Protein & Peptide Letters, 2020, *27*, 456-462

REVIEW ARTICLE

The Renin-Angiotensin System in Huntington's Disease: Villain or Hero?

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ARTICLE HISTORY

Received: June 11, 2019
Revised: August 22, 2019
Accepted: November 15, 2019

DOI:
10.2174/0929866527666200110154523

Abstract: Huntington's Disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by severe symptoms, including motor impairment, cognitive decline, and psychiatric alterations. Several systems, molecules, and mediators have been associated with the pathophysiology of HD. Among these, there is the Renin-Angiotensin System (RAS), a peptide hormone system that has been associated with the pathology of neuropsychiatric and neurodegenerative disorders. Important alterations in this system have been demonstrated in HD. However, the role of RAS components in HD is still unclear and needs further investigation. Nonetheless, modulation of the RAS components may represent a potential therapeutic strategy for the treatment of HD.

Keywords: Renin angiotensin system, angiotensin peptides, Huntington's disease, neurodegenerative disorder, pathophysiology, peptide hormone.

1. INTRODUCTION

Huntington's Disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, associated with a variable-length expansion of the CAG trinucleotide repeat in exon 1 of the Huntingtin (HTT) gene [1, 2]. Most evidence suggests that HD pathology derives from a gain of toxic function of mutant Huntingtin (mHTT). Conformational changes lead to protein aggregation and are related to mHTT interference with gene transcription and cellular metabolism [3, 4]. Medium spiny neurons of the striatum region are exceptionally vulnerable to mHTT [1]. Nonetheless, neuronal dysfunction and neurodegeneration have also been reported in the cerebral cortex [5], cerebellum [6] and substantia nigra [7, 8].

Normally, human HTT alleles contain between 6 and 35 CAG repeats, whilst patients with fully penetrance HD present more than 40 repeats. In these cases, longer CAG expansions are associated with earlier disease onset. An intermediate number of 36-40 trinucleotide repeats typically characterize incomplete penetrance, with a steadier progression of the disease [2, 9].

The prevalence of HD in the Western Population is of 5-13 cases per 100,000 people [10, 11]. There are exceptions in areas where there is a larger population of patients with HD, such as the region around Lake Maracaibo in Venezuela, which has a prevalence of 7 cases per 100 people [12]. Although the worldwide prevalence of HD is low, this disease is characterized by severe symptoms, including motor impairment, cognitive decline, and psychiatric disorders [1, 3].

Motor disturbances arise in two phases: a hyperkinetic and a hypokinetic one. The initial hyperkinetic phase consists of involuntary movements of the limb and facial muscles. As the disease progresses, this symptom diminishes and hypokinetic impairments such as bradykinesia and incoordination become more prominent. Common motor dysfunctions additionally include postural instability and changes in gait and muscular tonus [13, 14]. Collectively, these features lead to a progressive limitation in the ability to perform voluntary movements. Regarding cognitive dysfunction, the most frequently observed symptoms consist of impairment in executive functions and difficulty in the acquisition of new motor skills [1, 15]. On the other hand, the major psychiatric features of HD include depression, irritability, aggressiveness and, in later stages of the disease, apathy [9].

Aside from these classical manifestations, studies increasingly demonstrate the role of peripheral alterations in the pathology of HD. As such, patients frequently present weight loss, muscle atrophy, impaired insulin production, osteoporosis, and cardiac failure. Interestingly, cardiac failure is one of the primary causes of death in patients with HD [1, 14].

Additionally, several systems, molecules, and mediators have formerly been associated with the pathophysiology of HD. Among these, there are mitochondrial dysfunctions [16], oxidative stress [16, 17], neuroinflammation [18], and

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1875-5305/20 $65.00+.00

alterations in the glutamatergic [19, 20] and dopaminergic systems [21-24]. Furthermore, it has been demonstrated that the Renin-Angiotensin System (RAS) might be disturbed in HD [25-28].

The RAS is a complex peptide hormone system classically associated with the regulation of renal and cardiac physiology [29, 30]. However, all of its components have been characterized in the Central Nervous System (CNS) and exist independently of the peripheral RAS [31-33]. In this context, the components of the RAS have been implicated in neuropsychiatric and neurodegenerative disorders, such as depression and anxiety [34-36], Alzheimer's [37-39], Parkinson's [40-42] and Huntington's diseases [25-28].

