REVIEW

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Dopamine and Glutamate in Huntington's Disease: A Balancing Act

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Huntington's disease (HD) is caused by a CAG repeat expansion in exon 1 of the HD gene resulting in a long polyglutamine tract in the N-terminus of the protein huntingtin. Patients carrying the mutation display chorea in early stages followed by akinesia and sometimes dystonia in late stages. Other major symptoms include depression, anxiety, irritability or aggressive behavior, and apathy. Although many neuronal systems are affected, dysfunction and subsequent neurodegeneration in the basal ganglia and cortex are the most apparent pathologies. In HD, the primary hypothesis has been that there is an initial overactivity of glutamate neurotransmission that produces excitotoxicity followed by a series of complex changes that are different in the striatum and in the cortex. This review will focus on evidence for alterations in dopamine (DA)–glutamate interactions in HD, concentrating on the striatum and cortex. The most recent evidence points to decreases in DA and glutamate neurotransmission as the HD phenotype develops. However, there is some evidence for increased DA and glutamate functions that could be responsible for some of the early HD phenotype. Significant evidence indicates that glutamate and dopamine neurotransmission is affected in HD, compromising the fine balance in which DA modulates glutamate-induced excitation in the basal ganglia and cortex. Restoring the balance between glutamate and dopamine could be helpful to treat HD symptoms.

Introduction

Huntington's disease (HD) is a neurodegenerative disorder caused by the mutation of a gene inducing expansion of the polyglutamine tract on the huntingtin (htt) protein [1]. Patients carrying the mutation display motor dysfunction, manifested as chorea in early stages, then as akinesia and sometimes dystonia in later stages. Other symptoms include depression, anxiety, irritability or aggressive behavior and apathy that typically precede the onset of motor abnormalities by many years and can be more devastating than movement disorders [2]. Brain MRIs indicate that abnormalities occur in the absence of overt motor signs in both cortical and subcortical regions and especially in the basal ganglia [3].

Although early studies stressed neuronal loss and degeneration, it remains unclear whether cell loss is "necessary" or if cell dysfunction alone or in combination with degeneration can lead to many of the symptoms in HD. We have proposed that a progressive disconnection between cortical and subcortical structures occurs as the disease becomes more severe [4]. This disconnection probably occurs because of abnormal neurotransmission due to imbalances among excitatory and inhibitory neurotransmitters like glutamate and gamma-amino butyric acid (GABA), in both cortex and subcortical structures. This disconnection is especially apparent between the prefrontal cortex (PFC) and the striatum, interrupting the flow of information arising from the cerebral cortex to the basal ganglia. We also proposed that many of the symptoms of HD are associated with alterations in dopamine (DA) function and DA modulation of excitation and inhibition in cortex and basal ganglia nuclei. In this review, we will summarize findings concerning

alterations in cortical and striatal glutamate and DA neurotransmission in HD, and in animal models of HD. We will show how these neurotransmitter systems interact and how their dysfunctions contribute to the progression of the disorder.

Animal Models of HD

Excitotoxic Lesions of the Striatum

Intrastriatal Injection of Glutamate Analogs

Testing the hypothesis that lesions of the striatum were responsible for HD, the first excitotoxic models examined the effects of intrastriatal injection of kainic acid in rats. These injections caused neurochemical, histological, and behavioral changes similar to those present in HD patients [5]. Lesions of the striatum can be induced by using other glutamate analogs like ibotenic acid, quisqualic acid, *N*-methyl-D-aspartate (NMDA), and quinolinic acid [6,7]. Use of quinolinic acid became a standard early excitotoxic HD model because this molecule was a powerful agonist of NMDA receptors [6] and led to the hypothesis that NMDA receptor function was abnormal in HD.

Alteration of Mitochondrial Function

The HD mutation alters mitochondrial function which in turn activates apoptotic pathways. The first mitochondrial HD models studied chronic blockade of succinate oxidation by systemic administration of the mitochondrial toxin 3-nitro-propionic acid (3NP). This model also replicated most of the clinical and pathophysiological hallmarks of HD, including spontaneous choreiform and dystonic movements, frontal-type cognitive deficits, and progressive striatal neuronal degeneration [8].

Genetic Models

Homozygotic knock-out (KO) of the mouse HD gene *HDh* is embryonically lethal in mice and mice heterozygous for *HDh* inactivation do not reproduce HD symptoms [9,10] suggesting that HD is not caused by a simple loss of function. Therefore, transgenic mice with glutamine expansion in the coding region of the HD gene were created. Other genetic models include knock-in and conditional models. Many reviews of the available HD mouse models have been published [11–13]. We therefore will provide only a short description of the mouse models referenced in this review. All transgenic mice with polyglutamine expansion in the HD gene present symptoms and neuropathology resembling the human condition, that change with the progression of the disease. However, depending on the length of repeats and/or on the length of htt, the progression of the neurological phenotype differs. For each model it is therefore important to determine behavioral and pathological changes corresponding to the early or late stages of the disease.

