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The Mas Receptor as a Future Perspective in Parkinson's Disease

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Abstract

The current review sheds light on the importance of the cerebral renin angiotensin system (RAS) in Parkinson's disease (PD), as a neurodegenerative disorder. Local RAS has been identified in the nigrostriatal pathway and plays a pivotal role in the progression of PD *via* binding to the upregulated angiotensin II type-1 receptor (AT-1R). Activation of AT-1R induces an oxidative stress neuroinflammatory status that results in further deterioration of dopaminergic neurons. Mas receptor (MasR) together with AT-2R, are considered major components of RAS protective arm, which mediates actions opposing AT-1R activation. Accordingly, angiotensin converting enzyme-2 (ACE-2)/Angiotensin 1-7 (Ang 1-7)/MasR axis has been emerged as a novel therapeutic target to ameliorate the devastating effects of Ang II/AT-1R cue in a 6-hydroxydopamine (OHDA) lesioned PD model. Stimulation of MasR *via* its physiological ligand Ang 1-7 attenuated 6-OHDA induced neurotoxicity as evidenced by the improved motor performance and coordination along with the preservation of the dopaminergic neurons. *Via* enhanced MasR/PI3K/Akt/ CREB/ BDNF/TrKB neurogenesis cascade, besides both antioxidants and anti-inflammation mechanisms, Ang 1-7 proved its therapeutic benefits in PD, partly through MasR, to open up a new avenue for treatment.

Introduction

Parkinson's disease (PD) is the second leading most common neurodegenerative disease after Alzheimer's disease (AD) that is currently afflicting more than 1% of those older than 60 years and up to 4% of those older than 80 years[1]. PD is characterized by a progressive loss of the dopaminergic neurons in the substantia nigra pars compacta (SNpc) with the presence of intra-neuronal proteinaceous cytoplasmic inclusions of Lewy bodies. This results in a marked deficiency in striatal dopamine (DA) and the appearance of major clinical symptoms of PD namely; akinesia, muscle rigidity and resting tremor[2,3]. Currently, no cure or disease-modifying therapy that stops or slows disease progression has been proven in PD. Treatments for PD are not always effective in the early stage of PD, indicating that other approaches are needed to be uncovered to halt the progressive loss of SN dopaminergic neurons. Eventually, preserving viable nigrostriatal neurons could delay disease progression and prolong the efficacy of treatments[4].

Neurotrophic factors (NTFs) have shown effectiveness in neurodegenerative disorders including PD preclinical studies; however, their exact role to manage PD motor symptoms is still elusive. The goal of this mini-review is to gather the currently available data and to address the potential future prospects for Mas receptor (MasR)/ brain-derived neurotrophic factor (BDNF) activation as an innovative approach to manage PD.

Etiopathology of PD: role of BDNF

Several genes such as; alpha-synuclein (α-syn) and parkin are deleted or mutated of in the early onset familial PD, while in late-onset sporadic idiopathic PD, which accounts for most PD cases, environmental factors play the major role. Though the clinical phenotype of PD is relatively homogeneous, the pathogenic mechanism seems to be multifactorial. A constellation of events has been implicated in the degeneration of dopaminergic neurons in PD, including mitochondrial dysfunction, microglia activation, neuroinflammation, an enhanced oxidative milieu, accumulation of aberrant or misfolded proteins, and ubiquitin-proteasome system dysfunction[5,6].

A multitude of studies implicated an imperative role for BDNF and cAMP response element binding (CREB), among other protective factors, in regulating synaptic plasticity in PD. Indeed, BDNF supports differentiation, maturation, and survival of neurons in the CNS[7]. This trophic factor is co-localized with SN dopaminergic neurons to function as a neuronal preservative molecule in PD. Indeed, BDNF inhibition participates in the death of nigral dopaminergic neurons[8], since BDNF acts as a compensatory mechanism to halt the disease progression[9]. Actually, a 70% reduction in SNpc BDNF mRNA expression has been reported in both clinical[10] and neuropathological typical PD[11]. Recently in the pathogenesis of PD, α-syn-induces axonal dysfunction by impairing trafficking and signaling of BDNF as shown in a mouse PD model[12]. The DATATOP trial revealed a slower PD symptoms progression in early unmedicated PD subjects with the minor/minor rs6265 genetic BNDF variant that delayed the need for dopaminergic medications[13].

The partial deletion of the BDNF receptor tyrosine kinase B (TrKB), with the consequent suppressed BDNF biosynthesis, reduces SN neuronal count and tyrosine hydroxylase (TH) expression associated by α-syn deposition[14]. On the other side, dysfunctional mutated parkin overexpression prevents dopaminergic neuronal regeneration *via* the deactivation of the CREB pathway to contribute to PD[15].

