REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Molecular and Cellular Insights into Huntington's Disease Pathophysiology

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Abstract

Huntington's disease (HD) is a fatal, inherited neurodegenerative disorder characterized by progressive motor dysfunction, cognitive deterioration, and psychiatric symptoms. It primarily affects the basal ganglia, especially the striatum, resulting in both structural and functional abnormalities. At the molecular level, the disease is driven by a toxic gain-of-function mutation in the huntingtin gene, leading to intracellular dysfunctions including protein misfolding, impaired axonal transport, transcriptional dysregulation, mitochondrial failure, oxidative stress, and excitotoxicity. This review provides a comprehensive overview of HD pathophysiology, emphasizing the mechanisms underlying striatal vulnerability and basal ganglia circuit disruption. Particular attention is given to mitochondrial dysfunction, oxidative damage, neuroinflammation, and the role of the renin-angiotensin system (RAS), including the emerging neuroprotective potential of the ACE2/Ang-(1–7)/Mas receptor axis. Insights into these interconnected pathways not only deepen our understanding of disease progression but also highlight novel therapeutic targets. Despite substantial advances in elucidating HD pathology, a cure remains elusive, reinforcing the urgency of exploring targeted interventions that may mitigate neurodegeneration and enhance patient outcomes.

Keywords: Huntington's disease; neurodegeneration; basal ganglia; mutant huntingtin; mitochondrial dysfunction.

1. Background

Huntington's disease (HD) is a severe and progressive neurodegenerative condition initially identified by George Huntington in 1872. Historically referred to as Huntington's chorea, it was later distinguished from other choreiform disorders as a unique clinical entity **(Aubeeluck and Wilson, 2008)**. Globally, HD affects approximately 2.7 individuals per 100,000, with symptom onset typically occurring between the ages of 30 and 50 years. When symptoms appear before the age of 20, the disorder is classified as juvenile Huntington's disease **(Quarrell et al., 2012)**.

Clinically, HD is characterized by a gradual onset of motor, cognitive, and psychiatric impairments that worsen over time. The average survival following clinical diagnosis ranges from 10 to 20 years, although the rate of progression varies substantially between patients. Exploring the determinants of disease progression remains

essential to deepen our understanding of the natural course of this currently incurable condition **(Chao et al., 2017)**.

2. Clinical manifestations

Huntington's disease presents with a range of motor and non-motor symptoms.

2.1. Motor symptoms

A hallmark clinical feature of HD is chorea, which consists of rapid, involuntary, and semi-purposeful movements that can affect various parts of the body. These movements may present as facial twitching, eyelid lifting, nodding of the head, and irregular writhing or jerking motions of the limbs. In some cases, chorea may become more generalized, significantly impacting gait and coordination **(Jayasree et al., 2024)**. During the early phases of the disease, these movements may appear subtly and blend into normal motor activity; however, over time, they become increasingly apparent and begin to disrupt routine tasks **(Ross and Tabrizi, 2012)**. As HD advances, additional motor impairments such as bradykinesia, dystonia, and gait instability worsen, ultimately leading to severe physical disability and confinement to bed **(Stoker et al., 2022)**.

2.2. Non motor symptoms

In addition to motor abnormalities, Huntington's disease is also marked by a range of non-motor symptoms, primarily psychiatric and cognitive in nature. During the early stages, individuals often exhibit deficits in problem-solving, attention, and visuospatial processing, which may contribute to a noticeable decline in occupational performance **(Mehanna and Jankovic, 2024)**. Personality alterations are also common and frequently present alongside symptoms of depression (**Epping and Paulsen, 2011)**. Other psychiatric manifestations may include emotional instability, episodes of aggression, paranoia, psychosis, anxiety, irritability, manic episodes, obsessive-compulsive behaviors, and apathy. As the disease progresses, cognitive functions deteriorate further, often culminating in dementia **(Snowden, 2017)**.