Transgenic Mouse Models

Studies in transgenic models have indicated that truncated portions of htt are more toxic than the full-length protein. The R6 transgenic lines contain exon 1 of the human HD gene that generates a short N-terminal fragment of htt [14]. R6/2 mice manifest a rapidly progressing form of HD while R6/1 mice display a more protracted time course. Onset ages of overt behavioral changes are approximately 4–5 weeks in R6/2 and 4–5 months in R6/1 mice. Reductions in brain weight are also present at 4–5 weeks, whereas decreased neostriatal volume and striatal neuron area, with a reduction in striatal and cortical neuron number, appear later, at 13 weeks in R6/2 mice [15,16]. The mice display progressive weight loss and R6/2 mice typically die between 12 and 16 weeks of age while R6/1 mice survive for a longer time. The movement disorder includes irregular gait, stereotypic grooming movements, tremor and both hindlimb and forelimb clasping. N171-82Q is another mouse model of HD with a N-terminal truncation of htt that also shows rapid and aggressive progression of the disease [17]. It has been suggested that R6/2 mice recapitulate the juvenile form of the disease, questioning its validity as a model of adult HD. However, there are numerous commonalities between juvenile and adult-onset HD that make the R6/2 a very reasonable model for both types.

HD46 mice and HD100 mice express an extended N-terminal one-third of htt with either 46 or 100 CAG repeats [18]. Both lines show neurological impairment and motor deficits starting between 3 and 10 months with severity increasing with age. In these mice striatal inclusions preceded the onset of the behavioral phenotype, whereas cortical changes, like the accumulation of htt in the nucleus and cytoplasm and the appearance of dysmorphic dendrites, predicted the onset and severity of the behavioral deficits.

Full-length models have used yeast (YAC) or bacterial artificial chromosomes (BAC). YAC mice with 72 or 128 CAG repeats show a biphasic motor phenotype with hyperactivity at 3 months followed by hypoactivity in the open field at 12 months [19]. Modest striatal atrophy occurs at 9 months with both striatal and cortical atrophy at 12 months and loss of striatal neurons along with a decrease in striatal neuron area is apparent at 12 months. This suggests that symptoms appear well before the loss of striatal or cortical neurons. The BACHD model

expresses full-length human mutant htt with 97 CAG repeats. BACHD mice exhibit progressive motor deficits and neuronal synaptic dysfunction at 6 months, followed by late-onset selective neuropathology at 12 months, which includes significant cortical and striatal atrophy and striatal dark neuron degeneration [20].

Knock-in Mouse Models

CAG knock-in lines express mutant htt with 50–150 glutamines under the endogenous mouse promoter in a manner comparable to the expression of mutant htt in HD patients [21]. Early abnormalities are mild, resembling the presymptomatic stages of the disease in which subtle motor anomalies occur. Knock-in mice with 94 and 140 CAG repeats display biphasic changes in motor behavior, characterized by increased motor activity at 2 months of age, followed by hypoactivity at 4 months [22,23]. A progressive gliosis and decreases in DARPP32 staining start at 12 months while a loss of striatal neurons is present at 2 years.

Glutamate and DA Pathways

Cortex

Prefrontal and motor cortices have important roles in motor and cognitive functions. Therefore, impairment of sensorimotor integration in motor areas would interfere with motor programs and contribute to the movement disorders in HD. The PFC receives major glutamatergic inputs from thalamic nuclei and a DA input from the ventral tegmental area (VTA) [24,25]. Pyramidal neurons in superficial cortical layers project collaterals to other pyramidal neurons, while deep layers pyramidal neurons project to subcortical structures like the dorsal striatum involved in motor control and cognition, as well as the nucleus accumbens involved in motivated and cognitive behaviors [26,27]. Thus, the corticostriatal pathway provides information used in motor planning and execution [28] as well in the control of cognition and motivation. Its disconnection, or abnormal input to the striatum and other subcortical pathways will have widespread effects.

Striatum

Afferent information to the striatum is filtered, integrated and transmitted to two target regions, the globus pallidus (GP) and the substantia nigra pars reticulata (SNr) via two primary output pathways originating from different subpopulations of medium-sized spiny neurons (MSNs). MSNs comprise over 90% of striatal cells in rodents. The remainder of striatal neurons are different classes of interneurons. The two primary striatal output pathways are termed the direct and indirect pathways because of their connections. Direct pathway MSNs project preferentially to SNr and to the internal GP (GPi), while indirect pathway MSNs project to the external GP (GPe) which connects to the subthalamic nucleus (STN). STN projects to GPi and SNr [29,30]. Direct and indirect pathway MSNs can be differentiated by the proteins they express. Direct pathway MSNs preferentially express DA D1-like receptors, substance P (SP) and dynorphin while indirect pathway MSNs preferentially express D2-like receptors and met-enkephalin [31]. MSNs receive three main inputs: glutamate inputs from the cortex and the thalamus, GABA inputs from striatal interneurons and to a lesser extent from other MSNs, and DA inputs from substantia nigra pars compacta (SNc). In addition, MSNs receive intrastriatal cholinergic inputs from the large cholinergic interneurons.

