STROKE

Indip—a novel neuroprotective agent?

A new class of neuroprotective agents that target downstream proteins in the *N*-methyl-D-aspartate glutamate receptor (NMDAR) pathway may reduce neuronal damage after stroke or brain trauma. This finding, from Taghibiglou *et al.*, indicates the therapeutic potential of targeting the NMDAR pathway to treat stroke, despite the failure of NMDAR antagonists to reduce neuronal damage in clinical trials. "We developed a peptide inhibitor [and] demonstrated that systemic application of this peptide can significantly reduce the infarct volume and improve neurological performance" explains Yu Tian Wang, the study's lead investigator.

The researchers observed an increase in the activation of the transcription factor SREBP-1 following NMDAR-mediated excitotoxic events. SREBP-1 has an established role in sterol biosynthesis and lipid metabolism, and Wang and colleagues hypothesized an additional role for this protein in promoting neuronal damage. They discovered in a rat model that mature SREBP-1 is released following proteasomal degradation of the endoplasmic reticulum membrane protein INSIG-1 and, therefore, they designed an inhibitor of INSIG-1 degradation, called INSIG-1-derived interference peptide (Indip).

> "...neuronal damage was ... reduced in rats treated with Indip 120 min after transient middle cerebral artery occlusion..."

Wang's team found that Indip prevented NMDAR-dependent excitotoxic effects, through inhibition of SREBP-1 activation, in oxygen-deprived and glucose-deprived cortical neuronal cultures from rats (an *in vitro* stroke model). Furthermore, *in vivo* studies confirmed that administration of Indip 90 min before transient middle cerebral artery occlusion prevented SREBP-1 activation and reduced neuronal damage. The researchers also noted a marked improvement in the combined behavioral outcome of rats pretreated with Indip compared with that in controls. Crucially, neuronal damage was also significantly reduced in rats treated with Indip 120 min after transient middle cerebral artery occlusion, which suggests that this agent has neuroprotective therapeutic potential after stroke.

"Given that excitotoxicity is thought to be a common neuropathology associated with a large number of neurological disorders ... our study may have broad implications beyond stroke and raises the potential for designing new therapeutics for clinical treatment of these neurological disorders," write the authors. They next want to determine the precise mechanisms by which activation of SREBP-1 leads to neuronal damage following stroke and they plan to conduct further tests to assess the clinical potential of Indip as a stroke treatment.

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Original article Taghibiglou, C. *et al.* Role of NMDA receptor-dependent activation of SREBP1 in excitotoxic and ischemic neuronal injuries. *Nat. Med.* **15**, 1399–1406 (2009)