STROKE

S-roscovitine—a potential neuroprotectant for stroke

A drug that targets cell cycle proteins could protect the brain from injury after stroke, according to new research conducted in France by Serge Timsit and colleagues. The team showed that the cyclin-dependent kinase (CDK) inhibitor *S*-roscovitine could cross the blood–brain barrier and provide neuroprotection to the brain when delivered systemically in animal models of stroke.

"This work stems from studies concerning apoptosis, stroke and the cell cycle," explains Timsit. "According to the so-called 'cell cycle theory of neuronal apoptosis', cell cycle proteins are re-expressed in dying neurons in the adult brain."

After demonstrating in mice that *S*-roscovitine could reduce the volume of infarcts caused by permanent distal middle cerebral artery occlusion, the researchers turned their attention to a rat model of transient focal ischemia, which is believed to be a more accurate mimic of human stroke. Compared with a drug vehicle control, *S*-roscovitine was found to reduce the size of the resulting brain infarct when administered either 15 min before or 2 h after middle cerebral artery occlusion, with lower doses (1 mg/kg/h or 5 mg/kg/h) tending to produce stronger neuroprotection than a high dose (10 mg/kg/h).

The neuroprotective effects of *S*-roscovitine seem to be mediated, at least in part, through inhibition of CDK5, which is not thought to be directly involved in the normal cell cycle but has been implicated in the regulation of neuronal death and survival. In their mouse stroke model, Timsit and colleagues found that systemic administration of *S*-roscovitine could attenuate an increase in CDK5 activity that was usually detectable 3 h after artery occlusion.

Previous attempts to translate putative neuroprotective therapies from the laboratory to the clinic have met with little success, possibly owing to deficiencies in the design of the preclinical studies. To address this problem, the Stroke Academic Industry Roundtable (STAIR) has issued a set of guidelines in an attempt to enhance the quality of preclinical studies of potential stroke therapies. According to Timsit, "the STAIR recommendations were of great help in designing our methodology—our study successfully meets seven of the 10 STAIR criteria."

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The researchers acknowledge that further preclinical studies are required to assess the long-term efficacy of *S*-roscovitine, and to test whether the drug has beneficial effects on animal behavior. "After completion of these complementary preclinical studies—and if, of course, our results are encouraging—we will move forward towards clinical development," says Timsit.

Heather Wood

Original article Menn, B. *et al.* Delayed treatment with systemic (S)-roscovitine provides neuroprotection and inhibits *in vivo* CDK5 activity increase in animal stroke models. *PLoS ONE* **5**, e12117 (2010)