Nature Reviews Neuroscience | AOP, published online 9 February 2011; doi:10.1038/nrn2997

MEMORY

A growing role for IGF2

Insulin-like growth factor 2 (IGF2) is important in body growth and development, but its role in the adult brain has not been established. It is highly expressed in the hippocampus, and Alberini and colleagues now show that in this region it has a crucial role in memory consolidation and can improve memory retention.

The authors showed that in rats, inhibitory avoidance training — a hippocampus-dependent learning task — increased hippocampal IGF2 mRNA and protein levels 20 h later. Double injections of antisense oligonucleotides against *Igf2* mRNA bilaterally into the hippocampus, immediately and 8 h after training, resulted in disrupted memory retention 24 h after training — an effect that could be prevented by simultaneous administration of recombinant IGF2. Antisense treatment 24 h and 32 h after training also impaired retention a day later, but the same injections 4 days after training had no effect. Thus, IGF2 is crucial in the hippocampus for memory consolidation during a prolonged, but limited, time window.

MACMILLAN

If IGF2 is crucial for memory retention, does increasing IGF2 levels improve it? Indeed, exogenously administered IGF2 administered into the hippocampus immediately after training enhanced memory retention measured up to 3 weeks later — a time at which vehicle-treated animals had already significantly forgotten the memory, indicating that IGF2 also prevents forgetting.

A consolidated memory can become transiently labile if it is reactivated, for example when an animal is asked to retrieve or recall the learned task; the memory needs to reconsolidate to be stabilized. IGF2 administered immediately after a retrieval test (24 h after training) improved memory 1 day later, whereas it had no effect when administered 24 h after training in the absence of such a reactivating test. This indicates that IGF2 promotes memory during reconsolidation.

The memory enhancing effect of IGF2 administration was mediated by the IGF2 receptor but not the IGF1 receptor, and required protein synthesis. A protein that is rapidly upregulated in activated synapses and that is required for long-term plasticity is activity-regulated cytoskeletal-associated protein (ARC), and bilateral hippocampal injections of an *Arc*-antisense 1 h before a retrieval test blocked the memory enhancing effects of IGF2 injections.

The authors showed that IGF2 treatment immediately after training was associated with increased synaptic levels of the AMPA receptor subunit GluA1 (but not GluA2) and activation of glycogen synthase kinase 3 beta (GSK3β), both of which could be blocked by simultaneous injection of an IGF2 receptor antibody. Moreover, blocking the function of GSK3 immediately after a retrieval test prevented IGF2-induced memory enhancement. In hippocampal slices, IGF2 treatment promoted long-term potentiation (LTP), and this effect was also blocked by pretreatment with an IGF2 receptor antibody.

These findings show that IGF2 has an important role in memory consolidation and that its effect requires synaptic activation of ARC, GSK3β and the GluA subunit. Moreover, they point to IGF2 as a potential target for cognitive enhancement therapies.

Leonie Welberg

ORIGINAL RESEARCH PAPER Chen, D. Y. *et al.* A critical role for IGF-II in memory consolidation and enhancement. *Nature* **469**, 491–497 (2011)