

Review

# Striatal Vulnerability in Huntington's Disease: Neuroprotection Versus Neurotoxicity

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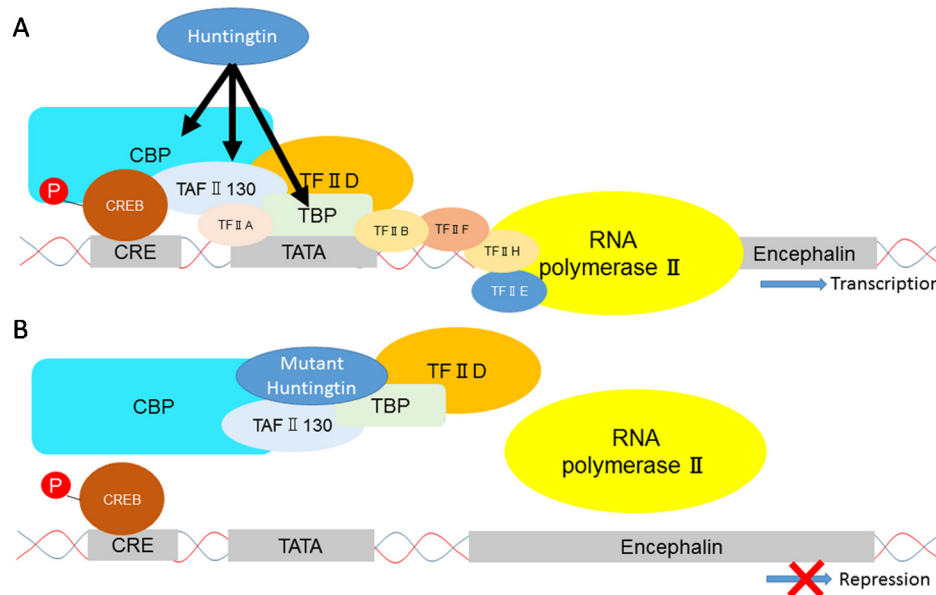
**Abstract:** Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by the expansion of a CAG trinucleotide repeat encoding an abnormally long polyglutamine tract (PolyQ) in the huntingtin (Htt) protein. In HD, striking neuropathological changes occur in the striatum, including loss of medium spiny neurons and parvalbumin-expressing interneurons accompanied by neurodegeneration of the striosome and matrix compartments, leading to progressive impairment of reasoning, walking and speaking abilities. The precise cause of striatal pathology in HD is still unknown; however, accumulating clinical and experimental evidence suggests multiple plausible pathophysiological mechanisms underlying striatal neurodegeneration in HD. Here, we review and discuss the characteristic neurodegenerative patterns observed in the striatum of HD patients and consider the role of various huntingtin-related and striatum-enriched proteins in neurotoxicity and neuroprotection.

**Keywords:** Huntington's disease; huntingtin; striatum; medium spiny neuron; pathophysiology; striosome; matrix

## 1. Introduction

Huntington's disease (HD) is an autosomal dominantly inherited neurodegenerative disorder characterized by the late onset of gradually worsening motor, cognitive, and psychiatric disturbances [1]. At present, HD is largely untreatable and the mean survival time of individuals with HD is 17–20 years after symptom onset [2]. In HD, a mutation of the protein huntingtin (Htt), which involves the expansion of a cytosine-adenine-guanine (CAG) repeat encoding an extended glutamine tract (PolyQ), causes transcriptional dysregulation (Figure 1) resulting in multiple cellular dysfunctions such as intracellular signaling pathway alterations, protein trafficking defects, synaptic transmission impairments, proteasome dysfunction, and mitochondrial alterations [3–5]. Htt is highly conserved among vertebrates and is expressed ubiquitously in the human body [6]. Its highest levels are found in the brain, where it is expressed in all neurons and glial cells [3]. Despite the ubiquitous expression of mutant Htt (mHtt) throughout the brain, human pathology has shown that degeneration is specific to certain neuronal subpopulations affecting the striatum and, to a lesser extent, the cerebral cortex in patients with HD [4]. In the striatum, a differential involvement of striosome and matrix compartments has been reported in HD [5–12]. Moreover, ongoing neurodegeneration is preferentially found in medium spiny neurons (MSNs) and parvalbumin-expressing interneurons in the striatum [13–18]. These findings indicate that striatal cell type- and compartment-specific vulnerabilities may underlie the etiology

of striatal pathology in HD [19]. Here, we discuss striatal cell type- and compartment-specific degeneration in HD as well as neuroprotection and neurotoxicity associated with Htt-related and striatum-enriched proteins.



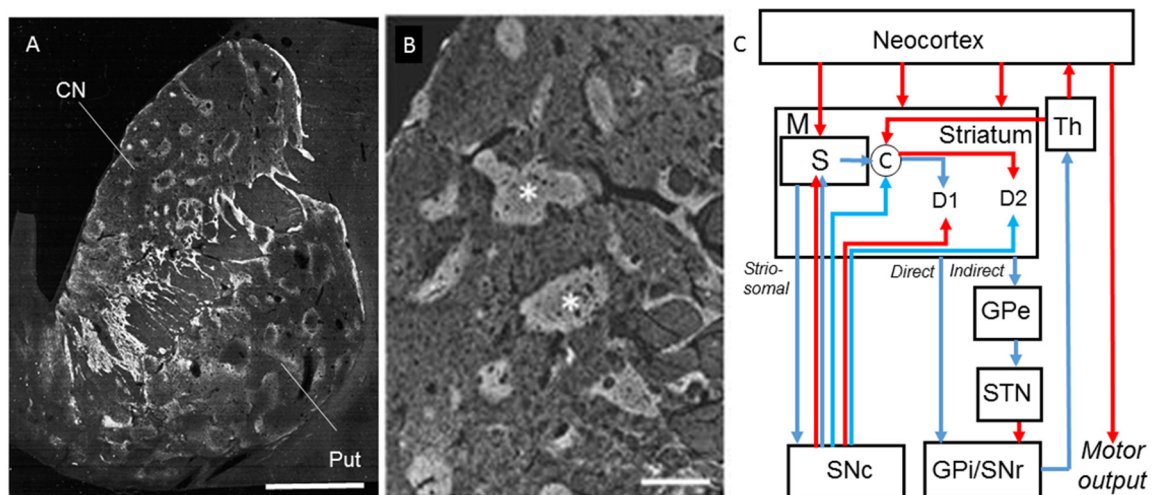
**Figure 1.** An example of transcriptional dysregulation by mutant Huntingtin protein. (A) Wild-type Huntingtin interacts with CREB-binding protein (CBP) and possibly with TATA box binding protein associated factor (TAF) II 130 and/or TATA box binding protein (TBP). Huntingtin promotes transcription of enkephalin; (B) Mutant Huntingtin binds CBP, TAF II 130 and TBP and prevents these transcription factors from recruitment. P: phosphorylation, TF: transcription factor, CRE: cAMP response element, CREB: cAMP response element-binding protein.

