ally when hydrogen-terminated diamond was exposed to the atmosphere (*6*, *7*). In this electrochemical variant of surface transfer doping, the redox potential of the hydrated ions effectively determines the effective acceptor level of the electronic system (*8*).

There are several reasons why diamond is particularly susceptible to p-type transfer doping. First, its electron affinity can be tailored to the lowest value of all semiconductors by simple hydrogen termination of the surface bonds. Second, because no solid oxide is present on its surface, intimate contact with surface dopants is possible. Finally, the bulk conductivity is low and will not mask the effect of the transfer doping.

Under similarly favorable conditions, p-type surface transfer doping was very recently observed for silicon (*9*). In these experiments, the sheet conductivity of very thin silicon layers (10 to 40 nm) on top of a SiO substrate was measured. After appropriate preparation, the Si surface atoms rearrange and form rows of asymmetric dimers. With this reconstruction, unoccupied surface states close to the valence band maximum of silicon are formed; these states play the role of the LUMO, with an activation energy of 0.3 eV. [This energy is called "effective band gap" in (*9*).]

In the field of carbon nanotubes, surface transfer doping is in fact the method of choice for manipulating electronic conductivity. Nanotubes essentially consist of one or a few rolled-up sheets of graphene, and donors or acceptors are naturally positioned on the surface of these tubes rather than incorporated into the rigid graphene layers. The electrical conductivity of carbon nanotubes changes markedly upon exposure to different gases (*10*, *11*). In some cases, this behavior has shown striking similarities to electrochemical surface transfer doping of diamond (*12*).

Surface transfer doping thus appears to be the mechanism behind a variety of surface electronic phenomena. When controlled, it may become a valuable tool for engineering micrometer- and nanometer-scale electronic devices.

**References**


1. J. Ristein, *J. Phys. D: Appl. Phys.* **39**, R71 (2006).
2. P. Strobel *et al.*, *Nature* **430**, 439 (2004).
3. P. Strobel *et al.*, *Diam. Rel. Mat.* **14**, 451 (2005).
4. L. Hedberg *et al.*, *J. Phys. Chem. A* **108**, 4731 (2004).
5. F. Maier *et al.*, *Phys. Rev. Lett.* **85**, 3472 (2000).
6. I. M. Landstrass, K. V. Ravi, *Appl. Phys. Lett.* **55**, 975 (1989).
7. I. M. Landstrass, K. V. Ravi, *Appl. Phys. Lett.* **55**, 1391 (1989).
8. M. Riedel, J. Ristein, L. Ley, *Diam. Rel. Mat.* **13**, 746 (2004).
9. P. Zhang *et al.*, *Nature* **439**, 703 (2006).
10. P.G. Collins *et al.*, *Science* **287**, 1801 (2000).
11. J. Kong *et al.*, *Science* **287**, 622 (2000).
12. J. Foord *et al.*, *Diam. Rel. Mat.* **11**, 856 (2002).


10.1126/science.1127589

NEUROSCIENCE

# ZAP and ZIP, a Story to Forget

How are memories stored and retrieved? Long-awaited evidence shows directly that the strength of synaptic connections in hippocampal neurons underlies both processes.

**Tim V. P. Bliss, Graham L. Collingridge, Serge Laroche**

How do brains store memories? The leading candidate for the role is a form of synaptic plasticity known as long-term potentiation (LTP), a persistent increase in the strength of synapses linking interconnected neurons in cortical networks. LTP can be induced experimentally by the application of a brief train of electrical stimuli, known to practitioners of the art as the tetanus or ZAP (*1*, *2*). On pages 1093 and 1141 of this issue, Whitlock *et al.* and Pastalkova *et al.* substantially advance the case for LTP as a neural mechanism for memory (*3*, *4*). Both studies focus on LTP in the hippocampus, a region of the brain necessary for the formation of episodic memories in humans and for spatial learning and memory in rodents. Pharmacological or genetic manipulations that suppress the induction of LTP generally lead to impairment of spatial learning, as predicted by the LTP and memory hypothesis. But there has been little evidence for two other critical predictions: (i) Hippocampus-dependent learning should lead to observable LTP at hippocampal synapses, and (ii) suppression of LTP after learning a task should abolish the memory of that task. It is these gaps in the evidence for the LTP and memory hypothesis that are addressed in the new studies.

Enhanced online at www.sciencemag.org/cgi/content/full/313/5790/1058

T. V. P. Bliss is in the Division of Neurophysiology, MRC National Institute for Medical Research, Mill Hill, London NW7 1AA, UK. G. L. Collingridge is at the MRC Centre for Synaptic Plasticity, University of Bristol, Bristol BS8 1TD, UK. S. Laroche is at Neurobiologie de l'Apprentissage, de la Mémoire et de la Communication (NAMC), CNRS UMR 8620, Universite Paris Sud, 91405 Orsay, France. E-mail: tbliss@nimr.mrc.ac.uk; g.l.collingridge@bristol.ac.uk; serge.laroche@ibaic.u-psud.fr

An important advance was made earlier this year when an LTP-like increase in hippocampal synaptic responses was observed in mice that were trained in a hippocampus-dependent procedure known as trace eyeblink conditioning (*5*). Learning and synaptic potentiation both failed to develop in the presence of a drug that blocks the *N*-methyl-D-aspartate (NMDA) receptor, the glutamate receptor subtype that controls the induction of LTP (*6*). This finding strongly suggests that the potentiation is indeed LTP rather than some other facilitatory process.

