Title: A peptide mimetic of tyrosine phosphatase STEP: a potential therapeutic agent for treatment of stroke under hypertensive condition

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ABSTRACT

Background: Hypertension is a complex multifactorial disease that is influenced by both genetic and environmental factors. Although hypertension can develop at any age, the prevalence of hypertension is particularly evident in the aging population. It is also the most common comorbid condition in ischemic stroke patients and accounts for ~54% of all strokes. Despite advances in understanding the pathophysiology of stroke, current pharmacologic therapies are still limited to rapid reperfusion using thrombolytic agents, and neuroprotective approaches that can reduce the consequences of ischemic and reperfusion injury are still not available. To bridge this gap, we have evaluated the long-term efficacy of a novel peptide-based neuroprotectant TAT-STEP, derived from the brain-enriched and neuron specific tyrosine phosphatase STEP.

Methods: The study utilized spontaneously hypertensive (SHR) rats as an animal model of ischemic stroke, which was induced through transient occlusion of the middle cerebral artery for 60 min followed by reperfusion. The STEP-derived peptide (TAT-STEP) was administered intravenously 6h after the onset of the insult and brain infarct size was evaluated at 1, 7 and 28 days after the insult using the non-invasive magnetic resonance imaging (MRI) approach. Functional deficits were also assessed using a battery of motor, sensory and cognitive tests.

Results: Our findings show that a single intravenous administration of the peptide reduces mortality rate. In the surviving rats, MRI scans show significant reduction in infarct size and improvement of structural integrity within the infarcted area following peptide treatment. Behavioral assessments show significant improvement in motor coordination, sensory motor function and spatial memory following peptide treatment.

Conclusion: The study demonstrates for the first-time efficacy of a peptide mimetic derived from the tyrosine phosphatase STEP in attenuating ischemic brain damage under hypertensive condition and facilitating long-term recovery.

NON-EXPERT SUMMARY

Stroke is the second leading cause of death worldwide, and current pharmacologic therapies are limited to recanalization with thrombolytic agents. There is substantial need for the development of therapeutic agents to protect the brain from damage prior to and during recanalization and extend the therapeutic time window for intervention. The current study highlights the efficacy of a novel peptide based therapeutic agent in neuroprotection and long-term recovery from stroke-induced brain damage under hypertensive condition.

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