## 2. Striatal Anatomy

In HD, the striatum has been identified as the primarily affected structure, which undergoes severe degeneration. As a core structure of basal ganglia circuits, the striatum integrates midbrain dopaminergic inputs and neocortical and thalamic glutamatergic inputs, and then sends GABAergic outputs to its target nuclei, such as the globus pallidus and substantia nigra. The striatum plays a critical role in processing information related to motor function and reward- and goal-oriented behavior. To facilitate the understanding of HD neuropathology, we briefly review normal striatal anatomy (Figure 2).

### 2.1. Fundamental Structure

Respectively, MSNs (10–24  $\mu\text{m}$  in diameter) and medium aspiny interneurons represent approximately 90% and 10% of striatal neurons in rodents, and approximately 75% and 25% of striatal neurons in primates [20,21]. The four GABAergic interneuron subtypes found within the striatum express (1) parvalbumin; (2) calretinin; (3) coexpressing nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase, nitric oxide synthase (NOS), neuropeptide Y (NPY) and somatostatin; and (4) tyrosine hydroxylase (TH) expressing interneurons [20–24]. Parvalbumin-positive interneurons (i.e., “fast-firing interneurons”) can block or delay the firing of more than 100 MSNs [22,25]. NOS-containing interneurons (i.e., “low-threshold spike interneurons”) release nitric oxide (NO) via dopamine  $D_1/D_5$  receptor ( $D_1R/D_5R$ ) activation and influence the induction of long-term depression (LTD) via the cyclic guanosine monophosphate (cGMP) pathway [26]. Large aspiny cholinergic interneurons (21–45  $\mu\text{m}$  in diameter) represent 1%–2% of the total cell population in the human striatum [27]. The cholinergic interneurons play a role in the spatiotemporal selection of convergent inputs to striatal MSNs [28].



**Figure 2.** Striatal structural anatomy and functional circuitry model. (A) A human striatum section immunostained with anti-Met-enkephalin antibody. (From Goto et al. (2015) with permission) [29]; (B) Low-power-magnified microscopic negative image of the caudate nucleus. Asterisks indicate striosomes (From Goto et al. (2015) with permission) [29]; (C) Striatum plays a central role of multiple feedback and feedforward regulations in motor processing. Connectivity diagram showing excitatory pathways as red and inhibitory pathways as blue. Scale bars: (A) 4 mm; (B) 1 mm. CN, caudate nucleus; Put, putamen; S, striosomes; M, matrix; C, Cholinergic interneurons; D<sub>1</sub>, medium spiny projection neurons expressing dopamine D<sub>1</sub> receptors; D<sub>2</sub>, medium spiny projection neurons expressing dopamine D<sub>2</sub> receptors; SNc, substantia nigra compacta; GPi, globus pallidus internus; SNr, substantia nigra reticulata; STN, subthalamic nucleus; GPe, glubus pallidum externus; Th, thalamus.

Striatal MSNs send inhibitory GABAergic efferents to their target brain regions. Approximately half of MSNs project via the “direct pathway” to neurons within the internal globus pallidus (GPi; i.e., the entopeduncular nucleus in some species) and substantia nigra pars reticulata (SNr) [30]. The rest of the MSNs project via the “indirect pathway” to neurons within the external globus pallidus (GPe) [30]. Direct pathway MSNs express the D<sub>1</sub>R subtype and muscarinic M<sub>4</sub> receptors and contain the neurotransmitters dynorphin and substance P. Indirect pathway MSNs express the dopamine D<sub>2</sub> receptor (D<sub>2</sub>R) subtype and adenosine A<sub>2A</sub> receptors (A<sub>2A</sub>R) and contain enkephalin [31,32]. Activation of D<sub>1</sub>R or A<sub>2A</sub>R increases cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling, whereas activation of D<sub>2</sub>R decreases it. Phosphodiesterase 10A (PDE10A) inhibitors decrease cAMP/PKA signaling in direct and indirect pathway MSNs [33,34]. The direct and indirect pathways converge at the GPi/SNr complex, which then transmits its GABAergic outputs to the thalamocortical pathway and brainstem locomotor region, including the pedunculopontine nucleus (PPN) [30]. MSNs receive excitatory glutamatergic inputs originating from the neocortex (i.e., layers III and V) and thalamus (i.e., mainly from the intralaminar thalamic nuclei). MSNs possess 10,000–15,000 spines; however, corticostriatal terminals form a small number of synapses with individual MSNs. This indicates that a massive convergence of cortical inputs may occur at this level [22,35]. Synaptic convergence may also apply to thalamic inputs since the number of thalamostriatal and corticostriatal synapses within the striatum is of a similar magnitude [35]. Striatal GABAergic interneurons receive cortical and thalamic excitatory inputs and provide strong feedforward inhibition (i.e., inhibitory postsynaptic potentials (IPSPs)) to the proximal dendrites of MSNs [22,36]. This feedforward inhibition is more powerful than the reciprocal feedback inhibition produced by MSN axons [28].

