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 S1P0, 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 Another important characteristic evaluated in animal models and clinical studies of organ transplantation is the endothelial barrier-modulating properties that have been well-evaluated in a murine model of sepsis-associated lung edema.4 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 lesion5 and the cerebral injury-induced immunosuppression,6 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.

Waltraud Pfeilschifter, MD
Department of Neurology and Department of General Pharmacology and Toxicology
University Hospital Johann Wolfgang Goethe-University
Frankfurt am Main, Germany

Bozena Czech, MSc
Department of General Pharmacology and Toxicology
University Hospital Johann Wolfgang Goethe-University
Frankfurt am Main, Germany

Tobias Neumann-Haefelin, MD
Department of Neurology
University Hospital Johann Wolfgang Goethe-University
Frankfurt am Main, Germany

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Waltraud Pfeilschifter, Bozena Czech and Tobias Neumann-Haefelin

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