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Diplom Biologin

Neuroprotective Effects of Exogenous Brain-Derived Neurotrophic Factor after Transient Forebrain Ischemia in Rats

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We investigated the effect of brain derived neurotrophic factor (BDNF) on neuronal degeneration, hippocampal long-term potentiation (LTP) and cognitive functions after global cerebral ischemia in the rat. After four-vessel occlusion, BDNF was continuously administered intracerebroventricularly *via* an osmotic minipump. For histological analyses, rats were sacrificed up to 7 days after ischemia and neuronal degeneration was estimated by TUNEL staining. Additionally, the glial reaction was investigated immunohistochemically and by measuring the activation of immunological nitric oxide synthase (iNOS) protein expression. Post-ischemic intracerebroventricular infusion of BDNF prevented neuronal death in the vulnerable CA1 region of the hippocampus. BDNF was demonstrated to inhibit the iNOS expression in hippocampus and prevented the activation of astroglia and macrophage infiltration associated with neuronal death.

The BDNF action on cognitive functions was analyzed repeatedly with a passive avoidance test, a hole-board test, and an activity center on the same animal. Transient forebrain ischemia resulted in a significant decrease in spatial discrimination performance but not of associative memory. The ratios for working memory (WM) and reference memory (RM) 15 days after ischemia were lower in the ischemic rats than in the sham operated control animals (WM = 22 ± 6 *vs*. 72 ± 7; RM = 30 ± 7 *vs*. 72 ± 5). Post-ischemic intracerebroventricular BDNF infusion increased both WM (63 ± 4) and RM (58 ± 5). The spontaneous locomotor activity did not differ significantly in all three groups.

Electrophysiological experiments were performed 14 days after cerebral ischemia. Test stimuli and tetanization were delivered to the Shaffer collaterals of the hippocampus and field excitatory post-synaptic potentials (fEPSP) were recorded in the CA1 region. In sham operated animals LTP was consistently induced after delivering a tetanus (increase of initial fEPSP slopes to 174 ± 11% of baseline). After transient forebrain ischemia LTP could not be induced (115 ± 8% of baseline). In ischemic animals treated with BDNF, LTP could be induced (165 ± 15% of baseline).

These data indicate a protective effect of BDNF on neuron degeneration, synaptic transmission and cognitive functions after transient forebrain ischemia and suggest a therapeutic potential of BDNF in cerebral lesions.