3. Neuropathology of the Basal Ganglia

The basal ganglia are a complex network of subcortical nuclei located at the base of the forebrain. They play a critical role in regulating both motor control and emotional processing through dynamic connections with sensorimotor, motivational, and cognitive regions of the brain **(Florio et al., 2018)**. Anatomically, the basal ganglia consist of the caudate nucleus and putamen (collectively referred to as the striatum), as well as the subthalamic nucleus, the internal and external segments of the globus pallidus, and the substantia nigra **(Simonyan, 2019) (Figure 1)**.

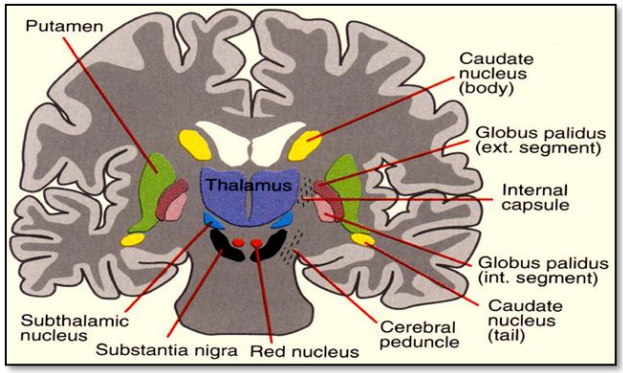

Figure 1. Structure of basal ganglia nuclei **(Leisman et al., 2013)**

Striatal neurodegeneration represents a central pathological hallmark of Huntington's disease. Analysis of post-mortem HD brains typically reveals bilateral atrophy of the striatum **(Tabrizi et al., 2020)**, with an average reduction of approximately 57% in the cross-sectional area of the caudate nucleus and 64% in the putamen. This degeneration intensifies with disease progression. On a structural level, neuronal loss initially begins in the tail of the caudate nucleus and spreads in a dorsal-to-ventral and rostral-to-caudal manner throughout the striatum **(McColgan and Tabrizi, 2018)**. This neuronal degeneration is accompanied by significant gliosis involving astrocytes and oligodendrocytes **(Gray, 2019)**. As the disease advances, neurodegeneration extends to other brain regions, ultimately leading to generalized cerebral atrophy **(Ross and Tabrizi, 2011)**.

Among the striatal neurons, the inhibitory GABAergic medium spiny neurons projecting to the globus pallidus externa (GPe) are especially susceptible and are among the first to degenerate. This early disruption impairs the function of the indirect basal ganglia pathway, which, along with the direct pathway, is essential for regulating voluntary movement. Specifically, the reduction in GABAergic inhibition from the striatum to the GPe

leads to excessive suppression of the subthalamic nucleus (STN). As a result, decreased excitatory output from the STN leads to diminished inhibition of the thalamus, ultimately enhancing the release of glutamate to the frontal cortex **(Figure 2)**. This disinhibited cortical excitation manifests clinically as chorea **(Wider and Lüthi-Carter, 2006)**.

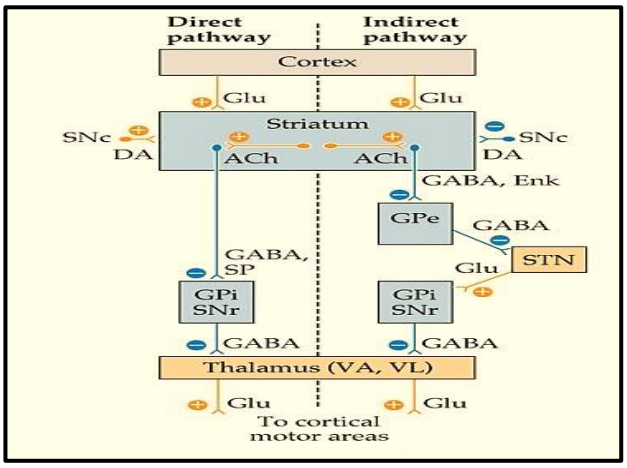

Figure 2. Circuit diagram for direct & indirect pathways of basal ganglia **(Leisman et al., 2013)**

As the disease affects both the direct and indirect motor circuits, it gives rise to the full spectrum of motor symptoms observed in HD **(André et al., 2010)**. In addition to motor control circuits, progressive neuronal loss within the basal ganglia also impacts fronto-subcortical loops involved in cognitive, emotional, and behavioral regulation, thereby contributing to the non-motor symptoms of Huntington's disease **(Pidgeon and Rickards, 2013)**.

