motor symptoms, but not rigidity [91]. Interestingly, YAC128 mice also display motor hyperactivity at early stages followed by motor deficits at late stages [49]. Similar effects are found in Q175 mice, including reduced DA release in the striatum consistent with late-stage hypokinetic symptoms [35, 58]. There is evidence that binding of tetrabenazine (TBZ), which decreases DA release by blocking VMAT-2, is significantly decreased in patients with akinesia and rigidity compared to patients with chorea [156]. Because motor symptoms vary with the stage of the disease, a thorough understanding of DA involvement is difficult to achieve when most postmortem studies are based on late-stage data.

In animal models, DA has been widely implicated in motor symptoms. For example, in hypokinetic Q175 homozygous mice, a loss of DA in the corticostriatal circuit impaired glutamate transmission and low gamma oscillations in striatal LFPs [58]. The change in gamma is interesting because in normal conditions an interaction between low and high gamma oscillations plays a role in motor states. Low gamma power in striatum, for example, occurs in response to movement initiation [256], while high gamma oscillations predominate during running [257]. In YAC128 mice, D_1 receptor-expressing MSNs show an age-related increase in the frequency of excitatory postsynaptic currents [217]. Because of the location of D_1 receptors on striatonigral axon terminals, D_1 receptors are closely related to movement disorders. It seems likely, therefore, that increased activity in the direct pathway is in part responsible for chorea-like symptoms. In agreement with this view, targeted ablation of striatal D_1 receptors in mice is sufficient to cause gait disturbances and involuntary movements [258]. In addition, optogenetic approaches have revealed that selective activation of the striatonigral pathway is directly involved not only in movement initiation but also in motor action sequences [66, 173]. This effect, moreover, seems to be mediated by the inhibition of subsets of SNpr neurons [67, 173]. In symptomatic Q140 KIs, when motor activation declines, burst firing increases in SNpr compared to wild-type controls [259]. More studies are needed to identify the role of D_1 receptors in SNpr activity and its relation to movement.

It is widely accepted that alterations in DA transmission in HD are biphasic with an increase in release occurring at early stages [260, 261] corresponding to chorea and hyperkinesia, and a subsequent decrease leading to late-stage hypokinesia [163, 165]. Changes in DA receptors are likely to accompany changes in release. To be effective in ameliorating motor symptoms, therefore, opposing DA treatments may be required for early- versus late-stage HD (see below).

DA in cognition and behavioral inflexibility

Cognition includes a wide range of mental processing such as attention, memory, perception, learning, decision-making, and problem-solving. All these aspects of cognition involve corticostriatal circuits. Here, we focus on cognitive flexibility, which is routinely affected in HD.

Cognitive flexibility is the ability to switch strategies during learning and refers to how rapidly a subject is able to adapt to changing circumstances [262]. The lack of cognitive flexibility or behavioral inflexibility can be measured in learning tasks, for example, by assessing perseverative responses during reversal learning [262–265]. Repetitive sequential behaviors are another extreme form of behavioral inflexibility also associated with some psychiatric conditions such as Tourette's syndrome and obsessive-compulsive disorder. Behavioral inflexibility has been observed in both HD patients and animal models [6, 7, 266].

Reversal learning impairments in HD were noted when HD patients performed significantly lower than controls in the Wisconsin Card Sort Task (WCST) [267], which measures abstract reasoning and the ability to change problem-solving strategies when needed. The impairment, moreover, was found in late but not early stages of HD [268, 269]. In another study, however, the only predictor of cognitive decline among nine neuropsychological tests was significantly poor WCST performance in asymptomatic patients at approximately 3.72 years before HD onset [270]. Reversal learning deficits also have been found in HD animal models. In R6/2 mice, reversal learning was altered along with presynaptic proteins associated with glutamate transmitter release [271]. Q175 mice also showed deficits in reversal learning [6]. In tgHD rats, both reversal learning and fear conditioning were impaired [272], similar results were found in YAC128 mice [273, 274]. Similarly, R6/2 mice have difficulty extinguishing conditioned fear, an effect that correlated with altered activity in prefrontal cortex [275]. In a two-choice swim test, Q175 mice showed an increased latency in decision making [55].