## 2.2. Striatal Compartments

The striatum encompasses a three-dimensional labyrinthine structure composed of striosome and matrix compartments [37–39]. Across mammalian species, striosomes occupy 10%–20% of the

striatum [40–42]. Striosomes are organized early in embryonic development and receive developmental cues from dopaminergic inputs originating in substantia nigra pars compacta (SNc) [43–45]. The striosomal and matrix compartments have MSNs containing D<sub>1</sub>R and D<sub>2</sub>R subtypes. In primates, D<sub>1</sub>R are predominantly localized in striosomes, whereas D<sub>2</sub>R are localized in the matrix [38,46]. Striosomal MSNs project to the ventral tier of the SNc or its immediate environs [47–49]. Striosomal MSNs also innervate the habenula, which projects to SNc dopaminergic neurons [50–54]. Reciprocal striosome-SNc innervation strongly regulates nigral dopaminergic neurons, thereby maintaining critical control over dopaminergic actions within the striatum [38,55]. Different cortical regions innervate the striosome and matrix compartments. The prelimbic, infralimbic, caudal orbitofrontal, and pregenual anterior cingulate cortices innervate striosomes, whereas sensorimotor cortices innervate the matrix [56–63]. These input fibers as well as striatal MSN dendrites and axons mostly remain within each compartment [64,65]. Large cholinergic interneuron cell bodies are located in the matrix at the edge of the striosome-matrix boundary [66–71]. The dendrites of cholinergic interneurons spread to both compartments, whereas their axons are densely distributed within the matrix. Cholinergic interneurons are thought to mediate inter-compartmental information processing [66,67,70–72]. Neurons of the centromedian-parafascicular thalamic nuclei innervate and modulate striatal cholinergic interneurons [73].

It is known that reward-related, limbic-based circuits and sensorimotor and associative circuits are concentrated in the striosome and matrix compartments, respectively [70]. However, differential activity in the striosomes possibly produces distinct reinforcement-related signals, which give rise to repetitive behaviors [74,75]. Moreover, the existence of a direct, reciprocal circuit between striosomes and dopamine-containing SNc neurons suggests that striosomes affect dopamine release within the matrix through a negative feedback mechanism [19,76–79]. An anatomically- and physiologically-based computational model of reinforcement learning revealed that the striosomes and matrix are responsible for motor focusing and scaling, respectively [72].

Striosomal MSNs receive cortical input from the infralimbic cortex, which evaluates and controls ongoing behaviors [80]. This evaluation cortex sends signals related to responsibility of selected modules to striosomes. Positive or negative responsible signals are conveyed from striosome into matrix via cholinergic or, possibly, palvalbumine interneurons [72]. Striosomal MSNs of the striatonigral pathway release substance P, which depolarizes cholinergic interneurons and induces acetylcholine release. The released acetylcholine excites matrix interneurons via nicotine receptors and inhibits matrix MSNs. Striosomal MSNs of the striatofugal pathway release enkephalin, which either directly or via  $\mu$ -opioid receptors (MORs) activation, hyperpolarizes cholinergic interneurons in the matrix. Thus, activation of striosomal MSNs results in the inhibition of acetylcholine release and subsequent disinhibition of matrix MSNs [70,81]. Cholinergic interneurons are called tonically active neurons (TANs), and always release acetylcholine into the striatum as background activity [71]. During sensorimotor learning, dopamine neurons in the SNc exhibit rapid and brief bursts of activity that coincide with TAN pause phase in response to a conditioned stimulus which predicts reward. TAN pause response amplifies the release of dopamine only in the targeted area in the matrix compartment [82,83]. The activation of dopamine receptors is required for spike timing-dependent long-term potentiation (LTP) at striatonigral direct-pathway MSNs and LTD at striatopallidal indirect pathway MSNs in the matrix compartment [84–86]. TAN pause exerts opposing plasticity effects to these two pathways in order to enhance the disinhibition of actions by direct-pathway MSNs and to reduce the inhibition of actions by indirect-pathway MSNs [86]. Thus, the striosomal activation and deactivation in selective modules might not only enhance the contrasts between modules but serve to limit the spatial extent of responsibility signaling via a surround inhibition-like mechanism [83]. Dopamine release in the matrix decides the scaling of the selected modules. Activation of striosomal MSNs inhibits dopamine-containing SNc neurons and terminates goal-directed behavior by reducing dopamine release in the matrix [70].

Imbalances in the activity of the striosome and matrix compartments could produce changes in the selection and release of motor and behavioral functions alternatives via inter-compartmental or striatonigral reciprocal pathways [19,72,74,87]. According to this “compartment” hypothesis, the

correlation between specific clinical symptoms and the activity of striatal compartments is important for understanding basal ganglia disorders, such as HD and dystonia [19,74,79,88,89].

### 3. Striatal Pathology

HD represents one of the main classes of basal ganglia disorders, as well as Parkinson's disease and dystonias. Accumulating evidence suggests that the basal ganglia circuit architecture participates in the creation of striatal pathology in HD [5–12,89]. Considering the recent advances in our understanding of the anatomy and functional roles of the striatum, we discuss cell type- and compartment-specific striatal vulnerabilities in HD (Table 1).

