Erythropoietin overcomes deficiencies in hippocampal precursor cell generation and short term memory

Heumann R (1), Leske O (2), Manns M (3), Gassmann M(4,5), Wolfer DP (5,6,7), Lipp HP (6), Bichler Z (1)

(1) Ruhr University Molecular Neurobiochemistry, Bochum, Germany.
(3) Ruhr University Institute for Cognitive Neuroscience, Bochum, Germany.
(4) Institute of Veterinary Physiology, Vetsuisse Faculty, Switzerland.
(5) Zurich Center for Integrative Human Physiology (ZIHP), Zurich, Switzerland.
(6) Institute of Anatomy, University of Zurich, Zurich, Switzerland.
(7) Institute for Human Movement Sciences, ETH Zurich, Switzerland

In the adult mammalian brain the production of new neurons is observed, yet is mainly restricted to the olfactory system and the hippocampal formation. However, its physiological and behavioural role is still debated. We have developed transgenic mice expressing permanently activated Ras under the direction of the neuronal promoter for synapasin-1 (named synRas mice) (1). In these mice the proliferation of adult progenitor cells is dramatically reduced in the dentate gyrus of the hippocampus but not in the subventricular region generating precursor cells for olfactory neuron turnover. Impaired hippocampal progenitor proliferation in synRas mice is associated with reduced spatial short-term memory assessed in the 8-arm radial maze (2). The growth factor erythropoietin (EPO) and erythropoietin receptors (EPOR) are expressed in the nervous system and peripherally administered EPO crosses the blood-brain barrier stimulating injury-induced neurogenesis and neuronal differentiation (3). When breeding synRas with mice overexpressing EPO in the brain, the reduced spatial short-term memory abilities were completely restored to the level of wt animals as judged from the 8-arm radial maze assay. Wt and EPO-expressing mice showed identical levels of short term memory performances. After peripheral injections of EPO protein in wt animals, doublecortin positive neuronal precursor cell numbers were enhanced and short term memory was improved. In conclusion, erythropoietin partially overcomes specific spatial memory deficiencies and reduced neuronal plasticity in the dentate gyrus of the hippocampus.

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