The classical RAS pathway initiates with angiotensinogen cleavage by renin, which originates Angiotensin I (Ang I). The Angiotensin-Converting Enzyme (ACE), in turn, converts Ang I to Angiotensin II (Ang II), a physiologically active peptide of the system. Ang II is able to exert its functions through the Ang II Type 1 receptor (AT_1) or the Ang II Type 2 receptor (AT_2). Opposite physiological responses can be seen according to the receptor with which Ang II binds; however, the AT_1 receptor is the primary mediator of Ang II effects [30, 43]. Further degradation of Ang II leads to the production of angiotensin III (Ang III), which presents similar actions to Ang II and binds mainly to the AT_1 receptor [43]. Moreover, cleavage of Ang III by aminopeptidase N produces the biologically active Angiotensin IV (Ang IV) peptide, the ligand for the Angiotensin IV receptor (AT_4). Alternatively, this peptide can be formed by aminopeptidases acting directly on Ang I or Ang II [29, 31, 43].

The current concept of RAS includes, in addition to the classical components, a homolog of ACE [Angiotensin-Converting Enzyme 2 (ACE2)], angiotensin-(1-7) [Ang-(1-7)], Mas receptor and, more recently, Alatensins (Angiotensin A and Alamandine) [44-46] and Mas-related G-protein coupled receptor, MrgD [46]. ACE2 and other enzymes (endopeptidases, for example) can form Ang-(1-7) directly or indirectly from either the decapeptide Ang I or from Ang II. Ang-(1-7) is a biologically active heptapeptide that binds to the G-protein–coupled receptor Mas [47], which is mainly expressed in the brain and testis but also in the kidney, heart, and blood vessels [48, 49].

In the CNS and, specifically, in neurodegenerative disorders, ACE/Ang II/AT_1 receptor axis is generally associated with neurodegeneration, as it promotes the accumulation of inflammatory markers, the increase in oxidative stress and cognitive impairment, and the decrease on neuronal survival. Besides, it has been reported that activation of this axis increases amyloid β–peptide production and tau phosphorylation in Alzheimer's disease and dopaminergic neurodegeneration in Parkinson's disease, reduces Long-Term Potentiation (LTP) and is related to learning and memory impairments [32, 33, 37-42, 50-54]. On the other hand, the counterregulatory axis formed by ACE2/Ang-(1-7)/Mas receptor present neuroprotective effects, such as decrease in neuroinflammation, decrease in oxidative stress, cognitive improvement, increase in neuronal survival, decrease in β–peptide formation and tau phosphorylation, improvement of LTP and learning and memory [33, 37, 41, 55, 56]. The activation of the AT_2 receptor by Ang II presents similar actions to the activation of the Mas receptor by Ang-(1-7) and counterbalances the effects of the AT_1 receptor activation, exerting mainly neuroprotective effects. Then, activation of AT_2 has been associated with increased neuronal survivor, cognitive improvement, decreased neuroinflammation and oxidative stress, and with learning and memory [33, 51, 57-59]. Ang IV, acting *via* the AT_4 receptor, presents a role in learning and memory. This peptide facilitates LTP, memory consolidation, novel object recognition, and spatial memory [60-64]. The role of Alatensins has not yet been evaluated in neurodegenerative disorders.

Furthermore, it is well established that the RAS interacts with several neurotransmitter systems, including the dopaminergic and the glutamatergic ones. On the dopaminergic system, Ang II facilitates dopamine release *via* the AT_1 receptor [65-68]. Similarly, Ang-(1-7) stimulates dopamine release [69] and ACE inhibition leads to an increase in extracellular dopamine [70]. As for the glutamatergic system, Ang II also increases the neurotransmitter levels *via* the AT_1 receptor [71, 72].

Considering that blockage of classic components of the RAS (Angiotensin Receptor Blockers and ACE inhibitors) or activation of ACE2/Ang-(1-7)/Mas receptor axis components leads to neuroprotection in CNS disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and traumatic brain injury [33, 73-75], the modulation of the RAS may be an interesting therapeutic strategy for treatment of HD. Therefore, the present review focuses on describing the participation of the RAS components in Huntington's disease.