#### 3.1. Wild-Type and mHtt Interacting Proteins

Wild-type Htt, a 347-kDa protein with multiple scaffolds, acts as a major protein interaction hub and an orchestrator of converging intracellular trafficking and signaling pathways [90,91]. Wild-type Htt has anti-apoptotic properties against starvation, mitochondrial toxins, and mHtt overexpression [92–94] and is essential for normal embryonic development [95–97]. The anti-apoptotic effects of wild-type Htt may be associated with the inhibition of pro-apoptotic protein caspase-3 or pro-caspase-8 through the sequestration of pro-apoptotic protein huntingtin-interacting protein 1 (HIP1) and HIP1 protein interactor (HIPPI) [98,99]. Wild-type Htt also acts as a positive transcriptional regulator of neuron-restrictive silencer element (NRSE)-regulated genes, such as brain-derived neurotrophic factor (BDNF) [100,101]. Moreover, wild-type Htt interacts with microtubule-based motor complex-related proteins (i.e., dynein/dynactin and kinesin), which are essential for the axonal transport of vesicles [101–105]. Decreased BDNF levels have been demonstrated in cellular and animal models of HD and patients with HD [106]. A quantitative proteomic analysis revealed that HD pathogenesis may be linked to changes in Htt interactions with stress granule-associated RNA-binding proteins (i.e., cytoplasmic activation- and proliferation-associated protein 1 (Caprin-1) and GTPase-activating protein Src homology 3 (SH3) domain-binding protein 1 (G3BP-1)) [91]. The Caprin-1/G3BP-1 complex regulates the transport and translation of mRNAs of proteins associated with neuronal synaptic plasticity, including BDNF [91]. Although BDNF deletion mutant mice had selective loss of olfactory bulb parvalbumin-containing interneurons via the phospholipase C gamma (PLC $\gamma$ ) pathway, other calcium-binding, protein-containing neuron populations were unaffected [107].

Autosomal dominant inheritance and other genetic studies strongly indicate that polyglutamine (polyQ) expansion confers a toxic gain of function to Htt [108–110]. mHtt protein is cleaved by caspases, calpain, and aspartic endopeptidase, and N-terminal fragments containing the polyQ expansion are sufficient to produce HD-like abnormal clinical syndromes and intranuclear inclusions in HD animal models [111–113]. In mice, inhibition of caspase-6-dependent cleavage retains full-length mHtt, which prevents behavioral and neuropathological dysfunction [114]. Thus, the cleavage of benign full-length mutant huntingtin into toxic fragments may be a rate-limiting step in HD pathogenesis [90]. The proteolysis and subsequent toxicity of mHtt can also be suppressed with the phosphorylation of Htt by protein kinase B (Akt), cyclin-dependent kinase 5 (Cdk5), and extracellular signal-regulated kinase 1 (ERK1) [90,115–117].

mHtt induces mitochondrial dysfunction by reducing adenosine triphosphate (ATP) generation [118], calcium buffering [119,120], and mitochondrial trafficking [121,122]. A quantitative proteomic analysis revealed that the most altered interactions occur between Htt and several mitochondrial proteins, including apoptosis inducing factor, mitochondria associated 1 (AIFM1) [91]. MSNs usually maintain electrophysiologically low levels of spontaneous discharge, which require a large amount of ATP for the maintenance of a hyperpolarized state [123]. This mechanism may underlie the vulnerability of MSNs to mitochondrial dysfunction [110].

**Table 1.** Neuroprotective or neurotoxic effects of structure-specific proteins.

Affected Structures or Cell-Types	Neuroprotective or Neurotoxic Effects	Factors	Hypothesized Mechanism
Striatum	Neurotoxic or neuroprotective	Predominant expression of Ras homolog enriched in striatum (Rhes) in the striatum	Neurotoxic: Rhes binds mHtt and increases cytotoxicity or decreases the autophagic capacity of the striatal neurons. Neuroprotective: Rhes activates autophagy of mHtt and induces gene expression promoting mHtt degradation.
		Brain-derived neurotrophic factor (BDNF) deletion in HD	BDNF is required for survival and dendritic growth of MSNs preferentially in indirect pathway.
MSNs	Neurotoxic	N-methyl D-aspartate receptor subtype 2B (NR2B) predominant expression in MSNs	High expression of NR2B in MSNs may promote NMDA excitotoxicity.
		Sensitivity to glutamate	MSNs are more sensitive to kainite, $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), N-methyl D-aspartate receptor (NMDA), and group 1 metabotropic glutamate receptor (mGluR) agonists than cholinergic interneurons.
		Increased NR2B containing extrasynaptic NMDA receptors	Extrasynaptic NMDA receptors increase the toxic mHtt and cause dysregulation in p38 mitogen-activated protein kinase-cAMP response element binding protein (MAPK-CREB) signaling.
	Neuroprotective	Requirement of higher energy in MSNs	Susceptibility for mitochondrial dysfunction induced by mutant-Htt.
		Expression level of superoxide dismutases (SODs)	MSNs contain low level of SODs, which indicates the vulnerability against oxidative stress.
		Increased expression of parvalbumin (PVA), calretinin, and calcium binding proteins	Calcium-buffering effect over excessive calcium-induced excitotoxicity.
PVAs	Neurotoxic	PDE10A deletion	Activation of extracellular signal-regulated kinase (ERK), CREB and predominant activation of D <sub>2</sub> R indirect pathway.
		BDNF deletion	Blockade of tropomyosin receptor kinase B-phospholipase C $\gamma$ (TrkB-PLC $\gamma$ ) pathway by BDNF deletion.
Interneurons	Neuroprotective	AMPA receptors expression	Enrichment in Ca <sup>2+</sup> permeable AMPA receptors induced calcium-induced excitotoxicity.
		Optineurin expression	Optineurin is predominantly expressed in striatal interneurons and negatively regulates glutamate receptors via interaction with Htt.

Table 1. Cont.