Interestingly, MSNs expressing enkephalin and projecting to the GPe forming the indirect pathway appear to be particularly vulnerable in HD and markers such as enkephalin are lost in postmortem brains of fully symptomatic patients, but also in early symptomatic and presymptomatic brains [32–34]. In contrast, MSNs expressing SP, projecting to the GPi are relatively spared, although the SP-containing projections to the SNr are more severely affected than the SP-containing projections to the GPi and SNc. These results are consistent with the hypothesis that chorea results from preferential dysfunction and ultimate loss of indirect pathway MSNs and possibly that akinesia and dystonia in HD is a consequence of the additional dysfunction and loss of direct pathway MSNs [35].

DA Inputs

DA is a major neuromodulator in the striatum as well as other neural areas and is involved in numerous functions, including motor activity, cognition, motivation, emotion, food intake, to name a few. The DA systems responsible for these functions have received much attention because their dysfunctions are involved in the etiology of numerous pathological conditions. Three major DA pathways innervate the forebrain and basal ganglia. The nigrostriatal DA pathway arises from the SNc and projects to the striatum. DA released from this pathway modulates activity of the direct and indirect striatal output pathways facilitating movement or inhibiting unwanted movement [36]. The mesocortical DA pathway arises from the VTA, projects to cingulate, entorhinal, and PFCs and plays a critical role in normal cognitive processes and neuropsychiatric pathologies [37]. The mesolimbic DA pathway arises from the VTA and projects to the limbic striatum

(nucleus accumbens) and olfactory tubercle [38]. The mesolimbic DA system is part of the reward circuit involved in addiction and depression [39].

Roles of DA and Glutamate

DA Exerts Opposite Actions on Glutamate Ionotropic Receptors

DA exerts its actions through activation of multiple receptors. D1 and D2 receptors were initially identified [40,41], followed by the D3 [42], the D4 [43], and the D5 [44] receptors. Based on their transduction mechanism and pharmacological properties, the five DA receptors are classified into D1-like, encompassing D1 and D5 receptors, and D2-like, encompassing D2, D3, and D4 receptors. In the striatum, DA modulates ionotropic glutamate receptors by altering glutamate currents and by modifying glutamate receptor surface localization. Postsynaptically, it is widely recognized that activation of D1-like receptors increases striatal NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) currents while activation of D2-like receptors decrease them [45]. Activation of D1 receptors increases NMDA and AMPA receptor function through different signaling pathways. Among them, cAMP formation, NMDA receptor subunit phosphorylation and activation of voltage-gated Ca^{2+} channels [46–52].

In the PFC, the D1 receptor family outnumbers the D2 family, and data show that signaling via the D1 receptor subtype plays a prominent role in modulating neuronal activity underlying working memory [53,54]. In the cortex, DAs effects on glutamate currents are contradictory. Our group and others found that D1 receptor family activation facilitates postsynaptic glutamate (AMPA and NMDA) currents while D2 receptor family activation decreases these currents in rodents and in human cortex [55–59]. In contrast, other groups reported that DA or activation of D1 receptors decreased non-NMDA excitatory postsynaptic currents [60,61]. However, glutamate release probability is also modulated by DA and D1 agonists [60,62] suggesting that DA could also modulate glutamate release through activation of presynaptic D1 receptors and this action could account for the contradictory findings.

DA Regulation of Glutamate and DA Release

The effects of DA on glutamate release are also contradictory, due to the complexity of the circuitry and the multiple neurotransmitters and modulators involved in controlling release. In the dorsal striatum, while D2 receptors are located on corticostriatal terminals and postsynaptically on MSN cell somata [63,64], D1 receptors are preferentially located postsynaptically on MSN cell somata. Therefore, DA can modulate glutamate release from corticostriatal terminals directly by activating D2 receptors [65,66]. In addition to DA's effect decreasing glutamate release through activation of D2 receptors on corticostriatal terminals, we and others also observed that DA can increase glutamate release through a combination of pre- and postsynaptic mechanisms [67,68]. Glutamate release by corticostriatal and thalamostriatal terminals is regulated by other receptors located on presynaptic glutamatergic terminals. The metabotropic glutamate (mGlu) receptors, $GABA_B$, serotonin, adenosine, endocannabinoids (CB1), and vanilloid (TRPV1) receptors can all modulate striatal glutamate transmission [69,70]. These receptors ultimately may become targets to alleviate abnormal glutamate transmission in HD (see section on therapy).

Striatal DA is released by nigrostriatal terminals onto MSNs, corticostriatal terminals, and interneurons. D2 receptors are located on nigrostriatal DA neurons and act as autoreceptors, decreasing DA release when activated [71]. Initial studies showed that neuroleptics (D2 family receptor antagonists) increase whereas apomorphine (a DA receptor agonist) decreases evoked release of DA [72]. DA release is also influenced by TRPV1 receptors located on nigrostriatal terminals [73].

In the cortex, less is known about DA regulation of glutamate and DA release. In contrast to the striatum, cortical glutamate terminals contain D1 receptors and studies examining activation of presynaptic D1 receptors have yielded contradictory outcomes [60,74]. Similar to the striatum, it is possible that DA regulation of glutamate release in the cortex depends on a combination of pre- and postsynaptic DA receptors as well as on other modulators. For example, recent studies report that cortical glutamate inputs are also modulated by CB1 via presynaptic CB1 receptors that decrease glutamate release when activated [75]. Cortical DA release is also modulated by presynaptic D2 receptors [76,77].

