Genetic disruption of mineralocorticoid receptor leads to impaired neurogenesis and granule cell degeneration the hippocampus of adult mice

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Adrenal steroids affect neuronal birth and death in the hippocampus, a brain structure important for learning and memory. They act via two receptors: mineralocorticoid (MR) and glucocorticoid receptor (GR). We used genetic mouse models to dissect the effects of MR- and GR-mediated signaling on neuronal birth and death. MR KO mice were generated by homologous recombination. Since mice with overall disruption of the GR gene die perinatally, GR was studied in mice with a brain-specific GR KO using the Cre/loxP-recombination system. Neuropathological analyses exhibited a decreased density of granule cells together with a reactive activation of astrocytes in the hippocampus of adult MR but not GR KO mice. MR KO mice at postnatal day 8 (P8) did not reveal CNS pathology, indicating that corticosteroid signaling via MR is not necessary for the formation but for the maintenance of hippocampal integrity. Studies with proliferation marker Ki67 showed in adult MR KO mice a significant reduction of granule cell neurogenesis to 65% of controls. Neurogenesis was normal in adult GR KO mice, indicating that the basal rate of granule cell proliferation does not depend on steroid signaling mediated by GR. In summary, we could attribute long-term trophic effects of steroids on dentate granule cells to MR but not GR. This indicates that MR related alterations could participate in the pathogenesis of hippocampal changes observed in aging, chronic stress and major depression.
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