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Peroxynitrite could be a critical therapeutic target for preventing hemorrhagic transformation and poor outcome in ischemia-reperfused rat brains with delayed thrombolysis

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Aim: Tissue plasminogen activator (t-PA) is the only FDA approved drug for acute ischemic stroke, but its use is limited with the therapeutic time window within 4.5 hours and hemorrhagic transformation (HT). We aim to test the hypothesis that peroxynitrite ($ONOO^-$), a representative of reactive nitrogen species, could be a critical therapeutic target for preventing delayed thrombolytic HT and improving outcome in ischemic stroke. We tested whether peroxynitrite decomposition catalyst (PDC) could prevent such complication. Furthermore, we investigated that baicalin, a natural antioxidant, could scavenge $ONOO^-$ and prevent HT in ischemic stroke animal model with delayed t-PA treatment.

Methods: Male Sprague-Dawley (SD) rats were subjected to middle cerebral artery occlusion (MCAO) with t-PA (10 mg/kg) or t-PA plus FeTMPyP (3 mg/kg, a representative PDC) or baicalin (10, 25, 50 mg/kg) at MCAO for 2 or 5 h and reperfusion for 22 or 19 h, respectively. HT was assessed with hemoglobin assay. Neurological deficit was evaluated with Modified Neurological Severity Score (mNSS). Peroxynitrite was examined by detecting 3-nitrotyrosine (3-NT) and our newly developed high selective $ONOO^-$ fluorescent probe. The expression and activity of MMP-9/MMP-2 were assessed by Western blotting and gelatin zymography.

Results: T-PA infusion at 2 h after cerebral ischemia did not induce HT but attenuated neurological deficit, whereas at 5 h significantly induced HT and worsened neurological outcome. Co-treatment of FeTMPyP revealed to prevent HT and improve neurological functions. Early t-PA infusion at 2 h inhibited iNOS activity, $ONOO^-$ production, MMP-9/MMP-2 expression and activity, whereas delayed t-PA infusion at 5 h up-regulated iNOS activity, increased 3-NT formation, and down-regulated MMP-9/MMP-2 expression and activity. Co-treatment of FeTMPyP revised those changes in the ischemic brain with delayed t-PA infusion 5 h. Meanwhile, Baicalin revealed strong $ONOO^-$-scavenging activity and protected the neuronal cells from $ONOO^-$-induced neurotoxicity, reduced infarct size and attenuated apoptotic cell death and HT.

Conclusion: Peroxynitrite could be a critical therapeutic target for preventing hemorrhagic transformation and improving neurological outcome in ischemic brains with delayed t-PA treatment.

Biography

Jiangang Shen is a Professor in School of Chinese Medicine, University of Hong Kong. He also serves as Associate Director (Research) and Chair of Department of Research Postgraduate Students Committee in the School. His major research interests focus on molecular regulations of oxidative stress and redox signaling in brain damage and brain repair in post-stroke and neurodegenerative diseases. He is also interested in the experimental and clinical studies on Chinese herbal medicine for cerebral and cardiovascular diseases. His studies have been supported by many prestigious research funds from Hong Kong, Mainland China and others. He has published more than 150 peer-reviewed papers in prestigious academic journals and 14 book chapters. He has received many academic and research awards and appointed as honor professorship 15 universities from China and USA. He serves as the Editorial Board Members for many international academic journals including *Toxicology and Applied Pharmacology, Scientific Reports* and others.

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