Glutamate in HD

Symptomatic HD

Studies of glutamate in humans with HD have revealed a variety of alterations. While some studies report selective reductions of NMDA and AMPA receptors in patients in both caudate and cortex [78,79], others found a non-significant loss of excitatory amino acid receptors in the caudate and no change in the cortex [80]. However, reduction of glutamate uptake was found in the PFC of HD patients, suggesting that impairment of glutamate uptake

may also contribute to neuronal dysfunction and degeneration in HD [81]. In this study, the level of synaptic and astrocytic markers were unchanged suggesting that the loss of glutamate transporters was not due to neurodegeneration. In animal models, mostly decreases of striatal glutamate receptors and release have been reported. Studies in symptomatic animals show decreases of striatal NMDA mRNA in 8–12 week R6/2 mice and decreases of AMPA receptors in 12-week R6/2 mice [82,83]. In these studies, there was a loss of cortical glutamate receptors that occurred later than in the striatum. Basal striatal glutamate levels were also reduced by 43% in R6/1 mice at 16 weeks [84]. Li et al. report that decreases in [^{3}H]glutamate release correlated with the increase in neuropil aggregates [85]. They observed that axons containing mutant htt aggregates had fewer synaptic vesicles and proposed that mutant htt binds tightly to synaptic vesicle membranes, inhibiting uptake and release of glutamate.

Presymptomatic HD

In contrast to studies reporting decreased striatal glutamate currents, we found that AMPA and NMDA currents were increased in presymptomatic R6/2, HD100, and YAC128 mice. These increases might have been overlooked because only subpopulation of cells demonstrated larger glutamate currents [86–88]. In addition, increases were transient, observed only in early stages while in later stages, NMDA and AMPA currents were reduced. Glutamate vulnerability also might depend on the receptor subunit composition. Expression of mutant htt has been shown to enhance currents and excitotoxicity mediated by predominantly NR2B-type NMDA receptors suggesting that interaction between NR2B and mutant htt may contribute to selective neuronal dysfunction and degeneration [89]. Interestingly, endogenous quinolinic acid levels were elevated in the cortex and striatum of several mouse models showing neurodegeneration and motor and cognitive dysfunction, supporting the hypothesis that glutamate analogs play a role in neuropathology in HD [90]. Another study has shown decreased mRNA levels of the astroglial glutamate transporter in the striatum and cortex of R6 mice, accompanied by a concomitant decrease in glutamate uptake that could lead to neuronal damage [91]. In addition to increased glutamate receptors in presymptomatic animals, we found that glutamate neurotransmission was specifically increased in MSNs of the direct pathway in 50-day old YAC128 [92]. Overactivation of direct pathway MSNs could lead to excessive inhibition of GPi and SNr neurons, to disinhibition of the thalamus and to abnormal movement [93]. In contrast, excessive glutamate could result in dysfunction and degeneration of the more vulnerable enkephalin-containing MSNs forming the indirect pathway, which would disinhibit GPe, inhibit the STN and GPi and also induce abnormal movements (Figure 1). In support of this hypothesis, increased firing rate in GPe and decreased firing rates in GPi were found in an HD patient [94]. These findings may explain why deep brain stimulation of the GPi can improve abnormal movements in some HD patients [95–97].

Cortical Glutamate Changes

In contrast to the striatum, cortical NMDA and AMPA receptor-induced currents were decreased in presymptomatic R6/2 mice and were unchanged in symptomatic R6/2 mice compared to controls [82,98]. Decreased postsynaptic glutamate currents in pyramidal neurons could account for decreased vulnerability in cortical structures compared to the striatum. However, in symptomatic R6/2, YAC128 and CAG140 knock-in mice, glutamate synaptic neurotransmission was increased and pyramidal neurons showed signs of hyperexcitability [99] suggesting that glutamate inputs are increased in cortex in models of HD while striatal glutamate inputs appear to be decreased [100]. The differential changes in glutamate currents observed in the striatum and cortex suggest that alterations induced by mutant htt are not solely cell dependent, but also depend on more complex interactions such as cell type, inputs and circuitry.

DA Receptors and DA Release in HD—Correlation with Neuropathology

Too Much or Too Little DA?

In patients with HD, the guiding hypothesis is that presynaptic activation of the nigrostriatal DA pathway induces chorea while loss of DA inputs induces akinesia [101,102]. While there is no indication of an absolute increase in DA activity in chorea, relative overactivity in the nigrostriatal system might arise from a deficiency in GABA which normally inhibits DA release by activating GABA receptors on nigrostriatal cell somata and terminals [103,104]. It is possible that an initial increase of DA release or abnormal extracellular levels of DA (along with elevated extracellular glutamate levels) induces excitotoxicity, loss of cortical and striatal neurons, and loss of DA terminals that could then lead to later symptoms such as akinesia or dystonia (Figure 1). However, it is not clear that DA levels are elevated in HD and bradykinesia (probably caused by low levels of DA in basal ganglia) is also observed in patients with chorea. In addition, some HD patients show dyskinesia that appears similar to