2. RENIN-ANGIOTENSIN COMPONENTS IN HUNTINGTON'S DISEASE

In the late 1970s, Arregui *et al.* investigated ACE activity in the striatum and substantia nigra of HD patients, as these two brain regions present the highest levels of ACE activity in the human brain [25, 26]. Considering that HD neuropathology is characterized by neuronal death in the striatum and, secondarily, in the substantia nigra, with consequent loss of nigrostriatal projections [76, 77], it was expected that ACE activity in the before mentioned brain regions was altered. Accordingly, a reduction in ACE activity was observed in the striatum as well as in the substantia nigra of HD patients' brain homogenates. In the striatal area, the enzyme's activity was reduced in the globus pallidus and in the caudate and putamen [25]. In the substantia nigra, the pars reticulate presented a more expressive reduction on ACE activity when compared to the pars compacta. Additionally, a smaller, but significant reduction of enzymatic activity was observed in the nucleus accumbens [26]. Correspondingly, Butterworth *et al.* identified a significant decrease in ACE activity in homogenates of the caudate nucleus of HD patients [78].

Controversially, Schweisfurth and colleagues demonstrated increased ACE activity in the cerebrospinal fluid of HD patients. The same study also indicated that the ratio of cerebrospinal fluid ACE to total protein, representing specific enzyme activity, was increased in HD patients [27].

The discrepancy between these studies could be explained by the different techniques employed. Three studies were performed with homogenates of brain areas of HD patients [25, 26, 78]. These brains were collected and stored frozen; however, the time between the collection of tissue and storage varied from 5 to 65 h. Longer intervals could lead to loss of enzymatic activity. This problem is not relevant to the lumbar puncture technique [27]. Nonetheless, the discrepant results could be related to the different SNC areas analyzed.

Alterations in the levels of angiotensin receptors AT_1 and AT_2 in brain homogenates of HD patients were also reported [57]. AT_2 receptor levels were increased by 90% in the caudate nucleus of HD patients, whilst AT_1 receptor levels remained unaltered. However, considering that AT_2 receptor is expressed at low levels in this brain region in non-pathological conditions, the increase of its expression in the brain of HD patients should be taken cautiously. In the putamen, AT_1 receptor levels were decreased by 30%, whilst AT_2 receptor levels were not significantly altered. In the substantia nigra, AT_1 and AT_2 receptors levels were not significantly different from control patients.

Additionally, it is known that there is variability in the age of onset in HD, which has been associated primarily with the length of the CAG repeat in the HTT gene [2, 9]. Nonetheless, the age of onset could also be related to an association between genetic and environmental factors. Panegyres and colleagues examined, among other genetic factors, the effect of ACE polymorphisms in the age of HD onset. However, ACE genotypes had no significance on the age of development of symptomatic HD [79].

One of the mechanisms implicated in HD pathology is mitochondrial dysfunction, with consequent release of reactive oxygen species, leading to neuronal death. 3-Nitropropionic acid (3-NP) inhibits complex II enzyme succinate dehydrogenase of the mitochondrial respiratory chain, inflicting mitochondrial damage. Therefore, it can reproduce some neuropathological features and symptoms observed in HD. Animals injected with 3-NP present striatal damage and can mimic the hyperkinetic and hypokinetic phases of HD, depending on time and dose administrated [80]. Hariharan *et al.* utilized the 3-NP model to test the effects of Trandolapril, an ACE inhibitor, on neurobehavioral, oxidative and mitochondrial impairment induced by 3-NP in rats. Considering that ACE inhibitors have been shown to be effective in preventing cognitive decline and reducing oxidative stress, it was hypothesized that Trandolapril would improve these features of the 3-NP rat model. Accordingly, treatment with Trandolapril attenuated weight loss and the impairments in memory and locomotion presented by 3-NP rats. Trandolapril also restored the levels of mitochondrial enzyme complexes, increased the levels of antioxidant enzymes and reduced lipid peroxidation. Finally, 3-NP animals treated with Trandolapril presented only mild degeneration in the striatal and hippocampal areas, whereas animals treated with solely 3-NP presented severe neurodegeneration in these areas [81].