This conclusion has now been further strengthened by the study of Whitlock *et al.*, who recorded from multiple sites in the hippocampus. The authors looked for evidence of LTP in rats that had learned to avoid entering the dark compartment of a two-compartment box where they had previously received a mild electric shock. The findings are illuminating. LTP was indeed observed, but at only a small proportion of recording electrodes. In a critical further experiment, Whitlock *et al.* show that after a ZAP, less LTP is seen at these electrodes than at those where no change was seen after learning. This partial occlusion of LTP establishes that the learning-induced potentiation is itself genuine LTP. The field response seen at each electrode reflects the activity of many neurons in the immediate vicinity and may conceal a combination of LTP at some synapses and its counterpart, long-term depression (LTD), at others. Whitlock *et al.* used a clever biochemical assay to differentiate between LTP and LTD, based on the fact that different phosphorylation sites on the GluR1 subunit of the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor are phosphorylated in LTP and LTD. After learning, changes in phosphorylation were seen that reflect LTP but not LTD. This is surprising, given the widely held view that LTP at one subset of synapses needs to be balanced by LTD at another subset to maintain stability in the hippocampal network. This finding suggests that other forms of activity-dependent depression are recruited.

But perhaps the biggest puzzle thrown up by this study is why LTP—given that it could be detected at all at the population level—was

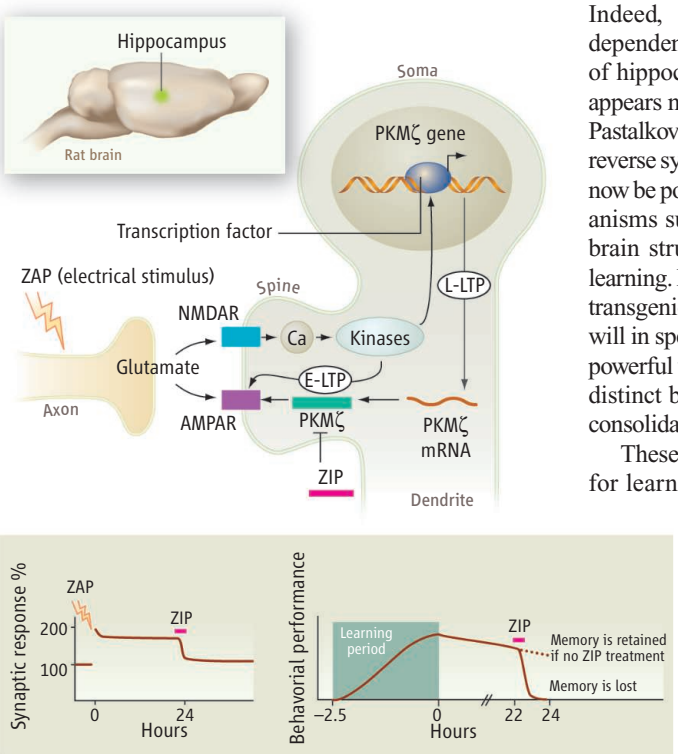
seen at only some electrodes. The assumption is usually made that memory is sparsely but uniformly distributed across the hippocampal neural network (*7*). The present results suggest instead a "currant-bun" model of memory storage, with clumps or hotspots of synaptic change concentrated in cell subpopulations that are themselves distributed so sparsely that only a small proportion of electrodes placed 0.25 mm apart are close enough to a hotspot to detect an increased response.

The transient nature of the biochemical changes noted by Whitlock *et al*. (*3*) suggests that the particular AMPA receptor phosphorylation states they examined mark only the early cellular events in the life of potentiated synapses. So what could be responsible for encoding longer-lasting changes? In the search for molecules that could be involved in the maintenance of LTP, a prime candidate called protein kinase M zeta (PKMζ) has recently emerged. PKMζ is the constitutively active, catalytic fragment of PKCζ, an atypical form of protein kinase C that does not require $Ca^{2+}$ or diacylglycerol for its activation. PKMζ is transcribed independently of PKCζ under the control of an internal promoter in the PKCζ gene, and its mRNA is then transported to dendrites (*8*). Here, PKMζ maintains the late, protein synthesis–dependent phase of LTP by increasing the number of AMPA receptors that are expressed at synapses (*9*). This area of research has been greatly advanced by the introduction of ZIP, a specific, membrane-permeant peptide that mimics the autoregulatory domain of PKMζ and thus acts as an inhibitor (*10*). ZIP blocks preestablished late-phase LTP when applied to hippocampal slices an hour or two after the induction of LTP, thereby demonstrating the importance of PKMζ in the maintenance of LTP (*11*).

