Thorsten Döppner

Effects on TAT-Bcl\textsubscript{xl}-mediated neuroprotection on endogenous neurogenesis after focal cerebral ischemia in mice

Stroke still remains the third leading cause of death and the leading cause of long-term disability in the Western world. Increased knowledge of the pathophysiological mechanisms underlying ischemic stroke led to new experimental approaches and strategies; one of them focuses on an improvement of endogenous neurogenesis, which has also been observed within the subventricular zone (SVZ) and the dentate gyrus (DG) of the adult brain.

In this study, effects of the anti-apoptotic membrane permeable protein TAT-Bcl\textsubscript{xl} on endogenous neurogenesis, neuroprotection and functional post-ischemic outcome were analysed in a model of focal cerebral ischemia in mice. Immunohistochemical analysis of neuronal density and injury showed that TAT-Bcl\textsubscript{xl} treatment led to a significantly higher neuronal density and lower neuronal injury within the basal ganglia (BG) than in controls on day 4 (control: 540 ± 171, TAT-Bcl\textsubscript{xl}: 178 ± 59 TUNEL\textsuperscript{*} cells/mm\textsuperscript{2}) but not on day 28 after induction of cerebral ischemia. Focal cerebral ischemia led to an increase/induction of cell proliferation in the ischemic BG, SVZ and hippocampal formation as could be assessed after 5-bromo-2´-deoxyuridine-5´-monophosphate (BrdU) labelling. However, no difference in the number of BrdU\textsuperscript{*} cells between control and TAT-Bcl\textsubscript{xl}-treated animals could be observed, neither on day 4 nor on day 28. Determination of the fate of differentiation of BrdU\textsuperscript{*} cells by means of double staining against different neuronal, oligodendro- and astroglial markers yielded no co-localization. Some cells, however, co-localized with the microglial marker IB4 on day 4, suggesting phagocytation rather than microglial co-expression of BrdU\textsuperscript{*} cells. Using the rota rod and tight rope test, TAT-Bcl\textsubscript{xl}-treated animals showed a reduced initial post-ischemic loss of motor function skills and an accelerated full functional recovery compared to controls. Additionally, TAT-Bcl\textsubscript{xl}-treated animals showed improved learning and spatial memory capabilities in a modified water maze test on day 27 and 28 after induction of cerebral ischemia.

TAT-Bcl\textsubscript{xl} reduces cerebral ischemic injury after 4 days, accelerates motor coordination recovery and improves learning and spatial memory capabilities. However, further studies will be necessary to analyse TAT-Bcl\textsubscript{xl}-mediated effects on cell proliferation and endogenous neurogenesis after cerebral ischemia.