4. Molecular Mechanisms of Neurodegeneration in Huntington's disease

Huntington's disease is a multifaceted neurodegenerative disorder characterized by a cascade of pathological events that, over time, lead to extensive neuronal loss. Central to this process is the presence of mutant huntingtin protein, which induces a wide array of intracellular disturbances. These include the activation of proteolytic enzymes, abnormal protein folding, impaired proteasomal degradation, transcriptional dysregulation, disrupted axonal transport, and synaptic dysfunction. In addition to these cellular disturbances, multiple converging mechanisms contribute to disease progression. These include excitotoxicity, mitochondrial dysfunction, metabolic failure, oxidative stress, impaired autophagy, apoptosis, neuroinflammation, and activation of microglia **(Gil and Rego, 2008, Möller, 2010) (Figure 3)**.

4.1. Mitochondrial dysfunction

Mitochondria are essential for meeting the energy needs of metabolically active tissues like the brain. When mitochondrial function is compromised, neuronal resilience decreases, making neurons more vulnerable to metabolic stress and degeneration **(Farshbaf and Kiani-Esfahani, 2018)**. In addition to energy production, mitochondrial respiration generates a significant amount of reactive oxygen species (ROS), which have been extensively linked to the development of various neurodegenerative diseases **(Nissanka and Moraes, 2018)**. A growing body of research has identified bioenergetic failure and mitochondrial anomalies in conditions such as HD, Alzheimer disease (AD) **(Wang, et al., 2014)**, Parkinson disease (PD) **(Winklhofer and Haass, 2010)**. These impairments include reduced efficiency of oxidative phosphorylation (OXPHOS) complexes II and III, loss of mitochondrial membrane potential, and diminished aconitase activity in basal ganglia structures **(Johri et al., 2013)**. Furthermore, metabolic deficits in the striatum have been detected even before clinical onset in HD carriers, while advanced stages of the disease are associated with marked reductions in electron transport chain activity, particularly in the caudate nucleus and putamen **(Carmo et al., 2018)**.

The transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) plays a crucial role in mitochondrial biogenesis, oxidative phosphorylation, and cellular antioxidant defense mechanisms **(Puigserver and Spiegelman, 2003; Abu Shelbayeh et al., 2023)**. Research has shown that PGC-1α expression is selectively and markedly reduced in HD-affected striatal neurons and tissue. This downregulation appears to result from transcriptional repression by mutant huntingtin, which interferes with the cAMP response element-binding (CREB)/TAF4 pathway, suppressing CRE-mediated transcription of the PGC-1α gene (**Cui et al., 2006; Qian et al., 2024)**. Notably, diminished CRE-driven transcriptional activity has been identified as an early molecular defect in HD **(Erro et al., 2021)**. The suppression of PGC-1α disrupts energy metabolism and diminishes the capacity of striatal neurons to meet metabolic demands, contributing to neuronal dysfunction and