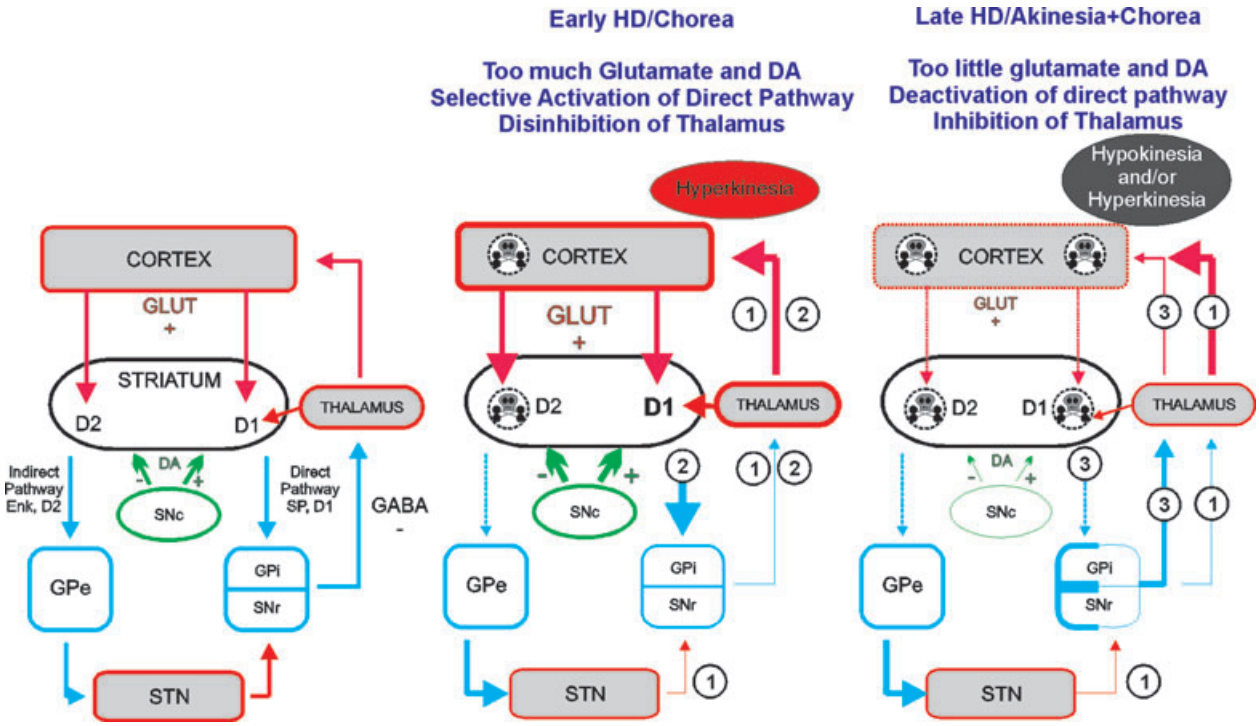

Figure 1 Glutamate and DA in basal ganglia function in intact brain and during HD. Left is a simplified schematic showing normal basal ganglia circuitry. Glutamate inputs are represented in red, GABA in blue and DA in green. Under normal conditions (left), the thalamus is inhibited by GPi and SNr GABA projections. In early HD (middle), cortical dysfunction induces excessive glutamate release in the striatum. Abnormally elevated striatal glutamate and DA levels trigger selective dysfunction of enkephalin-containing MSNs. Imbalance between the direct and indirect pathways induces hyperkinesia via two pathways: (1) Selective dysfunction/degeneration (dashed lines) of enkephalin-containing MSNs leads to decreased release of GABA in the GPe and to its disinhibition. In turn, overactivation of GABA neurons of the GPe leads to increased release of GABA and to inhibition of STN which decreases glutamate release and decreases activity of the GPi and SNr. (2) Overactivation of the direct pathway MSNs (by abnormal DA modulation and/or excessive glutamate) leads to increased release of GABA and to inhibition of GPi and SNr. Together, alterations in direct and indirect pathways in early HD induce inhibition of GPi and SNr GABA neurons and to a decreased release of GABA in their output structure, the thalamus. Disinhibition of the thalamus is responsible for abnormal movements. In late HD (right), corticostriatal and nigrostriatal inputs progressively degenerate, leading to decreased striatal glutamate and DA release. Low striatal glutamate and DA levels trigger dysfunction of both direct and indirect pathway MSNs. Imbalance between the direct and indirect pathways induces hyperkinesia and hypokinesia via two pathways: (1) Alterations in the indirect pathway are similar to early HD and lead to hyperkinetic movements. (3) Dysfunction/degeneration of direct pathway MSNs induces decreased release of GABA and disinhibition of GPi and SNr. Increased activity in GPi and SNr leads to inhibition of the thalamus and hypokinesia. Depending on the stage of dysfunction of direct and indirect pathway MSNs, activity in the basal ganglia could result in hypokinesia or hyperkinesia and would explain why some symptomatic patients display both chorea and akinesia. Enk = enkephalin; GLUT = glutamate; GPe = external segment of the globus pallidus; GPi = internal segment of the globus pallidus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus.