Affected Structures or Cell-Types	Neuroprotective or Neurotoxic Effects	Factors	Hypothesized Mechanism
Striosomes	Neurotoxic	Phosphodiesterase 10A (PDE-10A) decrease in cortical regions projecting to striosomes	PDE-10A decrease induces neurodegeneration in cortical neurons projecting to striosomes.
		Dopamine D <sub>1</sub> R	Enrichment of D <sub>1</sub> R in striosomes induces dopamine excitotoxicity.
		SOD2	Lower expression level of SOD2 in striosomes induces vulnerability against oxidative stress.
		Olfactory type G-protein $\alpha$ subunit (G $\alpha$ olf)	Enrichment of G $\alpha$ olf in striosomes induces D <sub>1</sub> R and A <sub>2A</sub> R mediated neurotoxicity (decreased level of Rhes increases A <sub>2A</sub> R/cAMP/protein kinase A (PKA) activity).
Matrix	Neuroprotective	Cyclin-dependent kinase 5 (CDK5)	Matrix enrich protein CDK5-pY15 induces phosphorylation of Htt which results in decrease of toxic effects against mutant-Htt.
		Decrease of calcium diacylglycerol guanine nucleotide exchange factor 1 (CalDAG-GEF1)	Matrix and MSNs predominant expression pattern of CalDAG-GEF1 protects them from mutant-Htt induced toxicity.
		Dopamine D <sub>2</sub> R	Enrichment of D <sub>2</sub> R in matrix is protective against dopamine excitotoxicity.
		Neuropeptide Y (NPY)	Enrichment of NPY in matrix is protective against glutamate excitotoxicity and microglial activation.
		28 kDa calbindin (Calbindin-D28K)	Enrichment of Calbindin-D28K in matrix is protective against excessive Ca <sup>2+</sup> influx by calcium-buffering.
		Post synaptic density 95 kDa (PSD-95)	Matrix enrich protein PSD-95 is protective against glutamatergic or dopaminergic excitotoxicity.

Some authors have reported a “dying-back” pattern of neuronal degeneration in HD, which suggests that deficits in axonal transport underlie the increased vulnerability of projection neurons to mHtt [108,124,125]. mHtt inhibits axonal transport through the activation of the c-Jun N-terminal kinase (JNK) pathway and phosphorylation of molecular motor proteins [126].

Wild-type Htt and mHtt interact with transcriptional factors, including cAMP response element-binding (CREB)-binding protein (CBP), TATA-binding protein (TBP), p53, specificity protein 1 (Sp1), transcriptional repressor element-1 transcription factor/neuron restrictive silencer factor (REST/NRSF), TAF II 130, and peroxisome proliferator activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) [127]. However, these proteins are diffusely expressed throughout the brain and do not appear to explain cell type- or compartment-specific neuronal degeneration.

### 3.2. Positron Emission Tomography (PET) Imaging Studies

PET imaging studies provide important insights about HD pathogenesis. PET can detect various molecular changes in HD gene expansion carriers before disease manifestation [128,129]. Currently, one of the most important biomarkers for patients with HD is PDE10A, which is highly expressed in MSNs, but not in interneurons [33,130–133]. PDE10A is a dual substrate that regulates cAMP/PKA signaling and hydrolyzes cAMP and cGMP with an approximately 20-fold higher affinity for cAMP [134]. The inhibition of PDE10A activates cAMP/PKA signaling within direct- and indirect-pathway neurons [34]. Previous PET studies have shown that PDE10A expression decreased in the striatum and pallidum and increased in the motor thalamus of premanifest HD gene carriers compared to matched healthy controls [135]. PET imaging research using [<sup>11</sup>C] IMA107 demonstrated a 25%–33% reduction in striatal PDE10A 25 years earlier than predicted symptomatic onset [135,136]. Decreased PDE10A expression was mostly restricted to the dorsal sensorimotor striatum [135], and lower striatal PDE10A expression was associated with disease burden and severity [137]. The PDE10A signal decreased by 33%–34% in the striatum and increased by 35% in the motor thalamus [135]. In HD animal models, PDE10A inhibition reduced neurodegeneration in striatal and cortical neurons and delayed neurological deficit development [138,139]. PDE10A inhibition causes an up-regulation of cAMP/PKA signaling and CREB phosphorylation and increases BDNF expression in striatal neurons [138]. Moreover, PDE10A inhibition has a greater facilitatory effect on the corticostriatal synaptic activity of indirect-pathway neurons than on that of direct-pathway neurons [140].

Increased microglial activation begins at approximately 15–20 years before symptom manifestation [141–143]. Moreover, several studies have reported decreases in D<sub>2</sub>Rs, brain metabolism, and cortical gray and white matter volume at approximately 10 years before disease manifestation [128,129]. In premanifest HD gene carriers, D<sub>1</sub>Rs and D<sub>2</sub>Rs are significantly reduced by 25%–50% [144,145]. At the premanifest stage, the mean annual decline rate is 2% for D<sub>1</sub>Rs and 4%–6.3% for D<sub>2</sub>Rs [144,146].

### 3.3. Striatum-Predominant Neurodegeneration in HD

Along the sagittal axis of the brain, the caudal caudate nucleus (CN) and putamen show greater neuronal loss than the rostral CN and putamen. Moreover, along the coronal axis of the brain, the dorsal and medial striatum are more degenerated than the ventral and lateral striatum [3]. Magnetic resonance imaging (MRI) studies have shown the same striatal atrophy gradients [147,148]. In the early stages of HD when chorea is most apparent, there is a preferential loss of neurons from the indirect pathway projecting to the GPe [13]. The increased frequency of movement release associated with the early and selective involvement of indirect-pathway neurons may explain the genesis of chorea in HD. This notion is supported by evidence obtained from a transgenic mouse model study in which indirect-pathway neurons bearing D<sub>2</sub>Rs were selectively ablated [149].

Wild-type Htt and mHtt are expressed in the brain without significant inter-regional variation, which suggests that the pathogenic process is not a direct effect of mHtt toxicity [150,151]. Increased glutamine tract lengths of mHtt are more prominent in the striatum than in the cortex [152,153]. Although striatal vulnerability is correlated with the size of the CAG repeat expansion in the Htt



located on the short arm of chromosome 4 [154], the mechanisms causing this increasing vulnerability of the striatum are yet to be elucidated [3].