Furthermore, it is known that the immune system plays a role in HD pathology since HD patients exhibit activation of the peripheral immune system and up-regulation of the innate immune system. The activation of adaptive immune responses and the presence of auto-antibodies in HD patients, however, have not been well characterized. Considering this, Lee *et al*., investigated the presence of anti-AT_1 receptors antibodies, known to play a role in inflammatory processes, in HD patients. HD patients presented higher anti-AT_1 receptor antibody levels when compared to control subjects, which implies an increase in the adaptive immune system activation. Additionally, the higher the antibodies level, the earlier was the disease onset. The presence of anti-AT_1 receptor antibodies, however, could not be related to the length of CAG repeat or with motor and cognitive function [82].

Neurons from mouse models for HD present altered electrophysiological properties, which could contribute to neuronal dysfunction and neurodegeneration. The effects of Ang II and Ang-(1-7) in this neuronal dysfunction, however, had not been characterized in HD. Because of that, de Mello *et al*. investigated the effects of Ang II and Ang (1-7) utilizing immortalized progenitor striatal cell lines expressing mHTT [28]. Ang II decreased the potassium current, hence increasing the resting potential, in control cells. In mHTT expressing cells, however, Ang II had a negligible effect on potassium current. This reduced effect of Ang II on potassium currents in HD cells could be related to the decreased expression of AT_1 receptor in these cells. On the other hand, Ang (1-7) decreased the potassium current in mutant cells, an effect mediated by the Mas receptor. In control cells, the same peptide evoked a small, but significant, increase of potassium current. These results suggest that mHTT expressing striatal cells are highly sensitive to Ang-(1-7) and that the effect of Ang II in these cells is negligible probably due to the reduced expression of AT_1 receptor [28].

Imamura and colleagues [83] analyzed the effect of Ang III, among other substances, on animal and cellular models for HD. Ang III exerted minor effects on the phenotype of the R6/2 mouse model for HD. This peptide reduced body weight decline suffered by R6/2 mice and prolonged its lifespan. However, Ang III did not improve R6/2 motor functions. Ang III treatment recovered the DNA damage of the striatal neurons of R6/2, yet, it did not reduce the frequency of inclusion bodies of mHTT in the striatum. These results indicate that Ang III inhibited the interaction between mHTT and its target physiological molecule but not by suppressing protein aggregation. On human neurons derived from induced Pluripotent Stem cells (iPS) of HD patients, Ang III improved dendritic length and restored dendritic spine density. However, this peptide did not reduce the number of inclusion bodies. In conclusion, Ang III exhibited therapeutic effects on HD that were independent of inclusion body formation [83]. Figure **1** summarizes the changes in the RAS components that can be associated with HD.

CONCLUSION

The results regarding the participation of the RAS components in HD are still inconclusive and need further investigation. Nonetheless, RAS is altered in the CNS in this disease, which suggests that this system participates in the