Motor activity also seems inflexible. Repetitive, inflexible or stereotypic behaviors have been observed in HD patients [276] and HD animal models [85, 86, 217, 277]. Interestingly, DA innervation of the striatum has long been known to play a critical role in the repetitive movements triggered by psychomotor stimulants [278], and D_1 receptor agonists administered systemically or directly in the ventricle produce robust stereotypic grooming [279–281]. Whether a hyperdopaminergic state underlies the chorea and related-motor signs of HD remains to be established.

Flexibility in learning appears to involve the circuit from prefrontal cortex (PFC) to dorsomedial striatum [282–284], while the neural pathway from sensorimotor cortex (SMC) to dorsolateral striatum is associated with repetitive behaviors [285, 286] and decision-making [287]. Corticostriatal dysfunction has been correlated with cognitive impairment even at very early stages of HD [288, 289]. When striatal feedback to cortical areas via striato-BG-thalamocortical loops becomes dysfunctional, an inability to switch behavior is the result (for review [285]).

In pre-symptomatic and symptomatic HD patients, striatal D_2 receptors are significantly decreased in patients with poor cognitive performance, but a D_1 receptor decrease was associated only with altered sequential organization tasks [269]. Interestingly, increased activation of PKA was associated with disrupted recognition and spatial memory in HD [247], which could be explained by the lack of activation of D_2 receptors or increased D_1 receptor signaling [113]. Accordingly, both receptor types decrease gradually with progression of HD as the pre-symptomatic patients approached clinical onset [269, 290]. In addition, aberrant cortical synaptic plasticity and DA dysfunction has been reported for R6/1 mice; both D_1 and D_2 receptors are decreased in perirhinal cortex and the effects are reversed by quinpirole, a D_2 receptor agonist [291]. Taken together, these data suggest that the ability of DA and its receptors to modulate corticostriatal circuitry contributes to the cognitive decline in HD.

DA in psychiatric symptoms

Although the diagnosis of HD is mostly based on motor and cognitive symptoms, psychiatric alterations also can be present, sometimes even years before the other symptoms become prominent [292, 293]. The prevalence of psychiatric symptoms in

HD is variable, but mood disorders, irritability, aggression, impulsivity, psychotic episodes, rigidity, compulsive behavior and sexual disorders have been found in pre-symptomatic gene carriers [10, 293, 294]. Apathy is one of the most prevalent psychiatric symptoms in HD. A lack of interest in life activities and social interactions appears early and continues during HD progression, becoming one of the most disabling symptoms over time. Although 62% of early symptomatic patients show apathy, this trait is already evident in 32% of pre-symptomatic patients [2, 295–297].

Depression is the most common mood disorder in HD and has an early onset in about 50% of symptomatic patients [298, 299]. In fact, suicide among HD patients is 4 to 6 fold higher than in the general population [10, 300]. Irritability, impulsivity, and aggression can be additional reasons for hospitalization but are less prevalent than apathy and depression [301–303]. Psychotic episodes are even less common, but the data are difficult to interpret because antipsychotic medication, which blocks D2-like receptors, is sometimes used to ameliorate the chorea or motor hyperactivity that appears in early stages of HD. The frequency of paranoia, delusional states, anxiety, compulsive behavior, obsessive thoughts, and hallucinations has been estimated to range from 35–75% in HD patients [10, 302].