In patients with HD, striatal vulnerability may be associated with reduced corticostriatal input due to impairment of BDNF, an important neuromodulator and trophic factor. Wild-type Htt positively regulates BDNF, whereas mHtt fails to regulate BDNF [155]. BDNF is reduced in the brains of mice and humans with HD. This reduction in BDNF may be attributable to mHtt-induced reduction of anterograde axonal transport within cortical neurons [101,103,156], decreased BDNF endocytosis by MSNs [157], or both of these mechanisms [110]. BDNF supports MSN survival and is required for the dendritic growth of striatal neurons [106,158]. Interestingly, decreased BDNF levels induce selective neuronal degeneration in enkephalinergic, indirect-pathway MSNs [159].

Rhes is a guanine nucleotide-binding protein that may affect small ubiquitin-like modifier (SUMO) modification and preferentially interact with mHtt [160]. Rhes is predominantly expressed in the striatum and, to lesser extent, in other forebrain areas affected by HD. Htt and Rhes interactions may underlie the regional specificity of HD [160,161]. Rhes binds to mHtt and acts as a SUMO E3 ligase to stimulate sumoylation of mHtt, which increases mHtt toxicity [160,162]. In a toxin model of HD, the deletion of Rhes dramatically reduced striatal degeneration and motor dysfunction [163,164]. Moreover, Rhes normally binds to and activates the mechanistic target of rapamycin (mTOR), which inhibits autophagy (i.e., lysosomal degradation); however, in cells with robust autophagy, Rhes activates autophagy via inhibitory binding of Bcl-2 to Beclin-1 [165]. Proteasomal degradation of mHtt prevents cytotoxicity early in life; however, when proteasomal function is compromised by normal aging, autophagy is required. Thus, functional changes associated with aging may explain delayed symptom onset in HD [165,166]. In the striatum, Rhes and mHtt interactions augment cytotoxicity and diminish the autophagic capacity of the neuron [165]. On the other hand, other authors postulate that Rhes is a neuroprotective protein against mHtt-induced neuronal cell death. Rhes levels are reduced in HD patient caudate nucleus and HD mouse model striatum [167,168]. siRNA knockdown of Rhes exacerbates striatal atrophy and behavioral phenotypes in transgenic HD mice [169]. In addition, restoring Rhes alleviates motor deficits and brain pathology in HD mice by activating autophagy of mHtt via increasing Beclin-1, and by altering mTORC1-induced gene expressions implicated in promoting mHtt degradation [168]. mHtt binds both Rhes and mTOR, which reduces the available level of these proteins for intact signaling. Concomitant loss of Rhes and mTOR may render the striatum more vulnerable to early degeneration in HD [168].

### 3.4. Cell Type-Specific Vulnerability

In HD, the most striking neuropathology is the primary and progressive degeneration of MSNs and parvalbumin interneurons and relative sparing of cholinergic and NOS-containing interneurons in the striatum [12–14,18,21,170,171]. Htt and its mRNA are widely expressed in the brain; however, they are less abundant in the striatum compared to many brain regions [150,172–175]. In HD, the amount of Htt and its mRNA present in surviving striatal neurons is not obviously altered, which suggests that Htt expression is not associated with cell type-specific loss in the striatum [175–179]. Moreover, mHtt overexpression may promote functional abnormalities in other neurons besides MSNs, which suggests that MSN vulnerability is not specific to mHtt [180,181].

#### 3.4.1. Glutamate Excitotoxicity

In HD, glutamate excitotoxicity within the striatum has been proposed as a possible cause of MSN vulnerability [182–187]. Cell type-specific loss of neurons is a hallmark of striatal excitotoxic lesions [188]. Previous studies have shown a reduction of *N*-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the CN and cerebral cortex of symptomatic patients [189,190] and animal models [191,192] with HD. In animal models of HD, decrease of striatal glutamate receptors and glutamate release has been reported [193,194].

In contrast to symptomatic HD models, AMPA and NMDA currents in pre-symptomatic animal models of HD increased only during the early stages and decreased during a later stage [195–197].

NMDA glutamate receptors form heteromeric dimers of NR1 and NR2 subunits [198]. The NR2B and NR2D subunits are highly expressed in MSNs and striatal interneurons, respectively [199,200]. NR1 subunits are essential for NMDA receptor function. When NR1 is heteromerized with NR2, the permeability of the NMDA channel increases over 100-fold and deactivation time also increases [201]. This differential expression pattern may explain the increased vulnerability of MSNs [110]. The balance between synaptic and extrasynaptic NMDA receptors activity may underlie the determination in neuronal cell survival in HD [202–205]. Synaptic NMDA receptor activity promotes formation of nontoxic mHtt aggregation [202]. Increased NR2B subunit containing extrasynaptic NMDA receptor expression, and current and associated reduction in CREB activation in HD mouse striatum, correlate with mutation severity [203,204]. Activation of extrasynaptic NMDA receptors increases the soluble and toxic mHtt, in part by increasing Rhes expression [202]. Increased toxic mHtt binds to CBP and causes transcriptional deregulation of the CREB-PGC-1 $\alpha$  cascade [202]. NR2B subunit containing extrasynaptic NMDA receptors also cause dysregulation in p38 MAPK and CREB signaling in HD model mice [205]. Calabresi et al. reported that MSNs were more sensitive than cholinergic interneurons to group I metabotropic glutamate receptor agonists and ionotropic glutamate receptor agonists, such as kainite, AMPA, and NMDA [184,185]. Moreover, in HD, increased expression of the calcium-binding proteins parvalbumin and calretinin is positively associated with interneuron survival [206]. Parvalbumin and calretinin exert calcium-buffering effects in response to excessive calcium-induced excitotoxicity and are thought to be neuroprotective and important for the survival of interneurons [207,208]. However, the enrichment of calcium-permeable AMPA receptors in parvalbumin interneurons may be a potential pathogenic mechanism [209]. Optineurin is preferentially distributed in interneurons within the naïve mouse striatum [210]. Through its interactions with postsynaptic density protein 95 (PSD-95) or optineurin, wild-type Htt becomes a negative regulator of glutamate receptors [211,212]. This indicates that, with PSD-95 or optineurin, wild-type Htt could exert neuroprotective effects against excessive glutamatergic input [210].