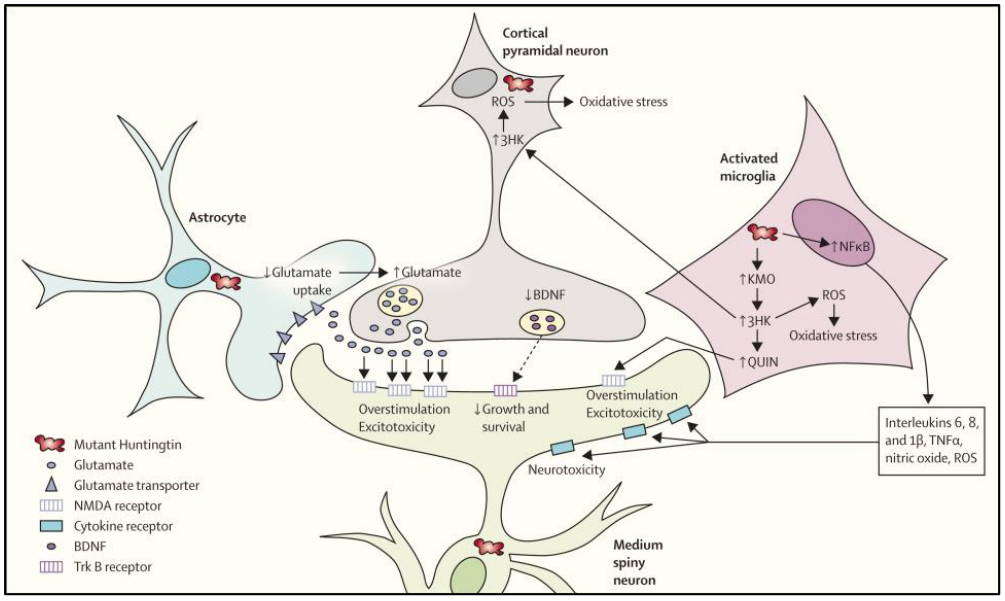

Figure 3. Intercellular pathogenesis of Huntington's disease **(Ross and Tabrizi, 2011)**

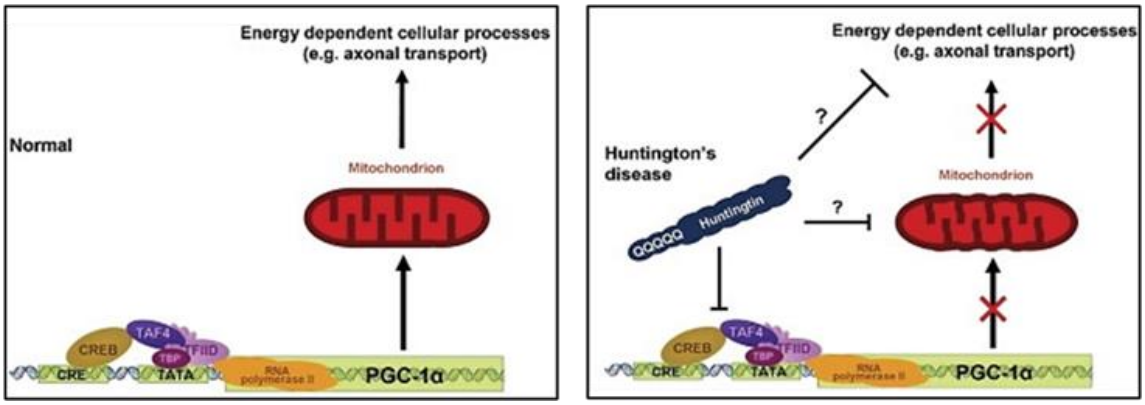

Figure 4. Proposed Mechanism for PGC-1α Regulation in Huntington's Disease. Under physiological conditions (right panel), PGC-1α plays a key role in coordinating metabolic processes and sustaining energy balance within the central nervous system. In the context of HD (left panel), mutant huntingtin disrupts the transcriptional regulation of PGC-1α by interfering with the CREB/TAF4 pathway. This repression results in diminished PGC-1α expression, compromising the capacity of susceptible neurons to meet increased energy demands and contributing to their degeneration (left panel) **(Cui et al., 2006).**

degeneration **(Panes et al., 2022)**. Additionally, mutant huntingtin impairs other energy-intensive processes such as axonal transport, further exacerbating cellular dysfunction in HD **(Dubey et al., 2024) (Figure 4)**.