The collective group of psychiatric symptoms has been linked to dysfunctional activity in the PFC [149, 304–306]. For example, PET studies have reported evidence of hypometabolism in the PFC of depressed patients [307], and increased DA transmission has been found in the PFC during hallucinations and delusions [304, 305]. The PFC receives DA innervation from the ventral tegmental area (VTA) [170, 308]. This pathway also innervates the nucleus accumbens or ventral striatum, which plays a key role in reward [261]. DA in cortical areas can modulate synaptic responses controlling glutamate transmission [309, 310].

Neuroimaging studies of HD patients have implicated the PFC in these same psychiatric symptoms [298]. It already is clear from work on the R6/2 mouse model that information processing in the PFC is altered in HD mice [57]. In fact, abnormal neuronal activity in the prelimbic cortex, a region of the PFC with close ties to the amygdala, is correlated with reduced fear conditioning [275]. Although dysregulation of the corticostriatal circuit has been linked to motor and cognitive alterations in HD [36, 85, 86, 275, 311], very few studies have addressed the issue of DA system changes in HD associated with psychiatric disorders. Renoir and colleagues [312], using the forced swim test, found impaired DA transmission in R6/1 mice. This effect was reversed by bupropion, a weak DAT blocker, and a D_1 receptor antagonist prevented the effect of bupropion, suggesting that D_1 receptors might be involved in depression-like behaviors in HD. In fact, among the wide range of psychiatric symptoms identified in HD, depression is the only one associated with a decrease in DA transmission [306]. Interestingly, however, depression is not commonly associated with the progression of HD neuropathology, most likely because this symptom is sensitive to social and family environmental factors, which can vary widely among HD patients [297, 313].

DOPAMINE AS THERAPEUTIC TARGET

Because of DA involvement in motor control, cognition, and psychiatric symptoms, HD pharmacotherapy has targeted the DA system. To date, however, the overall success of this approach has been limited owing, in part, to side effects resulting from actions at non-DA receptors and, perhaps most importantly, from the increasing severity of HD progression, which limits long-term efficacy.

Inhibitors of vesicular monoamine transport

The VMAT-2 inhibitor, TBZ (Xenazine®), is the only federally approved drug in the United States used to treat HD, specifically chorea or episodes of uncontrollable movement [314–317]. TBZ inhibits VMAT-2 with a $K_i \approx 100$ nmol/L [316, 318, 319]. By preventing the loading of DA into presynaptic vesicles, TBZ makes less DA available for release when DA neurons are activated [320].

Although VMAT-2 operates in norepinephrine and serotonin as well as DA neurons [315], TBZ has a higher affinity for striatal VMAT-2, making it possible to adjust the dose to limit the effects of this drug on monoamines in other brain regions [319]. The TBZ-induced reduction in chorea is evidence that this can be an effective strategy. Side effects, however, are still common. TBZ, for example, can exacerbate symptoms of depression and cognitive decline in HD patients [321]. Chronic treatment, moreover, results in the loss of efficacy and, more ominously, may cause cell death in the SNpc [322], suggesting that at least some of the side effect of TBZ could be caused by neurotoxicity. The pharmacogenetics of TBZ is another reason for concern. For

instance, the activity of the cytochrome involved in TBZ metabolism, CY2D6, is genetically determined, making for fast or slow TBZ metabolizers. Thus, an effective dose with few side effects in one person may not apply to another [323].

Interestingly, a novel VMAT-2 inhibitor, NBI-641449, is undergoing phase III clinical trials for the treatment of hyperkinetic disorders. This compound has a higher affinity for VMAT-2 in DA neurons than in other monoamine neurons. Importantly for HD, NBI-641449 also decreases mHTT aggregates in cortex [324]. Further testing will determine if this compound is a viable alternative to TBZ.

