STROKE

Can PSD95 inhibitors widen the therapeutic window?

Stroke is a leading cause of death and disability, and treatment options are limited. Currently, the only widely approved therapy is the reperfusion of occluded brain arteries with a fibrinolytic agent, but the therapeutic window for this strategy is limited to about 4.5 hours. Much effort has been put into the development of neuroprotective agents, but the translation of positive results in rodent studies to efficacy in higher-order brains has been very challenging. Now, two groups report promising results with inhibitors of postsynaptic density protein 95 (PSD95), providing new hope for a therapy that limits ischaemic injury and widens the therapeutic window for the treatment of stroke.

PSD95 is a synaptic scaffolding protein that forms a ternary protein complex with neuronal nitric oxide synthase (nNOS) and the *N*-methyl-D-aspartate receptor (NMDAR). This complex has a central role in mediating glutamatergic excitotoxicity, causing brain damage in the acute post-stroke period. The PSD95 protein interaction domains PDZ1 and PDZ2, which mediate the binding to NMDAR and nNOS, have shown promise as potential drug targets for the treatment of stroke in rodent models. Furthest in development is Tat-NR2B9c, which contains a peptide that binds to the PDZ domains of PSD95 and the HIV-1 Tat protein transduction domain to facilitate cell penetration.

Reporting in *Nature*, Tymianski and colleagues now show that Tat-NR2B9c also works in non-human primates. Cynomolgus monkeys were subjected to surgical middle cerebral artery occlusion (MCAO) and treated with Tat-NR2B9c by intravenous infusion 1 hour after the onset of MCAO. After 24 hours, treated animals were found to have a 55% reduction in infarct volume compared with saline-treated animals, and after 30 days there was a 70% reduction in infarct volume. This correlated with significantly improved outcomes in neurological assessments. In separate experiments, it was shown that Tat-NR2B9c is also effective in models of prolonged MCAO, and was still effective when treatment was delayed until 3 hours after the onset of MCAO. This indicates that treatment with a PSD95 inhibitor may constitute a clinically practical therapeutic strategy. Based on magnetic resonance imaging and neurological evaluations, the authors argue that there is also the potential for using Tat-NR2B9c as an early neuroprotectant to extend the benefits of reperfusion therapy beyond the 4.5-hour window.

Meanwhile, reporting in *PNAS*, Strømgaard and colleagues show that the binding affinity of Tat-NR2B9c can be significantly improved. The authors created a dimeric peptide, Tat-N-dimer, which binds simultaneously to the tandem PDZ1 and PDZ2 domains of PSD95. Compared to Tat-NR2B9c it displays a 1,000-fold increase in affinity for PSD95 relative to the monomeric Tat-NR2B9c, and increased stability in biological fluids. In a mouse model of stroke, the authors showed that a single intravenous injection of Tat-N-dimer, 30 minutes after the induction of permanent MCAO, reduced infarct volume at 6 hours by 40%, whereas Tat-NR2B9c or saline treatment had no effect. In behavioural tests, mice treated with Tat-N-dimer performed significantly better than Tat-NR2B9c- or saline-treated mice.


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These studies highlight the potential for neuroprotection via PSD95 inhibition in stroke, and clinical trials with Tat-NR2B9c are underway.

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ORIGINAL RESEARCH PAPERS Cook, D. J., Teves, L. & Tymianski, M. Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain. *Nature* 29 Feb 2012 (doi:10.38/nature10841) | Bach, A. *et al.* A high-affinity, dimeric inhibitor of PSD-95 bivalently interacts with PDZ1-2 and protects against ischemic brain damage. *Proc. Natl Acad. Sci. USA* **109**, 3317–3322 (2012)