L-DOPA induced dyskinesia in Parkinson's disease patients (a result of too much DA or overactivation of DA receptors). Initial studies found that DA levels and activity of TH, the biosynthetic enzyme for DA were increased in the striatum of postmortem HD brains [102]. Also, binding for the presynaptic DA transporter was reduced in the caudate of HD patients [105,106]. Although this could be interpreted as a loss of nigrostriatal terminals, another interpretation is that nigrostriatal DA transmission is altered, leading to choreatic movements (Figure 1) [101]. The neurochemical basis for this suggestion is based on the observations that antagonists of DA receptors and DA-depleting agents reduce chorea, and that L-DOPA exacerbates chorea in HD.

More recent imaging studies provide evidence supporting reduced DA function in HD patients. In presymptomatic and symptomatic patients, positron emission tomography for D1 and D2 ligands found that both striatal D1 and D2 receptor levels were reduced by 45–50% and that the loss progressed by 3–5% per year [107,108]. Decreases in DA receptors also correlated with the duration of the disease, and with a decrease of

GABA content, reflecting a loss neurons in the putamen [106].

Animal Studies

In contrast to human studies, in most animal models of HD, striatal DA receptors, DA release, and nigrostriatal terminals are reduced. The R6/2 mouse model displays decreases in D1 and D2 receptor binding at 6 weeks [14,82]. Functionally, D1-dependent modulation of AMPA currents was decreased in R6/2 mice at 6 weeks [109]. D1 receptor-dependent striatal long-term potentiation was also decreased in R6/2 mice compared to WT littermates [110]. Microdialysis studies showed that DA release was progressively reduced in R6/2 mice between 6 and 14 weeks [111,112]. In the 3NP model of HD, striatal DA content was unchanged but evoked DA release was decreased [113]. Although DA receptor density was unchanged in 12-month old YAC128 mice [114], this may represent a compensatory mechanism for decreased dopamine availability because the number of striatal neurons is reduced by 15% in this age group [19]. Our studies showed that in young YAC128 mice (1 month), D2 receptors are functional, but become much less effective at 12 months [115]. Interestingly, YAC128 mice exhibit initial hyperactivity, followed by the onset of a motor deficit and finally hypokinesis correlated with striatal neuronal loss [19]. In other models where lesions are more likely to be confined to the striatum, such as the quinolinic acid model, and the 3NP model, hyperkinesia occurred [116,117]. It becomes important to determine loss of DA function relative to the general neuropathology in order to understand the role of DA in HD.

Glutamate, DA, and Glutamate-DA Excitotoxicity

The excitotoxicity hypothesis of HD suggests that neurodegeneration in the striatum is caused by an excess of excitatory neurotransmitters such as glutamate or by overactivation of glutamate receptors, more probably the NMDA receptor. As pointed out earlier, this hypothesis was based on the observation that intrastriatal injections of glutamate receptor agonists induce neuronal loss and reproduce the symptoms similar to those seen in HD [6,118]. *In vitro*, striatal and cortical neurons of HD mutant mice are more susceptible to NMDA-induced cell death than control mice [86]. In mutant htt-expressing neurons, elevated glutamate toxicity can be induced through elevation of intracellular Ca^{2+} concentrations and through proteolysis of caspases involved in apoptotic cascades [119–121].

High doses of DA also are able to directly induce cell death of striatal neurons *in vitro* [122,123]. *In vivo*, striatal injection of DA induces loss of tyrosine hydroxylase (TH) immunoreactivity, a marker for DA terminals [124]. Increased DA release by methamphetamine has also been shown to be neurotoxic to nigrostriatal and mesolimbic projections [125]. DA can induce cell death through several mechanisms. The molecule itself, via receptor-dependent mechanisms binds to D1 (or D2) receptors, which increases (or decreases) intracellular Ca^{2+} and activates (or inactivates) cascades leading to cell death [126]. DA also generates toxic metabolites via products of its metabolism or via autoxidation. Possible mechanisms include the generation of radical oxygen species and interactions with excitatory amino acids [127]. Another possibility is that DA plays a role in preferential vulnerability through interactions with mitochondria. Primary cultures of striatal neurons expressing mutant htt are vulnerable to DA, and this is correlated with a reduction in the level of complex II activity [128]. Interestingly, the same study found that the DA-induced down-regulation of complex II was mediated by D2 receptors. However, several lines of evidence suggest that DA toxicity is induced in part by activation of D1 receptors. D1 antagonists can limit cell death in cortical and striatal neuronal primary cultures incubated with DA [123]. In HD, NMDA receptors specifically potentiate the vulnerability of mutant htt cells (STHdh^{Q111}) to DA toxicity as pretreatment with NMDA increased D1R-induced cell death in mutant but not wild-type cells [129].

Thus, abnormal DA/glutamate interactions could explain why the striatum and cortex are vulnerable in HD. Tang et al. showed that in primary MSN cultures from WT and YAC128 mice, DA in the presence of glutamate induced apoptosis in YAC128 cells and this effect was produced via glutamate-induced Ca^{2+} signaling [130]. *In vivo*, they showed that MSN loss in 11-month old YAC128 mice was increased by administration of L-DOPA and reversed by tetrabenazine (TBZ), a monoamine depleting agent. Therefore, modifying glutamate or DA release modifies HD neuropathology. In agreement, hyperdopaminergia induced by knocking out the DA transporter (DAT) exacerbated mutant htt aggregates in the striatum and cortex of *Hdh*Q92/Q92 mice as well as potentiating the emergence of behavioral symptoms [131]. In contrast, decreasing striatal DA or glutamate content by SN lesions or by decortication improved the neuropathology and behavioral performance in R6/2 mice [132].

