Letter to the Editor

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Targeting the Sphingolipid Signaling Pathway in Stroke

To the Editor:

We congratulate Hasegawa et al.1 for their innovative and thoroughly conducted study on the neuroprotective effect of the immunomodulatory sphingosine 1-phosphate (S1P) analog FTY720 (fingolimod) in a rat stroke model. Making use of a selective agonist of S1P receptor-1 (S1P1) and an antagonist selective for the sphingosine 1-phosphate receptors S1P3 and S1P6, they identified S1P1 as the crucial receptor that mediates the reduction of lesion size and the improved outcome after treatment with FTY720.

Besides the new mechanistic insight concerning the protective signaling pathway in stroke, this study corroborates the finding that the sphingolipid mediator FTY720 has a strong neuroprotective effect in experimental stroke, which has already been shown in mice by Shichita et al.2 and our group.3 Also, Wacker et al.4 described that cerebral ischemia induces sphingosine kinase-2, the enzyme responsible for the phosphorylation and thus activation of FTY720, which is abundantly expressed in the brain.5 They found that inhibition of sphingosine kinase-2 could abolish the protective effect afforded by hypoxic preconditioning, whereas pretreatment with FTY720 before middle cerebral artery occlusion could mimic hypoxic preconditioning and co-application of hypoxic preconditioning and FTY720 led to an even greater reduction of lesion size after middle cerebral artery occlusion. These data are all the more exciting because FTY720 has already been applied to patients in clinics to treat multiple sclerosis6 and is currently tested in phase III trials. Spurred by this success, the industry has made efforts to develop more selective S1P agonists for the 5 known S1P receptors.

Hasegawa et al.1 did not discuss the strong immunosuppressive effect of FTY720 and its implications in stroke. FTY720, a synthetic derivative of the fungal metabolite myriocin, is a prodrug. To become active as a structural analog of S1P, it needs to be phosphorylated almost exclusively by sphingosine kinase-2 and acts on 4 of the known 5 S1P receptors, which are expressed in all tissues in varying ratios. Starting in the 1990s, it was first evaluated in animal models and clinical studies of organ transplantation, where it led to an instant and sustained near-complete depletion of all lymphocytes with a predominance of T lymphocytes. These findings were also confirmed in the stroke model by Shichita et al.2 and our group.3 Another important characteristic of FTY720 and other S1P analogs is the endothelial barrier-modulating properties that have been well-evaluated in a murine model of sepsis-associated lung edema.7 However, unexpectedly, in our study the early alteration of blood–brain barrier permeability to albumin in the first 2 hours after middle cerebral artery occlusion was not clearly influenced by FTY720. Given the growing knowledge on the importance of the infiltration of peripheral immune cells into the ischemic brain lesion8 and the cerebral injury-induced immunosuppression,8 it will be of great importance to discern whether the neuroprotective effect of FTY720 and other S1P analogs is attributable to a reduced infiltration of immune cells or direct protection of the blood–brain barrier, or even additional neuroprotective effects.

Disclosure

None.

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