Role of the brain local RAS in dopaminergic neuronal degeneration

In addition to the humoral classical and the intracrine renin-angiotensin system (RAS), a local RAS has been recognized in the basal ganglia[16]; the understanding of these systems can establish new perspectives for the management of RAS-related diseases, such as PD[17]. The local RAS in the basal ganglia includes high concentrations of angiotensin converting enzyme (ACE), angiotensin II (Ang II), angiotensin II type-1 receptor (AT-1R), AT-2R, prorenin receptors, and NADPH oxidase enzyme (Nox)[18]. Ang II is the main effector peptide of the RAS that acts *via* AT-1R and AT-2R[19]. Beside a cohort study in hypertensive patients that suggested a protective effect of the ACE-inhibitors (ACE-Is) for PD risk[20], a plethora of experimental data supports the involvement of brain RAS in dopaminergic neuronal degeneration in the SN[21,22]. The abnormal upregulation of local Ang II exacerbates neuro-inflammation and induces oxidative stress[23], hence, constituting early components of dopaminergic cell death by acting synergistically with other factors to progress PD[24,25]. Importantly, Nox inhibitors [26], as well as ACEIs[22,27] and AT-1R blockade[26,28] were reported to hinder neuronal loss in PD models. Of note, depletion of DA with reserpine or 6- hydroxydopamine (OHDA) provoked chronic dopaminergic denervation and increased the expression of AT-1R, besides the Nox-complex activity. These events were decreased as the DA function was restored[29] or upon the administration of levodopa (L-DOPA[30];).

ACE-2/Ang 1-7/MasR signaling cascade

In the brain, Ang 1-7 is primarily formed *via* the degradation of Ang II by ACE-2 to activate the MasR that is widely distributed in the cerebrum. It was located in the cerebral cortex, basal ganglia[31], in dopaminergic neurons, and glial cells in rat SNpc, as well as mesencephalic primary cultures[32]. The effects mediated by Ang 1-7 are in direct opposition to the actions of Ang II/AT-1R axis. Indeed, MasR can hetero-oligomerize with AT-1R to act as a direct antagonist[33] in the neurons[34] and microglia[35]. Moreover, Ang 1-7-mediated NF-κB inhibition has been also documented in several animal models, including hypertensive kidney disease[36], pulmonary fibrosis[37], and fatty liver disease[38].

The neuroprotective effect of Ang 1-7 was signified earlier in an ischemic stroke model[39] and in 2011, Mecca et al.[40], found that the intracerebroventricular infusion of Ang 1-7 attenuated the cerebral infarct size and neurological deficits elicited by endothelin-1-induced middle cerebral artery occlusion. Moreover, Ang 1-7 prevented Shiga toxin type 2-induced neuronal apoptosis, glial ultrastructural alterations, and demyelinated fibers in the rat corpus striatum[41]. Additionally, activation of ACE-2/Ang 1-7/MasR axis opposed AT-1R mediated apoptosis and reduced cognitive deficits in an AD[42]. Recently, Ang 1-7 inhibited the increase in cellular reactive oxygen species (ROS) produced by Ang II in dopaminergic neurons *in vitro*, confirming, thus, a neuroprotective role of the Ang 1-7/MasR axis[32].

Role of the Activation of the Ang-1-7/Masr Cue as a Therapy for PD

Local bone marrow (BM) RAS regulates hematopoiesis, erythropoiesis, and myelopoiesis, in addition to formation of monocytic and lymphocytic lineages. The local RAS affects tumor growth and metastases *via* the modulation of various carcinogenic events, including angiogenesis, apoptosis, cellular proliferation, immune responses, as well as cell signaling and extracellular matrix formation

in an autocrine and paracrine manner. Targeting local RAS actions could be a promising therapeutic potential for the management of neoplastic disorders[43].

In our study, a novel role for MasR activation by Ang 1-7 in PD has been established to open up a new avenue for the treatment of this neurodegenerative disease[44]. The unilateral intrastriatal Ang 1-7 post-administration improved motor performance and muscle coordination in a 6-OHDA PD model. Ang 1-7 was able to upregulate the striatal expression of MasR and stimulate the BDNF/TrKB axis. This was mediated by the activation of phosphoinositide 3-kinase /protein kinase B /CREB (PI3K/Akt/CREB) trajectory. Moreover, the MasR ligand Ang 1-7 preserved dopaminergic neurons by increasing SN TH immunoreactivity to enhance DA. Ang 1-7 also downregulated the striatal expression of AT-1R to halt neurodegeneration as indicated by the profound reduction in MAPK p38/NF-κB p65, as well as Nox/lipid peroxidation. Notably, both MasR cue activation and AT-1R cascade repression were in part reversed by the selective MasR antagonist A-779.

Conclusion

According to the previous data, we can conclude that activation of the MasR instigates survival dopaminergic neuronal signals and abrogates local RAS in the nigrostriatal pathway to advocate it as a potential therapeutic target for the management of PD.

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