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STROKE

Neuroprotection for patients with stroke moves one step closer to the clinic

Researchers in Canada have shown that poststroke administration of the neuroprotectant Tat-NR2B9c reduces infarct volumes and improves outcomes in cynomolgus monkeys. Despite promising results in rodents, "no neuroprotective strategy has ever been successfully translated to humans for acute stroke," says Mike Tymianski, who led the study.

Previous work by the group had established a central role for postsynaptic density protein 95 (PSD-95) in mediating the excitotoxic effects of glutamate during ischaemia in neurons. Tat-NR2B9c is a polypeptide that prevents PSD-95 from interacting with *N*-methyl-D-aspartate-type glutamate receptors, making the inhibitor a promising candidate for stroke treatment. "For this study, we used large primates with gyrencephalic brains, similar to those of humans," says Tymianski.

20 macaques received intravenous infusions of the drug or placebo 1 h after a 90-min middle cerebral artery occlusion (MCAO). Compared with the placebo group, infarct volumes in the Tat-NR2B9c group were significantly reduced at 24 h and 30 days, as measured by MRI.

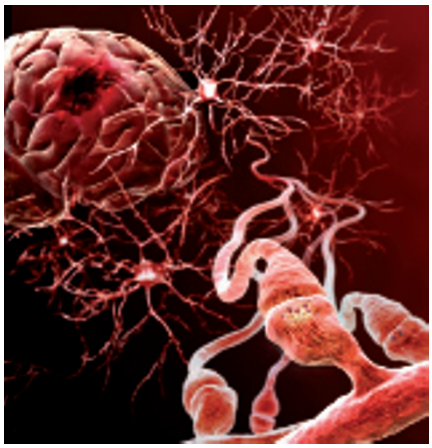

Image courtesy of M. Gail Rudakewich.

Neurobehavioural outcomes were also assessed over the 30-day observation period, using the nonhuman primate stroke scale (NHPSS) and a range of sensorimotor tasks. NHPSS scores were significantly improved in the Tat-NR2B9c group compared with the placebo group from 8 h after onset of MCAO, representing improved attention and perceptual ability in the treated macaques.

Importantly, the treatment also conferred benefit when administered as much as 3 h after a 3.5-h MCAO—a timeframe with potential for clinical translation.

Tymianski *et al.* also showed that the ischaemia-induced downregulation of several genes and pathways, including those involved in cytoprotective responses, was attenuated by Tat-NR2B9c treatment. "Given the similarity of the brains in this study to human brains, neuroprotection in humans should also be possible," says Tymianski. "Results of our Phase 2 trial of the compound are currently under review," he concludes.

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Original article Tymianski, M. *et al.* Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain. *Nature* doi:10.1038/nature10841