

Title: Tyrosine phosphatase STEP is a key regulator of post-ischemic inflammatory response under hypertensive condition

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Background: Hypertension, the most common comorbid condition in stroke patients worsens stroke outcome. The canonical pathway of stroke-induced brain damage involves excessive glutamate receptor activation. Post-ischemic inflammation further contributes to the pathogenesis of stroke outcome under comorbid conditions. In earlier studies we developed a novel therapeutic target TAT-STEP, derived from the brain-enriched and neuron specific tyrosine phosphatase STEP, which has been shown to be effective in reducing stroke induced brain damage in the absence of any associated comorbidities. In the current study we evaluated the post-ischemic inflammatory pathways that contribute to the exacerbation of ischemic brain injury under hypertensive conditions and further assessed whether the STEP-derived peptide can attenuate such post-ischemic inflammatory response.

Methods: Transient ischemic stroke was induced in both normotensive and hypertensive rats by occlusion of the middle cerebral artery for 60 min followed by reperfusion. In a subset of these rats the STEP-derived peptide was administered intravenously at the onset of reperfusion. Coronal brain sections were processed for histopathological studies and cortical lysates from the ischemic hemisphere were processed for RNA preparation or immuno-blotting.

Results: Evaluation of ischemic brain damage by Fluoro-Jade staining show an early onset and exacerbation of ischemic brain damage under hypertensive condition. An early onset in post-ischemic inflammatory response is also evident under hypertensive condition that involves sustained activation of ERK MAPK/ADAM10 signaling in neurons, increased expression of the neuronal chemokine, CX3CL1 and specific cytokines, increased microglial activation and blood-brain barrier permeability. Restoration of STEP signaling attenuates these post-ischemic inflammatory responses.

Conclusions: The ability of the STEP-derived peptide to attenuate such increase in post-ischemic inflammatory response under hypertensive conditions could lead to a new direction for stroke treatment that could reduce the detrimental impact of inflammation in the early stages of ischemia, without affecting its beneficial factors in the recovery phase.

NON-EXPERT SUMMARY

Ischemic stroke is a leading cause of death and disability worldwide, and predisposition to comorbidities such as hypertension worsens stroke outcome. However, successful treatment for stroke remains a major challenge. The current study highlights the role of a novel peptide-based neuroprotectant TAT-STEP, in regulating post-ischemic inflammatory response that contributes to exacerbation of ischemic brain injury under hypertensive conditions. The findings emphasize the therapeutic potential of the STEP-mimetic in a spectrum of neurological disorders involving inflammation.

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