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ADULT NEUROGENESIS

Uncoupling the roles of VEGF

Vascular endothelial growth factor (VEGF) is required for angiogenesis and is known to influence adult hippocampal neurogenesis and hippocampus-dependent memory. Investigating whether these roles are linked, Licht *et al.* now show that VEGF promotes hippocampus-dependent memory independently of its effects on neurogenesis and angiogenesis, by increasing synaptic strength.

The authors used transgenic mice in which VEGF signalling could be conditionally and reversibly induced (by increasing *Vegf* expression) or repressed (by sequestering VEGF). As expected, overexpression of hippocampal VEGF for 1 week resulted in new blood vessel formation and an increased number of proliferating neuroblasts. Furthermore, BrdU staining revealed an increased number of mature neurons 4 weeks from the onset of VEGF overexpression, and at this time the mice showed enhanced hippocampus-dependent, contextual memory. The authors subsequently showed that this effect on memory was apparent as early as 5 days after VEGF induction, before the newborn hippocampal neurons could have integrated into the hippocampal network.

Conversely, suppression of VEGF signalling for different lengths of time impaired memory performance. However, VEGF suppression for 1–7 weeks did not result in loss of blood vessels or decreased neurogenesis. Together, these results suggest that the role of VEGF in hippocampus-dependent memory is independent of its effect on neurogenesis or angiogenesis.

To determine whether the memory-enhancing effects of VEGF were reversible, the authors induced hippocampal VEGF in mice for 1 month. One month later, the performance of these mice in a fear conditioning paradigm was indistinguishable from that of control mice. However, the mice still showed more newborn neurons and neuroblasts, and increased microvascular density compared with control mice. This suggests that VEGF is required for the maintenance of hippocampus-dependent memory and that this cannot be attributed to its effects on neurogenesis or angiogenesis, which seem to be irreversible.

So, what mechanisms might account for VEGF-induced memory improvements? The authors performed *in vivo* tetanic stimulation of the perforant path in mice 5–15 days after induction or suppression of VEGF activity, and recorded the activity of granule cells in the dentate gyrus. They found that VEGF overexpression reversibly increased long-term potentiation (LTP). Conversely, suppression of VEGF signalling abrogated LTP, and this was partially rescued when the suppression was terminated.

By examining the effects of VEGF induction and repression at specific time points, the authors were able to uncouple the different roles of VEGF. This has revealed that VEGF promotes hippocampus-dependent memory, not by adding new neurons or increasing hippocampal perfusion but probably by increasing the connectivity among existing neurons. These findings will add fuel to the debate about the relative contribution of neurogenesis to hippocampus-dependent memory.

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STOCKBYTE

ORIGINAL RESEARCH PAPER Licht, T. *et al.* Reversible modulations of neuronal plasticity by VEGF. *Proc. Natl Acad. Sci. USA* **108**, 5081–5086 (2011)

FURTHER READING Deng, W., Aimone, B. & Gage, F. H. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nature Rev. Neurosci.* **11**, 339–350 (2010)