Modulation of hippocampal neurogenesis by neuronal activation of RAS in transgenic mice

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Although a number of factors are known to modulate adult neurogenesis, its mechanism of regulation is poorly understood. Proliferation and survival rate of newborn cells were measured in the dentate gyrus of synRas mice expressing constitutively activated V12-Ha-Ras in neurons (Heumann et al. 2000, J Cell Biol 151:153) at day 1 or day 28 after BrdU injection, respectively. Double labeling experiments using BrdU and glial fibrillary acidic protein (GFAP) or calbindin antibodies showed that the marked reduction in BrdU-labeled newborn cells found at day 1 was mainly due to a decrease in the neuronal subpopulation of synRas mice, as revealed at day 28. Consistently, the number of doublecortin positive cells was also strongly reduced in the subgranular zone of the dentate gyrus of synRas mice as compared to wt siblings. Furthermore, in synRas mice the number of caspase 3 positive cells was strongly reduced in the granule cell layer. In order to investigate if neurogenesis can be rescued in synRas mice we injected recombinant erythropoietin, intraperitoneally. The results show that erythropoietin partially reversed the blocked neurogenesis in the hippocampus of synRas mice.

Analysis of the spatial memory abilities in a radial maze task revealed that working memory errors were significantly increased in synRas mice. Breeding the synRas transgene into NMRI or C57Bl/6 x NMRI F1 mice, respectively resulted in the same behavioral phenotype, indicating that the effects of activated Ras were independent of the genetic background

These results support the hypothesis of a reduced adult neurogenesis by Ras that is activated in the neuronal granule cell layer of the hippocampus regulating specific working memory processes.

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