Although the main interest of this review is about glutamate and DA, it is important to keep in mind that GABA is also a key player in the striatum and the cortex. There are important changes in the GABA system that are likely

to play a role in the occurrence of symptoms and progression of HD. It has long been known that GABA content is decreased in the striatum of HD patients [102], due to the loss of MSNs. However, a recent study reported that $GABA_A$ and $GABA_B$ receptors are increased in output nuclei at all stages of the disease in HD patients, suggesting compensatory mechanisms to the loss of GABA terminals [133]. Our studies in animal models showing that striatal GABA currents are increased in HD also suggest compensatory mechanisms of the GABA system [134] that might be targeted for potential therapies.

Therapies

With the discovery of the gene in 1993 [1] and the ability to genetically test individuals at risk, various neuroprotective strategies designed to delay the progression of the disease have been examined. Drugs targeting glutamate and DA systems include typical and atypical neuroleptics, DA depleters, antidepressants, and antiglutamatergic drugs (for reviews, see [135–137]).

Targeting the DA System

TBZ causes depletion of brain DA, norepinephrine, and serotonin by binding to the presynaptic vesicular monoamine transporter, VMAT2. TBZ is the only FDA drug approved for treatment in HD and improves motor function in patients and in animals [130,138,139]. However, it can also produce side effects including depression and sleepiness in some patients, and has no effect on other items (total functional capacity, independence and behavioral scales, swallowing, speech and gait items of motor scale) of the Unified Huntington's Disease Rating Scale (UHDRS) (for review, see [137]). Beside its effect on striatal DA content, TBZ also has an effect on other monoamines [140] that could explain some of its side effects on cognition and depression. Although the trials assessing other anti-dopaminergic agents targeting D2 (sulpiride, D2 receptor antagonist) and D4 receptors (clozapine, D4 receptor antagonist) were smaller, they report those two agents either had no effect, or improved chorea severity, but had too many adverse effects [141].

Since blocking DA release induces major side effects and may exacerbate psychiatric symptoms, more specific DA blockers have been investigated. Charvin et al. showed that early pharmacological blockade of D2 receptors by haloperidol attenuated aggregate formation and the loss of DARPP-32 in a lentivirus-based HD rat model, reinforcing the potential role of D2 antagonists in neuroprotection in HD [142]. Typical neuroleptics or typical antipsychotics also used in schizophrenia have a high affinity for D2 DA receptors and are used for the treatment of psychotic symptoms as well as chorea in HD. However, their potential side-effects include parkinsonism, dystonias, tardive dyskinesia, and worsening of cognitive and affective symptoms, which can sometimes limit their therapeutic use. Haloperidol, tiapride, and sulpiride were generally well tolerated at low doses, but did not always reduce involuntary movements [135]. Clozapine is one of the only antipsychotics evaluated in clinical trials, and several studies show that the occurrence of adverse effects prevented an increase to a dose that might have produced a more potent antichoreic effect [143,144]. Other antipsychotics like olanzapine, risperidone, and ziprasidone were reported to improve some motor and psychiatric symptoms in HD.

Targeting the Glutamate System

Antiglutamatergic Drugs

Antiglutamatergic drugs (receptor antagonists or release blockers), such as amantadine, remacemide, riluzole, and ketamine have been tested in clinical trials. Although some of these drugs improved chorea and motor scores, most also had adverse effects. Amantadine proved to have beneficial effects on the choreic dyskinesias in some patients [145,146]. Contrasting results were found in other trials that reported no improvement in the UHDRS chorea scores [147] suggesting that amantadine may not be a potent antichorea medication at a dose of less than 400 mg/day [135]. Remacemide, a nonselective NMDA receptor antagonist, showed a trend toward improvement in chorea but did not impact functional decline and induced adverse effects such as psychiatric disturbances, gastrointestinal upset, and dizziness [148,149]. Riluzole, an inhibitor of glutamate release had no significant effect on chorea, behavioral, cognitive, independence, and functional scores in a 3-year study in Europe [150]. The NMDA blocker ketamine induced deteriorations in the total motor score and eye movements measured by the UHDRS [137].

Ampakines

Ampakines are benzamide drugs that increase excitatory transmission in the forebrain via allosteric modulation of AMPA-type glutamate receptors [151]. There is evidence that *in vivo*, ampakine treatment reduces neuronal death in animal models of Parkinson's disease and reduces excitotoxic brain damage [152,153]. In the CAG140 model of HD, the ampakine CX929 rescued long-term potentiation and reduced learning dysfunction in 8 and 16-week old animals, while having no effect on

locomotor activity [154] suggesting that, given that ampakines are well tolerated in clinical trials and are effective in this study after brief exposures, they could be used as a novel strategy for chronic treatment of the cognitive difficulties in the early stages of HD. One of the mechanisms by which ampakines might exert its neuroprotective effect is through the increase of brain derived neurotrophic factor that modulates MSN activity and has been shown to provide neuroprotection [155,156].