Succinate dehydrogenase (SDH), also known as Complex II of the mitochondrial respiratory chain, occupies a central role in cellular energy metabolism, linking the tricarboxylic acid (TCA) cycle and the electron transport chain. It catalyzes the conversion of succinate to fumarate while concurrently reducing ubiquinone to ubiquinol, supporting ATP synthesis by maintaining the mitochondrial membrane potential. Impaired SDH function can disrupt mitochondrial activity, reduce ATP production, and disturb cellular energy balance Additionally, fumarate accumulation, while required at low levels in energy-producing cells, can become detrimental when elevated, leading to a reduction in ATP synthesis **(Van Vranken et al., 2014)**. Excess succinate has also been identified as a major contributor to ROS generation and can further amplify oxidative stress by interacting with Complexes I and III of the electron transport chain **(Dröse et al., 2011; Ralph et al., 2011)**. Notably, SDH inhibition has been linked to striatal neuron loss and excitotoxic injury in HD models **(Túnez et al., 2010)**. As a result, SDH has been widely targeted in experimental

toxin models that aim to replicate HD-like pathology, with compounds such as 3-nitropropionic acid (3-NP) being commonly employed to induce selective striatal damage **(Makhdoomi et al., 2024)**.

4.2. Oxidative stress

Oxidative stress arises from an imbalance between the generation of ROS, such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (·OH), and the capacity of the biological system to neutralize or repair the resulting damage. The cellular impact of oxidative stress depends on the system's ability to restore homeostasis. However, when ROS levels become excessively high, they may lead to necrosis, depletion of ATP, and the failure to execute programmed cell death via apoptosis **(Azam et al., 2021)**.

Under physiological conditions, cells maintain a reducing intracellular environment through antioxidant enzymes. Disruption of this redox balance triggers toxicity by promoting the formation of reactive oxygen and nitrogen species, which in turn damage critical cellular components including proteins, lipids, and DNA **(Shukla et al., 2011)**.

In recent decades, numerous external antioxidant agents have been explored as potential therapies, though many have yielded limited clinical outcomes. As a result, research has increasingly shifted toward understanding endogenous antioxidant defense mechanisms, particularly signaling pathways involving nuclear factor erythroid 2–related factor 2 (Nrf2). Nrf2 is a redox-sensitive transcription factor belonging to the basic leucine zipper family, and it contains a domain that facilitates interaction with its cytoplasmic inhibitor, Kelch-like ECH-associated protein 1 (Keap1). Upon oxidative challenge, Nrf2 is released from Keap1 and translocate to the nucleus, where it forms heterodimers with small musculoaponeurotic fibrosarcoma homologs proteins (Maf). This complex then binds to antioxidant response elements (AREs) in DNA to activate transcription of a wide array of genes involved in cellular defense. The protective role of Nrf2 is largely mediated through the coordinated upregulation of genes responsible for detoxification and antioxidant activity **(Ngo and Duennwald, 2022)**.

In response to elevated ROS levels, cells attempt to adapt by enhancing the expression of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and reduced glutathione (GSH). However, when the oxidative burden exceeds the buffering capacity of these systems, oxidative damage accumulates, contributing to cellular dysfunction and disease progression.

4.3. Neuroinflammation

Neuroinflammation contributes to neuronal degeneration through the release of various soluble mediators, such as cytokines, prostaglandins, and nitric oxide (NO). A defining cellular marker of this process is the presence of activated microglial cells, which serve as key indicators of immune activation in the central nervous system (CNS). Research has demonstrated that immune system activation and dysregulated immune responses are detectable even during the premanifest stage of HD. This suggests that inflammatory mechanisms may play a triggering role in striatal and cortical neurodegeneration. Additionally, HD has been associated with deficits in immune cell migration, which may impair the regulation of cytokines and chemokines, leading to persistent elevations in proinflammatory signaling. Such chronic inflammation promotes microglial activation and perpetuates neurodegeneration in HD **(Saba et al., 2022)**.

Microglia are the primary effector cells in CNS inflammation and are increasingly recognized as central contributors to the development of various neurodegenerative conditions **(Ki et al., 2021)**. In HD, neuronal degeneration predominantly occurs within the basal ganglia nuclei, and this pathology is accompanied by marked microglial and astrocytic infiltration in affected regions. Notably, microglial activation has been observed in mutant huntingtin (mHTT) carriers even before clinical symptoms emerge **(Palpagama et al., 2019)**.

