Correlation between angiotensin 1-7-mediated Mas receptor expression with motor improvement, activated STAT3/SOCS3 cascade, and suppressed HMGB-1/RAGE/NF-əB signaling in 6-hydroxydopamine hemiparkinsonian rats

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Abstract

In the current investigation, a Parkinson's disease (PD) model was established by a single direct right intrastriatal injection of the 6-hydroxydopamine (OHDA) in male Wistar rats followed by 7 daily unilateral injection of angiotensin (Ang) 1-7 in the striatum. To confirm the putative role of Mas receptor (MasR), the selective antagonist A779 was also injected intrastriatally prior to Ang 1-7 injections and a correlation analysis was performed between MasR expression and the assessed parameters. Ang 1-7 upregulated MasR expression to correlate strongly with the improved rotarod ($r = 0.95$, $p = 0.003$) and spontaneous activity task ($r = 0.99$, $p < 0.0001$). This correlation extends to involve other effects of Ang 1-7, such as the increased striatal dopamine content ($r = 0.98$, $p = 0.0005$), substantia nigra pars compacta tyrosine hydroxylase immune-reactivity ($r = 0.97$, $p = 0.001$), active pY705-STAT3 ($r = 0.99$, $p < 0.0001$) and SOCS3 ($r = 0.99$, $p < 0.0001$). Conversely, Ang 1-7 inhibited inflammatory markers to correlate negatively with NF-əBp65 ($r = -0.99$, $p < 0.0003$) and its downstream targets, high mobility group box-1 (HMGB-1; $r = -0.97$, $p = 0.002$), receptor for advanced glycation end products (RAGE; $r = -0.98$, $p = 0.0004$), and TNF-Ŭ ($r = -0.99$, $p < 0.0003$), besides poly-ADP-ribose polymerase-1 ($r = -0.99$, $p = 0.0002$). In confirmation, the pre-administration of the selective MasR antagonist, A779, partially attenuated Ang 1-7-induced alterations towards 6-OHDA neurodegeneration. Collectively, our findings support a novel role for the anti-inflammatory capacity of the MasR axis to prove potential therapeutic relevance in PD via the upregulation/activation of MasR-dependent STAT3/SOCS3 cascade to negatively control the HMGB-1/RAGE/NF-əB axis hindering PD associated neuro-inflammation along with DA depletion and motor deficits.

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