Targeting Glutamate Release

Cannabinoids

Cannabinoid receptors CB1 modulate neurotransmitter release in virtually all brain regions [157,158]. Cannabinoid ligands and receptors are particularly abundant in basal ganglia structures (especially nuclei that receive striatal efferents, like the GPi, GPe, and SNr) compared with other brain regions [159,160]. The cannabinoid system plays a prominent role in basal ganglia function by modulating release of neurotransmitters that operate in the basal ganglia circuits [161,162]. In addition, cannabinoids that activate CB1 receptors have an important influence on motor responses [163]. Activation of CB1 receptors decrease locomotion while antagonizing CB1 receptors causes hyperlocomotion [164,165]. CB1 also bind to TRPV1 receptors located on DA terminals and can reduce hyperdopaminergia-related hyperactivity [166]. CB1 may potentially be useful to reduce the effects of neurodegeneration [167]. They were shown to protect neurons via CB1 receptor-mediated inhibition of glutamate exocytosis, closing of voltage sensitive calcium channels, and reducing antioxidant activity [168,169]. Therefore, cannabinoid-based treatment might be beneficial in basal ganglia disorders [170]. Although cannabinoid receptors are decreased in HD, CB1 could still have beneficial effects by decreasing glutamate release without inducing deleterious NMDA antagonist side effects. AM404, an inhibitor of the endocannabinoid reuptake process has been shown to reduce hyperlocomotion in an animal model of HD via activation of TRPV1 receptors [171]. Earlier studies reported no beneficial effect of cannabidiol in HD [172,173]. However, much has to be discovered about endocannabinoid ligands and receptors, in both healthy and pathological conditions to determine the potential therapeutic benefits of targeting this system in HD or other basal ganglia disorders. Another potentially beneficial effect of CB1 could take place through activation of CB2 receptors present on microglia which would in turn decrease microglia activation. Indeed, activation of CB2 receptors has been demonstrated to decrease neuroinflammation and motor symptoms in R6/2 mice [174].

Adenosine

Indirect pathway MSNs selectively express high levels of the neuromodulator adenosine A_{2A} subytpe of receptor [175]. A_{2A} receptors activate the cAMP/PKA pathway as opposed to D2 receptors, which inhibit adenylyl cyclase and decrease cAMP [176]. Another consequence of A_{2A} receptor activation is an increase in glutamate release via activation of A_{2A} receptors located on presynaptic glutamate terminals [177]. Therefore, high concentrations of adenosine and overactivation of A_{2A} receptors could lead to toxicity [178,179]. A transient increase in A_{2A} receptor density has been reported in presymptomatic (1–2 weeks) R6/2 mice while large reductions were found in later stages [180,181], suggesting adenosine could indeed exacerbate excitotoxicity in early stages of HD.

It has been proposed that A_{2A} receptor agonists could have beneficial effects in late HD, when A_{2A} receptors are downregulated. One study found that A_{2A} receptor agonists significantly attenuated the progressive deterioration of motor coordination and reduced brain atrophy [180]. However, another study showed that despite the neuroprotective effect on NMDA-induced toxicity in symptomatic R6/2 mice, treatment with an A_{2A} receptor agonist did not rescue the deficit in motor coordination and even worsened the performance of R6/2 mice [182]. It is possible that the motor effects of A_{2A} receptor agonists depend on mechanisms independent from those involved in neuroprotection. Several lines of evidence suggest that blocking presynaptic A_{2A} receptors can be beneficial because it decreases excitotoxicity while the blockade of the postsynaptic receptors can be deleterious [183]. Finally, since in HD brains, a dramatic loss of A_{2A} receptor binding was observed in grade 0 cases (34–35% of controls) and more advanced cases showed no detectable A_{2A} receptor binding [184], it remains unknown whether therapy targeting A_{2A} receptors will be beneficial in HD patients.

Conclusions

It is now clear that neuronal dysfunction occurs in both striatum and cortex well before a clinical diagnosis of HD is made. Because the cortex and striatum are interconnected, it is difficult to determine if cortical changes precede or follow striatal changes. However, the fact that HD patients experience cognitive and emotional disturbances before the occurrence of sensorimotor symptoms provides evidence that cortical dysfunction might precede striatal pathology. Activation of both D1 and D2

receptors can lead to toxic changes in cortical and striatal neurons as well as their terminals. It is therefore probable that diverse and complex interactions among glutamate and DA neurotransmission will contribute to the selective dysfunction of neurons in the cortex and basal ganglia. Subsequent and progressive dysfunction and degeneration are likely to be responsible for the complex and heterogeneous clinical phenotype in HD. The complexity of mutant htt-induced alterations throughout these systems renders the development of therapies difficult, and disease-modifying therapies preventing the onset of clinical symptoms in individuals at risk are still not available. While existing antidopaminergic or antiglutamatergic drugs seem to have a positive effect on motor symptoms, their use can be limited due to the side-effects they trigger. Therefore, it will be necessary to develop more specific drugs with selective targets. Other glutamate and DA release modulators such as adenosine or CB1 could have potential therapeutic benefits in HD.

Conflict of Interest

The authors have no conflict of interest.

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