Building on this observation, Pastalkova *et al*. have now used ZIP to eliminate synaptic potentiation in the dentate gyrus of the hippocampus in the awake rat after learning, to assess whether stored memory is lost. The authors first confirmed that ZIP effectively reverses established LTP when injected into the rat hippocampus 22 hours after LTP induction, without affecting baseline synaptic transmission, a prerequisite to their behavioral study. They were then able to reverse any LTP-like effect induced during learning, with the prediction that this would lead to retrograde amnesia. An avoidance task was used in which rats move on a slowly rotating circular platform containing a nonrotating shock zone defined by landmarks. Rats rapidly learn to avoid the shock zone whenever the rotating platform brings them close to it. Bilateral injection of ZIP into the hippocampus 22 hours after learning caused a complete and persistent loss of the acquired spatial memory. Thus, ZIP caused retrograde amnesia in this case. There was, however, no evidence that ZIP caused anterograde amnesia, because rats could relearn the task and form a long-term memory of it. Can ZIP affect a more remote memory? Evidently so, because the same loss of a previously established spatial memory was observed when ZIP was injected 30 days after learning. Hence, this study demonstrates that an agent that reverses synaptic potentiation by inhibiting PKMζ also erases an established memory.

Could ZIP potentially obliterate all established memories? A great deal of evidence suggests that the storage of episodic memories is eventually taken over by neocortical areas (*12*). Indeed, at 30 days some hippocampus-dependent memories are immune to blockade of hippocampal function (*13*), although this appears not to be the case for the task used by Pastalkova *et al*. (*4*). Using a similar strategy to reverse synaptic potentiation with ZIP, it should now be possible to test whether LTP-like mechanisms support memory storage in different brain structures and at different times after learning. Future studies could also benefit from transgenic strategies to turn ZIP on and off at will in specific cell types. This could provide a powerful way to address the function of LTP in distinct brain areas in processes of learning, consolidation, recall, and reconsolidation.

These new data support a two-phase model for learning and memory (see the figure). During learning, L-glutamate activates NMDA receptors in hippocampal neurons, and the associated $Ca^{2+}$ influx activates a variety of $Ca^{2+}$-dependent enzymes (kinases), triggering the early, protein synthesis–independent phase of LTP (E-LTP). This mechanism involves an increase in AMPA receptor function (*2*). In parallel, a signal passes to the nucleus and induces the transcription of PKMζ mRNA. The de novo synthesis of PKMζ maintains an increased number of AMPA receptors at potentiated synapses (L-LTP). The signal that leads to activation of PKMζ transcription during LTP is not known, although putative binding sites for transcription factors are present in the gene's promoter region. Zif268 is a transcription factor required for late-phase LTP (*14*), raising the pleasing prospect of a tale to tell of ZAP, ZIF, and ZIP.




**Learning hotspots in the brain.** Long-term potentiation (LTP), or enhanced synaptic strength, in the hippocampus underlies memory and learning. ZAP, or a train of electrical stimulation, induces LTP. The peptide ZIP abolishes LTP when infused into the rat hippocampus 22 hours after LTP is induced. Protein kinase M zeta is part of a neuronal signaling pathway that is involved in the maintenance of both late LTP (L-LTP) and memory.

CREDIT: P. HUEY/*SCIENCE*


**References**

1. T. V. P. Bliss, T. Lømo, *J. Physiol.* **232**, 331 (1973).
2. T. V. P. Bliss, G. L. Collingridge, *Nature* **361**, 31 (1993).
3. J. R. Whitlock, A. J. Heynen, M. G. Shuler, M. F. Bear, *Science* **313**, 1093 (2006).
4. E. Pastalkova *et al*., *Science* **313**, 1141 (2006).
5. A. Gruart, M. D. Muñoz, J. M. Delgado-Garcia, *J. Neurosci.* **26**, 1077 (2006).
6. G. L. Collingridge, S. J. Kehl, H. McLennan, *J. Physiol.* **334**, 33 (1983).
7. S. J. Martin, P. D. Grimshaw, R. G. M. Morris, *Annu. Rev. Neurosci.* **23**, 649 (2000).
8. A. I. Hernandez *et al*., *J. Biol. Chem*. **278**, 40305 (2003).
9. D. S. Ling, L. S. Benardo, T. C. Sacktor, *Hippocampus* **16**, 443 (2006).
10. D. S. Ling *et al*., *Nat. Neurosci.* **5**, 295 (2002).
11. P. Serrano, Y. Yao, T. C. Sacktor, *J. Neurosci.* **25**, 1979 (2005).
12. B. J. Wiltgen, R. A. M. Brown, L. E. Talton, A. J. Silva, *Neuron* **44**, 101 (2004).
13. I. Izquierdo, J. H. Medina, *Neurobiol. Learn. Mem.* **68**, 285 (1997).
14. M. W. Jones *et al*., *Nat. Neurosci*. **4**, 289 (2001).


10.1126/science.1132538





Published by AAAS