FEATURED ARTICLES

ZIP the memory shut

Neuroscience Gateway (September 2006) | doi:10.1038/aba1683

An unusual isoform of protein kinase C is necessary for the storage of long-term spatial memories.

Have you ever wanted to erase the memory of an embarrassing event? The first step would be to identify molecules that maintain long-term memory. Pastalkova *et al.* report the disruption of new and established long-term memories with an inhibitor to protein kinase M zeta (PKMz) in a recent article in *Science*.

PKMz is the catalytic subunit of protein kinase C zeta ([PKCz](#)), which is not regulated by calcium or diacylglycerol, unlike most isoforms of PKC. The authors blocked its constitutive activity with a synthetic z-substrate inhibitory peptide (ZIP) that mimics the regulatory subunit of PKCz.

ZIP inhibits long-term potentiation (LTP) in hippocampal slice cultures. ZIP also reversed LTP *in vivo*. Twenty-two hours after high-frequency stimulation to the perforant path, ZIP injection into the dentate gyrus blocked LTP in hippocampal regions more than 2 mm from the injection site.

ZIP also disrupted long-term memories. In the active place avoidance test, both memory acquisition and recall depend on the hippocampus. The authors placed rats on a slowly rotating platform and allowed them to explore the apparatus. During training, rats received shocks if they entered a 60-degree segment of the platform defined by the room, not the rotation. The rats learned to avoid this stationary shock zone despite the rotation of the platform. Twenty-four hours after repeated training sessions, the authors recorded the paths traveled by rats on the rotating platform without shocks. Control rats avoided the shock zone, but rats treated with ZIP before testing did not. However, rats treated with a scrambled ZIP peptide or the kinase inhibitor staurosporine avoided the shock zone similarly to control rats.

ZIP did not affect memory acquisition. Following long-term memory testing, the authors retrained the rats with shocks for one session and then immediately tested the rats without shocks. Like control rats, ZIP-treated rats avoided the shock zone.

The authors reasoned that if ZIP disrupted memory storage, then its effect would be permanent, but if ZIP disrupted memory retrieval, then its effect would be temporary. One week after training and vehicle or ZIP injection, the authors tested rats in a single training session. Vehicle-treated rats still avoided the shock zone, but ZIP-treated rats did not. Immunocytochemical analysis failed to detect biotinylated ZIP in the hippocampus, suggesting that ZIP-induced memory disruption persisted despite metabolism of the drug. Subsequent training reinstated the memory for at

least 24 hours. These data therefore suggest that PKM ζ is necessary for memory storage, not retrieval.

Thirty days after training, control rats still avoided the shock zone, but rats treated with ZIP two hours before testing did not. Therefore, PKM ζ activity in the hippocampus is important in the maintenance of established spatial memories. These data suggest that PKM ζ inhibitors may prove useful in treating diseases such as post-traumatic stress disorder and PKM ζ activators in treating diseases such as retrograde amnesia.

Debra Speert

1. Pastalkova, E. *et al.* Storage of spatial information by the maintenance mechanism of LTP. *Science* **313**, 1141–1144 (2006). | [Article](#) |