#### 3.4.2. Mitochondrial Dysfunction

In post-mortem studies of HD brain tissue, decreased activity in mitochondrial respiratory chain complexes II, III, and IV was found [213]. By maintaining a hyperpolarized state requiring high amounts of energy, striatal MSNs usually remain electrophysiologically silent [123,214]. The unique energy requirements of MSNs may be associated with their susceptibility to mitochondrial dysfunction [215]. Cholinergic interneurons are enriched in the superoxide free radical scavengers superoxide dismutase 1 and 2 (SOD1 and SOD2), whereas MSNs contain low levels of these enzymes [216]. Although oxidative damage is rarely reported in early-stage HD, it may be a major mechanism during later disease progression [217].

### 3.5. Striatal Compartment-Specific Degeneration

#### 3.5.1. Striosome vs. Matrix Neurodegeneration

Differential neurodegeneration of the striatal compartments has been implicated in HD [5–11,218]. In the early stage of the disease, a preferential loss of striosomal neurons that gradually spreads to matrix neurons has been reported [5–9]. However, some studies reported preferential loss of matrix neurons [9–12]. Tippet et al. demonstrated that HD cases with pronounced striosomal neuron loss had shorter CAG repeat lengths than cases with matrix neuron loss or mixed compartmental loss [9]. Moreover, individuals with pronounced striosomal neuron loss did not die during the early stages of disease progression and exhibited more severe mood disturbances [9]. There is a strong inverse relationship between mHtt CAG repeat size and age of onset [151,219] and death [220]. However, disease duration does not vary between individuals with short or long CAG repeats [220]. These results

potentially indicate that individuals with preferential matrix neuron loss have relatively rapid disease progression. The preferential neurodegeneration of striosomal MSNs has been reported in HD, as in cerebral ischemia and X-linked dystonia-parkinsonism, the other transcriptional dysregulation syndrome [8,79,184,188,221]. The preferential loss of MSNs in the striosome compartment relative to those in the matrix compartment is thought to be an important factor in the development of abnormal involuntary movements (e.g., dystonias) [19,79,88,188,222]. Tippet found that, in cases with preferential striosome or matrix neurodegeneration, there was no difference in the severity of motor disturbance, even at the end stage of the illness [9]. Neurons within the matrix compartment project from the striatum to the basal ganglia circuitry and are responsible for motor scaling [72]. Consequently, instead of producing chorea, matrix neurodegeneration only induces multiple system atrophy of the parkinsonian type [223]. The striosome compartment is organized early in embryonic development and occupies 10%–20% of the striatum across mammalian species [40–42]. If striosomal neurodegeneration reflects the D<sub>1</sub>R decrease observed in striatal PET studies, the annual striosomal degeneration rate is estimated to exceed that of D<sub>2</sub>Rs at the premanifest stage by 2–3-fold. We hypothesize that individuals with pronounced matrix neurodegeneration had prior striosomal neurodegeneration to some extent, and rapid matrix neuron loss may produce the matrix-predominant neurodegeneration pattern. Since the striosome and matrix compartments are responsible for motor focusing and motor scaling [72], striosomal neurodegeneration is sufficient to induce abnormal movements. Matrix D<sub>1</sub>Rs are required for the maintenance of exaggerated movements, and neurodegeneration of matrix D<sub>2</sub>Rs reinforces this enlargement in movements as well. Rapid matrix neurodegeneration may be associated with mHtt-related neurotoxicity. Since autopsied brains are usually acquired at the end stage of the disease, it may be useful to investigate the striatal neuropathology of animal models. In a study of a transgenic rodent model of HD, preferential loss of striosomal neurons was reported [224]. Moreover, a PET study of early premanifest HD gene carriers revealed that extra-striatal PDE10A expression decreased by 25% and 50% in the insular cortex and occipital fusiform gyrus, respectively [136]. These cortical areas are associated with cognitive and limbic functions and are striosome-related areas [225].

### 3.5.2. Dopamine Excitotoxicity-Induced Striosomal Cell Vulnerability

Preferential striosomal neurodegeneration may disinhibit dopaminergic neurons in the SNc via the striosomal pathway [19]. It is hypothesized that, in early-stage HD, striatal dopamine levels are up-regulated, which induces hyperkinetic movement disorder and striatal dopamine excitotoxicity [226]. This hypothesis is supported by evidence that anti-dopaminergic agents are effective suppressants of abnormal hyperkinetic movements in patients with HD [227]. A study quantifying dopamine and dopamine metabolite levels in autopsied HD human brains found increased dopamine levels in the striatum and substantia nigra [228]. These results were corroborated by a study that found increased dopamine metabolite levels in the cerebrospinal fluid of patients with HD [229]. TH, the rate-limiting enzyme for catecholamine synthesis, is highly concentrated in the neostriatum [230]. In HD, increased TH activity corresponds to increased cellular dopamine levels and neurotoxicity [231,232]. In a study of R2/6 transgenic mice, TH activity increased during early-stage HD and significantly decreased at a later stage [230]. In another previous study, dopamine levels in the CN and putamen of patients with HD were normal [233]; however, since striatal D<sub>1</sub>Rs and D<sub>2</sub>Rs were decreased, a relative increase in dopamine transmission could occur at the network level. Dopamine overflow in the striatum also results in a relative increase in striatal glutamatergic inputs.

