Nature Reviews Neuroscience | AOP, published online 5 December 2012; doi:10.1038/nrn3416

LEARNING AND MEMORY

Stressful pathways to memory

Stressful events are often better remembered than insignificant experiences. This is because glucocorticoids — hormones secreted into the blood stream by the adrenal gland during stress — enhance the stabilization of newly formed memories. The molecular pathways underlying this effect are incompletely understood, but a new study by Alberini and colleagues reveals the details of some of these pathways.

The authors used an inhibitory avoidance task to study the mechanisms by which stress influences learning in rats. In this task, rats received footshocks when they entered the dark compartment of a two-compartment chamber (the other chamber was light). To assess the animals' memory of this association, the authors tested the extent to which the rats subsequently avoided the dark chamber.

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Exposure to a footshock is a stressful event that is known to increase glucocorticoid levels in rats. The authors injected a glucocorticoid receptor antagonist (RU486) into the hippocampus just before each rat underwent training. Compared with vehicle-injected rats, RU486-injected animals showed impaired memory retention 7 days later. Interestingly, short-term memory retention, which was assessed 1 h after training, was not affected, and injection of RU486 immediately after training did not affect memory retention at 7 days. Thus, these results suggest that glucocorticoids rapidly and selectively affect the mechanisms that mediate long-term memory.

The hippocampus of vehicle-injected rats showed increases in the levels of phosphorylated cyclic AMP-responsive element-binding protein (CREB) and calcium/calmodulin-dependent protein kinase type II subunit-α (CaMKIIα) at 30 min post-training as well as other changes in memory-linked proteins, and some of these effects persisted for 20 h after training. These effects on CREB and CaMKIIα did not occur, however, in RU486-injected animals. RU486 did cause decreases in the levels of phosphorylated mitogen-activated protein kinase 3 (MAPK3), MAPK1, AKT and phospholipase Cγ at 30 min post-training (the levels of these phosphorylated proteins remained unchanged with training in the control rats). The phosphorylation of these four proteins can be activated by brain-derived neurotrophic factor (BDNF) and, accordingly, the authors found that RU486 treatment followed by training decreased the level of phosphorylated TRKB (tropomyosin-related kinase B; also known as NTRK2), the BDNF receptor. Together, these results suggest that glucocorticoid signalling exerts its effects on long-term memory formation through various pathways that are mediated by CaMKIIα, CREB and BDNF.

The authors found further evidence of a link between glucocorticoid and BDNF signalling in memory formation. Hippocampal injection of an anti-BDNF antibody just before training recapitulated many of the molecular changes induced by RU486 administered before training. Moreover, hippocampal injection of recombinant BDNF immediately after training in rats that had received RU486 just before the task rescued the impaired memory retention and reversed nearly all the molecular alterations that were associated with RU486 treatment.

This study provides evidence that hippocampal glucocorticoid receptors that are activated by glucocorticoids released during stress act rapidly to regulate long-term memory formation through various signalling pathways.

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ORIGINAL RESEARCH PAPER Chen, D. Y. *et al.* Glucocorticoid receptors recruit the CaMKIIα–BDNF–CREB pathways to mediate memory consolidation. *Nature Neurosci.* **15**, 1707–1714 (2012)