Activated microglia initiates a proinflammatory cascade involving cytokines such as interleukin-6 (IL-6), interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α). These proinflammatory mediators initiate downstream effects, including increased caspase level, elevated calcium levels, and heightened production of ROS and NO **(Peterson and Flood, 2012)**. One of the key regulatory elements involved in this process is the transcription factor nuclear factor kappa B (NF-κB), which is activated in response to the overproduction of cytokines. Once activated, NF-κB facilitates the transcription of various proinflammatory genes, including those coding for

enzymes like inducible nitric oxide synthase (iNOS). NF-κB functions through its interaction with CREB-binding protein (CBP), which further augments the expression of genes linked to inflammation **(Babkina, et al., 2021)**.

iNOS is a critical enzyme that generates significant amounts of nitric oxide and has been associated with various CNS disorders such as AD, and HD. Under inflammatory conditions, both astrocytes and macrophages are capable of producing iNOS and its harmful by-product, peroxynitrite, formed when NO reacts with superoxide radicals. The accumulation of peroxynitrite leads to oxidative stress, which intensifies neuronal injury and accelerates disease progression **(Brown, 2007)**.

4.4. The Renin-Angiotensin System (RAS) in Huntington's disease

The Renin-Angiotensin System (RAS) is a complex network of peptide hormones traditionally associated with cardiovascular and renal regulation. However, all components of this system have also been identified in the CNS, where they function autonomously from the peripheral RAS **(Wright and Harding, 2013)**. Within the CNS, RAS elements have been linked to various neurodegenerative and neuropsychiatric disorders, including anxiety and depression **(Kangussu et al., 2013)**, as well as Alzheimer's **(Jiang et al., 2016)**, Parkinson's **(Rocha et al., 2016)**, and Huntington's diseases **(De Mello et al., 2017)**.

The classical RAS cascade is initiated by the cleavage of angiotensinogen by renin, yielding angiotensin I (Ang I). Ang I is subsequently converted into the active peptide angiotensin II (Ang II) through the action of angiotensin-converting enzyme (ACE). Ang II primarily signals through two receptor subtypes: angiotensin II type 1 (AT1) and type 2 (AT2), with AT1 being the predominant mediator of Ang II's physiological and pathological effects. Ang II can be further metabolized into angiotensin III (Ang III), which exhibits similar biological activity and mainly acts through AT1 receptors **(Vargas et al., 2022)**. Ang III is then degraded by aminopeptidase N to form angiotensin IV (Ang IV), which exerts its functions via the angiotensin II type 4 receptor (AT4). Ang IV may also be generated directly from Ang I or Ang II through the activity of aminopeptidases (**Fyhrquist and Saijonmaa, 2008)**.

Recent advancements in the understanding of RAS have led to the recognition of a non-classical axis, which includes ACE homologs such as angiotensin-converting enzyme 2 (ACE2), the heptapeptide angiotensin-(1–7) [Ang-(1–7)], the Mas receptor, and newly identified peptides like Alatensins (angiotensin A and alamandine) **(Jankowski et al., 2007; Lautner et al., 2013)**. This extended system also includes the Mas-related G-protein-coupled receptor MrgD. Ang-(1–7) can be produced through multiple enzymatic pathways from either Ang I or Ang II, most notably via ACE2 or endopeptidases. It primarily exerts its protective effects by binding to the Mas receptor, which is highly expressed in the brain, and to a lesser extent in the heart, kidneys, and vascular system **(Santos et al., 2017)**.

