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PAK01: A Synthesized Small Molecule That Enhances Reperfusion, Neuroprotection And Avoids Hemorrhagic Transformation In Rodent Models Of Thromboembolic Stroke

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Abstract:
Tissue-type plasminogen activator (t-PA) is currently the only approved drug by the US FDA for treating the acute ischemic stroke within 3 hours of symptom onset, despite the fact that the therapy may cause serious hemorrhagic transformations and neurotoxicity that leads to enhanced brain injury. Here we developed a synthesized small pseudopeptide, PAK01, to address efficacy and safety issues observed in t-PA treatment in acute ischemic stroke by covalently combining a free radical scavenger, a thrombus-targeted platelet aggregation inhibitor and a non-t-PA thrombolytic peptide into a single structure. The thrombolytic activity induced by PAK01 was confirmed in murine *in situ* thromboembolic stroke model where mice were anesthetized before thrombin is injected into middle cerebral artery to produce the clot formation (as described by Orset *et al*.). To induce reperfusion, PAK01 (7.5 mg/kg) or t-PA (10 mg/kg) was administered intravenously 20 minutes after thrombin injection. The results showed that both PAK01 and t-PA promote reperfusion in mice with middle cerebral artery *in situ* thromboembolic occlusion. Furthermore, PAK01 yields better treatment results in reducing infarct volume and neurological deficit with lower risk of hemorrhagic transformation when compared to that of t-PA. In addition, rattus carotid artery thrombosis model where 1.4 mg/kg of PAK01 was intravenously administered 4, 6, and 24 hours after stroke onset showed improvements in neuronal behavior outcome and reductions of brain infarct size. In contrast to 3 mg/kg of t-PA, no bleeding was observed even in 7 mg/kg of PAK01-treated animals. HPLC-FT/MS monitoring indicated that PAK01 can cross blood cerebral barrier. A distinct action mechanism out of plasminogen pathway was also explored. In conclusion, based on a new action mechanism the treatment potential of PAK01, a small molecule, in acute ischemic stroke through enhancing reperfusion and neuroprotection, as well as avoiding hemorrhagic transformation was demonstrated in *in vivo* studies.
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