DA antagonists

DA antagonists, including both typical and atypical antipsychotic drugs, have been used to block the hyper-DA state that contributes to the motor and psychiatric disorders in HD. Typical and atypical antipsychotics such as haloperidol, sulpiride, pimozidem, flufenazine, clozapine, olanzapine and risperidone have been used for some HD symptoms treatment. Haloperidol, a typical antipsychotic, is a potent antagonist of D2-like receptors with a slow kinetic dissociation and a high affinity for D_3 receptors (0.74 nM) followed by D_2 (1.55 nM) and D_4 receptors (5–9 nM) [325–327]. Haloperidol is effective in reducing chorea [328–330] and also has been used for treating episodes of psychosis, aggression, and impulsivity [331]. Severe side effects, such as akathisia, dystonia, tardive dyskinesia, and neuroleptic malignant syndrome, have limited its use [331–333].

Sulpiride, another highly selective D2-like antagonist that has been used to treat dyskinesia in HD, has not been found to be very effective and induces side effects, such as drowsiness, in about 45% of patients [334]. Fluphenazine and pimozide are also typical antipsychotics that have been used to treat chorea [335]. The affinity of fluphenazine for DA receptors families is slightly higher for D1-like than D2-like receptors ($K_D \approx 0.7$ and ≈ 3.2 nM, respectively) [336]. Pimozide has a higher selectivity for D2-like receptors [332]. Both of these antipsychotics have shown some efficacy in the treatment of chorea but side effects are common, and in the case of fluphenazine, low white blood cell levels limit its long-term use [337].

Clozapine and olanzapine belong to a group of atypical antipsychotics that show differential affinities for DA receptors. In fact, the affinity for the D_2 receptor is lower ($K_i = 157$ nM) than for the D_4 receptor ($K_i = 25$ nM). Clozapine also displays affinity for the D1-like receptor family [338]. Although the drug has shown some efficacy in reducing chorea [339], high doses were needed and the effect was seen only in antipsychotic naïve patients. No beneficial effect was reported for patients with a history of antipsychotic treatment. Clozapine also had several side effects, including drowsiness, fatigue, hypersalivation, dizziness and walking difficulties [340]. Olanzapine, which also has an affinity for serotonin receptors, induces less akathisia and no dystonia or dyskinesia compared to haloperidol [333, 341], and is helpful in treating chorea and gait disturbances [342, 343]. Using the unified HD rating scale (UHDRS), olanzapine improved scores for chorea, depression, anxiety, irritability and obsessive thinking, but none reached statistical significance [344]. Increasing the dose appeared to have helped, but side effects also increased, resulting in a high risk of dyslipidemia, hyperglycemia and weight gain [345].

DA agonists

Unlike DA antagonists, which have been used to treat chorea, DA agonists, including L-DOPA, have been used as a treatment option for the hypokinetic symptoms or bradykinesia of HD. Aripiprazole (Abilify®) displays a very complex pharmacological profile. It is a partial agonist of D2-like receptors, with higher affinity for D_2 and D_3 receptors ($K_i = 1.6$ and 5.4 nM, respectively) than D_4 receptors ($K_i = 514$ nM). Adding to the complexity, aripiprazole also displays high affinity for $5HT_{1A}$, $5HT_{2A}$, and $5HT_{2B}$ receptors with K_i values ranging from 0.4 to 8.7 nM [346]. Aripiprazole also has been found to bind to adrenergic and muscarinic receptors but with lower affinities [347]. In clinical practice, treatment with aripiprazole showed improvement in motor disturbances and reduction of depression with fewer sedative effects than TBZ [348, 349]. Bromocriptine, another potent agonist of D_2 receptors, was proposed as potential therapy for HD bradykinesia after the drug was shown to be effective in treating the bradykinesia in Parkinson's patients, but despite some success in tests of animal models, no efficacy was found in HD patients [350].

L-DOPA, a DA precursor and hallmark treatment for Parkinson's disease, has been found effective in treating gait disturbances and rigidity in HD, but L-DOPA-induced dyskinesia is a common side effect [351–353].