Within the CNS, particularly in the context of neurodegenerative disorders, the classical ACE/Ang II/AT1 receptor signaling axis is generally associated with detrimental effects. This pathway has been implicated in promoting neurodegeneration by exacerbating neuroinflammatory responses, elevating oxidative stress levels, impairing cognitive functions, and compromising neuronal survival **(Xu et al., 2011; Almeida-Santos et al., 2017; Gironacci et al., 2018)**. Moreover, activation of this axis has been linked to pathological hallmarks across various diseases, including increased amyloid-β production and tau hyperphosphorylation in Alzheimer's disease **(Tian et al., 2012; Jiang et al., 2016)**, dopaminergic neuron degeneration in Parkinson's disease **(Labandeira-Garcia et al., 2024)**, as well as impaired long-term potentiation (LTP) that contributes to learning and memory deficits **(Tchekalarova and Albrecht, 2007; Bodiga and Bodiga, 2013, Tota et al., 2013)**.

One of the key mechanisms underlying these effects involves Ang II–mediated activation of the AT1 receptor, which stimulates NF-κB signaling, thereby enhancing the production of pro-inflammatory cytokines **(Benicky et al., 2011)**. In addition, AT1 receptor activation promotes NADPH oxidase (Nox) activity, further amplifying oxidative stress **(Garrido and Griendling, 2009)**. The activation of NF-κB-p65 by Ang II is thought to occur via upregulation of phosphorylated p38 Mitogen-activated protein kinase (p38 MAPK), which in turn activates IKKβ. This leads to phosphorylation and proteasomal degradation of IκB, allowing NF-κB-p65 to translocate into the nucleus and initiate transcription of inflammatory

genes **(Rabie et al., 2018)**.

In contrast, the non-classical RAS arm, comprising the ACE2/Angiotensin-(1–7)/Mas receptor axis, acts as a counter-regulatory mechanism and is increasingly recognized for its neuroprotective properties **(Santos et al., 2019; Brito-Toscano et al., 2023)**. Activation of this pathway has been shown to attenuate neuroinflammatory signaling and oxidative stress, enhance cognitive function and neuronal viability, suppress amyloid-β accumulation and tau pathology, and improve synaptic plasticity, learning, and memory (**Rocha et al., 2016; Gironacci et al., 2018)**. Likewise, stimulation of the AT2 receptor by Ang II appears to mimic the beneficial effects of Ang-(1–7)/Mas receptor activation, effectively opposing the neurotoxic actions mediated through AT1 receptor signaling. AT2 receptor activation is associated with enhanced neuronal survival, reduced oxidative and inflammatory markers, improved memory, and overall cognitive performance **(Almeida-Santos et al., 2017; Kangussu et al., 2022)**. Importantly, AT2 receptor activation has been linked to the phosphorylation of CREB, which in turn induces the expression of brain-derived neurotrophic factor (BDNF) via activation of the Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, further contributing to neuroprotection and synaptic resilience **(Hashikawa-Hobara et al., 2012; Guimond et al., 2013; Umschweif et al., 2014)**.

Recent studies have reported a significant downregulation of the neuroprotective ACE2/Ang-(1–7)/Mas axis within the striatum of Huntington's disease brains. Conversely, the classical ACE/Ang II/AT1 axis appears to be upregulated in HD, evidenced by increased expression of AT1 receptors in affected brain regions **(Kangussu et al., 2022)**.

5. Conclusion

Huntington's disease is a complex and multifactorial neurodegenerative disorder marked by progressive motor dysfunction, psychiatric disturbances, and cognitive decline. At the core of its pathophysiology lies the toxic gain-of-function of mutant huntingtin protein, which initiates a cascade of deleterious events including striatal neurodegeneration, mitochondrial dysfunction, oxidative stress, transcriptional dysregulation, and neuroinflammation. The preferential vulnerability of medium spiny neurons in the striatum leads to basal ganglia circuit dysfunction and the hallmark motor symptoms of HD.

In addition, emerging evidence highlights the contribution of systemic and central renin-angiotensin system components in HD pathogenesis, further broadening our understanding of the molecular underpinnings of the disease. Despite decades of research, there remains no curative treatment for HD, underscoring the need for continued investigation into the cellular and molecular mechanisms involved. A deeper understanding of these processes may pave the way for novel neuroprotective strategies that can delay disease progression and improve quality of life for affected individuals.

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