Preferential striosomal MSN degeneration may disrupt motor focusing via the acetylcholine-mediated transcompartmental pathway and increase motor scaling via increased striosomal pathway-mediated dopaminergic input [72]. In HD, excessive activity of the dopamine and glutamate pathways may exert neurotoxic effects on the striatum [161,227]. Generally, D<sub>1</sub>R overstimulation exerts a neurotoxic effect, whereas D<sub>2</sub>R stimulation can be neuroprotective [234]. The D<sub>1</sub>R and G-protein  $\alpha$  subunit (G $\alpha$ olf) are preferentially expressed in the striosome compartment, which may be associated with striosomal vulnerability [87,235]. Rhes normally reduces agonist-stimulated cAMP by binding to

G $\alpha$ i [236,237] or inhibiting Gs/olf-mediated signaling [237–240]. However, Rhes is not involved in the D<sub>2</sub>R/G $\alpha$ i-mediated adenylyl cyclase inhibition and does not directly interact with D<sub>1</sub>R [237]. Recent study suggests that decreased level of Rhes increases A<sub>2A</sub>R/cAMP/PKA activity selectively under the conditions of dopamine/adenosine-related drug challenge in A<sub>2A</sub>R/D<sub>2</sub>R-expressing MSNs [240]. A<sub>2A</sub>R is evenly distributed in the striatum [87], hence preferential striosomal expression of G $\alpha$ olf may decide excitatory neurotoxic effects of A<sub>2A</sub>R/cAMP/PKA signaling in A<sub>2A</sub>R/D<sub>2</sub>R-expressing MSNs [241].

### 3.5.3. The NPY System Exerts Protective Effects on the Matrix Compartment in HD

In HD, early-stage preferential striosomal neurodegeneration is followed by late-stage neuron loss in the surrounding matrix [5–8,10,79,188]. In patients with HD, the number of NPY-positive cells increases in the striatum [188,242]. NPY exerts an inhibitory effect on glutamate release and microglial activation [243]. Interestingly, NPY fibers are largely distributed in the matrix compartment of the striatum. This suggests that NPY exerts greater neuroprotective effects against excitotoxicity induced by excessive glutamate and microglial activation in the matrix compared to the striosomes [188].

### 3.5.4. Other Proteins May Underlie the Differential Excitotoxicity between Striosome and Matrix Compartments

Enhanced dopaminergic and glutamatergic inputs to the striatum may cause neurotoxicity due to impaired calcium-buffering capacity and subsequent neurodegeneration of the matrix compartment [225,244–246]. In HD, increased expression of calcium-binding protein calbindin-D28K is positively associated with interneuron survival [206]. Calbindin-D28K is predominantly found in the matrix and thought to exert neuroprotective effects that promote calcium-buffering in response to excessive calcium-induced excitotoxicity [207,208]. Crittenden et al. found that calcium diacylglycerol guanine nucleotide exchange factors (CalDAG-GEFs), which are striatum-enriched calcium and diacylglycerol binding proteins, are severely down-regulated in the R6/2 mouse model of HD and post-mortem striatal tissues from patients with HD [89]. Knockdown of matrix-predominant CalDAG-GEF1 protein expression protects against the deleterious effects of mHtt overexpression and may be a compensatory response to MSN vulnerability to mHtt expression [89]. Media et al. reported lower SOD2 expression levels in the striosomal compartment compared to the matrix compartment. This may be associated with preferential striosomal vulnerability to oxidative stress-induced free radical generation [216].

Wild-type Htt is a negative regulator of glutamate receptor and D<sub>1</sub>R activities via interaction with PSD-95 [211]. This indicates that wild-type Htt and PSD-95 could exert neuroprotective effects against excessive glutamatergic and dopaminergic inputs. PSD-95 not only negatively regulates NMDA glutamate signaling, but also dopamine D<sub>1</sub> signaling at post-synaptic transmission sites. These PSD-95 activities may also exert protective effects against excessive glutamatergic and dopaminergic inputs in the matrix compartment [247]. PSD-95 is predominantly distributed in the matrix relative to the striosomes, which suggests that striosomes are more vulnerable to glutamatergic or dopaminergic excitotoxicity [247]. By phosphorylating dopamine and cAMP-dependent protein kinase, Cdk5 also acts as a negative regulator of postsynaptic dopaminergic signaling [248] and may exert protective effects against excessive dopamine. Activated Cdk5 (i.e., Cdk5 with phosphorylation at the tyrosine 15 residue) is a matrix-enriched protein and may exert neuroprotective effects within the matrix compartment [249].

## 4. Conclusions

When examining pathophysiological changes in patients with Huntington's disease, several factors should be taken into consideration. For several reasons, in early-stage HD, preferential striatal MSN neurodegeneration and predominant striosomal neuron loss occur due to susceptibility, not specificity. This implies that it is important to examine the differences between MSNs and non-MSN

neurons or between the striosomal and matrix compartments of the striatum. Structure-specific protein expression may be a key contributor to the neurodegenerative phenomena of the HD brain (Table 1). These proteins exert neurotoxic or neuroprotective functions against oxidative stress, glutamatergic or dopaminergic excitotoxicity, and dysregulation in autophagy or axonal transport. MSNs are enriched in NR2B and deficient in optineurin, which may explain their susceptibility to glutamatergic excitotoxicity. Moreover, the higher energy requirements and low SOD expression of MSNs may be associated with their vulnerability to mitochondrial dysfunction. Striosomes are enriched in D<sub>1</sub>R and G $\alpha$ olf and deficient in calbindin-D28K, PSD-95, NPY, and CDK5-pY15. Consequently, striosomal MSNs may be more susceptible to D<sub>1</sub>R- and glutamate-mediated excitotoxicity than matrix MSNs. A better understanding of the pathogenic mechanisms by which neurodegeneration primarily and progressively occurs in the striatum in HD patients can be achieved with further in vivo and in vitro studies on striatal cell type- and compartment-specific vulnerability to neurotoxicity caused by mHtt.

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