DA stabilizers

Two pharmacological properties play an important role in DA receptor operation: kinetic dissociation and intrinsic activity. DA receptors have dual intrinsic activity referred to as a high-affinity (^{high}) state or low-affinity (^{low}) state. The effect of DA greatly depends on this particular pharmacological property. For example, tonic firing of DA neurons would activate ^{low}-state affinity receptors, while burst firing would activate ^{high}-state affinity receptors [354]. The affinity of a compound for its receptors depends of the type of interaction between association and dissociation constants (K_{on} or K_{off}, respectively) [355]. This is an important characteristic because DA has a higher affinity for D1-like receptors than for D2-like receptors [355]. Evidence suggests, however, that D_2 receptors located pre-synaptically to modulate the release of transmitters are in a high-affinity state (D_2^{high}) and display slower K_{off}, while post-synaptic receptors are equally distributed between high and low affinity states [356]. Thus, it may be possible to use the affinity state of DA receptors to develop more effective treatments. For example, we recently proposed that D_3 receptor-selective compounds with bitropic activity may be effective antipsychotics with relatively few side effects [357, 358].

In this context, a novel class of compounds known as dopidines was found to be effective in differentially activating high or low state affinity receptors depending on DA concentration. Thus, these drugs became known as "DA stabilizers". Pridopidine, the representative compound in this class, binds with different affinities to D_2 receptors. It has a $K_i = 7521$ nM for D_2 receptors^{high} but a $K_i = 17550$ nM for D_2 receptors^{low}. In addition, pridopidine rapidly dissociates from the receptor (K_{off}) and binds primarily to activated D_2 receptors [356].

Pridopidine has been shown to modulate motor activity by a dual action, antagonizing D_2 receptors and modulating glutamate [359]. In HD, pridopidine has shown promising results, although some individual differences and side effects have been reported [360, 361]. In R6/2 mice, pridopidine improved motor behavior, showed anti-apoptotic effects, promoted release of brain-derived neurotrophic factor, a neuroprotectant, and reduced mHTT aggregates. In HD clinical trials, pridopidine has been reported to cause small improvements in global motor scores, hand movements, and gait balance, but side effects such as falls, chorea, dizziness, and nausea also have been reported [360, 361].

Surprisingly, however, the effects of pridopidine are likely to include an action at sigma-1 receptors [362]. Several studies have reported potential benefits of selective sigma-1 receptor compounds in neurodegenerative diseases and stroke [363–365]. In fact, we have reported a highly selective sigma-1 receptor compound ($K_i = 3.5$ nM) that is neuroprotective, increases brain-derived trophic factor, reverses cognitive impairments, and decreases the behavioral effects of a potent hallucinogen [363, 366, 367]. Further confirmation of the pharmacodynamics of this compound is needed but seems a promising new treatment. Perhaps an action at both D_2 and sigma-1 receptors could lead the way toward an effective treatment.

CONCLUSIONS

Corticostriatal dysfunction is an early contributor to the HD behavioral phenotype. Abnormalities in cortical glutamate input to striatal MSNs and interneurons disrupts the activity of the direct and indirect pathways, changing GABA transmission in the direct and indirect downstream pathways of the BG. DA, a key modulator of these pathways, also has a role to play in HD. Both D1- and D2-like receptor families have been implicated in the motor, cognitive, and psychiatric symptoms. Dysregulation of D_1 receptor signaling, moreover, has been linked to the aggregation of mHTT and abnormal modulation of NMDA receptor activity. In fact, the majority of treatments for HD target DA even though the precise DA dysfunction has yet to be identified. DA, like glutamate and GABA, is intricately involved in striatal processing of cortical information and its progression through downstream BG circuits. Improved understanding of the mechanisms by which DA participates in the corticostriatal dysfunction underlying HD can have far-reaching effects in the ongoing search for an effective treatment.

ACKNOWLEDGMENTS

Preparation of this review was supported by CHDI.

CONFLICT OF INTERESTS

The authors have no conflicts to declare.

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