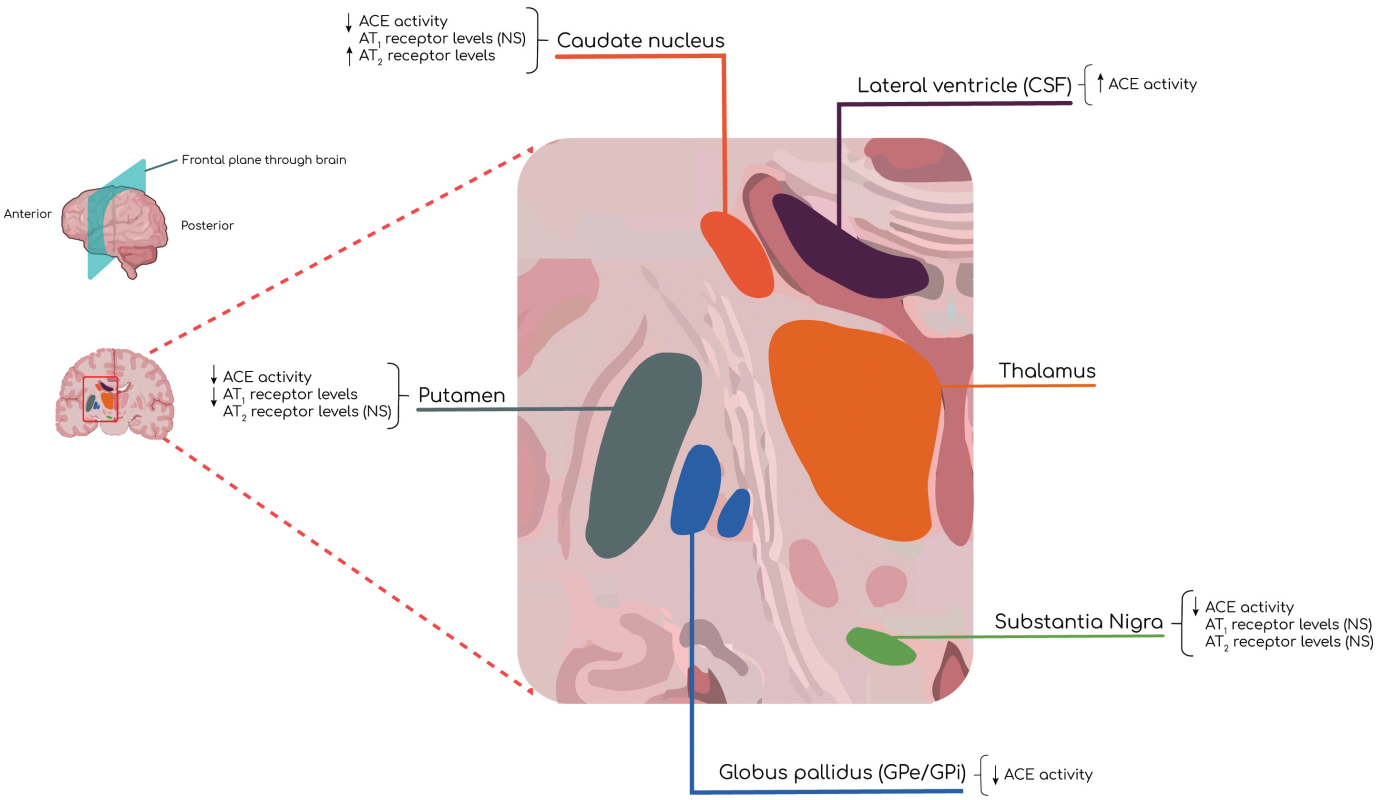

Figure 1. Changes in the renin-angiotensin system components within the Brain in Huntington's Disease. Abbreviations: ACE, angiotensin converting enzyme; AT_1, Angiotensin Type-1 receptor; AT_2, Angiotensin Type 2 receptor; CSF, Cerebrospinal Fluid; GPe, external Globus Pallidus; GPi, internal Globus Pallidus; NS, Non-Significant.

pathophysiology of HD. The characterization of RAS involvement in HD may lead to new therapeutic tools for the treatment of this disease.

LIST OF ABBREVIATIONS

3-NP	=	3-Nitropropionic Acid
ACE	=	Angiotensin-Converting Enzyme
ACE2	=	Angiotensin-Converting Enzyme 2
Ang I	=	Angiotensin I
Ang II	=	Angiotensin II
Ang III	=	Angiotensin III
Ang IV	=	Angiotensin IV
Ang-(1-7)	=	Angiotensin-(1-7)
AT_1	=	Angiotensin II type 1 receptor
AT_2	=	Angiotensin II type 2 receptor
AT_4	=	Angiotensin type 4 receptor
CNS	=	Central Nervous System
CSF	=	Cerebrospinal Fluid
HD	=	Huntington's Disease
HTT	=	Huntingtin
iPS	=	induced Pluripotent Stem cells
LTP	=	Long-Term Potentiation
mHTT	=	mutant Huntingtin
RAS	=	Renin-Angiotensin System

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study was funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil (Grant no. CNPq - #305382/2018-7) and Fundação de Amparo à Pesquisa de Minas Gerais, Brazil (Grant no. FAPEMIG - #APQ-00801-16).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Cristina Guatimosim is a productivity fellow from CNPq.

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