Acetylcorynoline Combined with Low-Dose tPA Improves Thrombolytic Therapy in a Mouse Model of In Situ Thromboembolic Stroke

林欣璉[1]，傅如輝[1]
Hsin-Lien Lin[1], Ru-Huei Fu[1]

Graduate Institute of Immunology, China Medical University, Taichung 40402, Taiwan[1]

Recombinant tissue-type plasminogen activator (rtPA) is the only approved drug for the treatment of acute ischemic stroke to reduce thrombus formation in vivo, owing to its ability to converts plasminogen into the clot-dissolving protease plasmin. However, tPA also increases risks of intracerebral hemorrhagic transformation and excitotoxic neuronal cell death. Acetylcorynoline is the major alkaloid component derived from *Corydalis bungeana*, a traditional Chinese medical herb. It has been reported to have anti-inflammatory and anti-Parkinson properties, but no studies have yet described the effects of acetylcorynoline on acute ischemic stroke and the vascular and parenchymal effects of rtPA during ischemia. Here, we confirmed that acetylcorynoline significantly increases rtPA-mediated plasmin generation by using in vitro activity assays. In a mouse *in situ* thromboembolic stroke model, acetylcorynoline not only enhances thrombolysis efficacy by rtPA, but also attenuats tPA-driven leakage of the blood-brain barrier, mortality, brain infarction, and hemorrhagic transformation. Combination therapy with tPA and acetylcorynoline at 2 h post-ischemia lessened the effective dose required for tPA by three-fold. Combining acetylcorynoline with tPA also prolonged the time window for thrombolysis. Moreover, acetylcorynoline attenuates the pro-neurotoxic outcome of tPA, by blocking its interaction with N-methyl-D-aspartate (NMDA) receptors and NMDA-induced neuronal Ca^{2+} influx. Our current findings show a promising new approach for improving tPA-based thrombolytic stroke therapy.