A Competitive Game of Synaptic Tag

LTP maintenance is thought to require an activity-dependent "synaptic tag" that allows potentiated synapses to sequester factors necessary for maintenance. In a paper in this issue of *Neuron*, Fonseca et al. show that synapses can compete with each other for such maintenance factors, so that additional potentiation of one input results in loss of potentiation of another. These data suggest that LTP maintenance is a dynamic and competitive process.

Learning theory has stressed the ability of experience to selectively modify individual synaptic weights (Martin et al., 2000). In this view, each synapse can act independently of the thousands of other synapses impinging on the same postsynaptic neuron, and this ability to act independently generates a huge capacity for information storage. But are synapses really such free agents, or do they instead operate in a global synaptic economy where the action of one influences all the rest? A number of recent observations support this latter view and suggest that changing the strength of one set of synapses leads almost inevitably to changes in others. Such heterosynaptic interactions can be highly complex. For example, potentiation of one set of synapses can lead to heterosynaptic depression of other nearby synapses, and vice versa (Lynch et al., 1977; Scanziani et al., 1996; Royer and Pare, 2003), while homeostatic forms of synaptic plasticity can adjust the strength of all synapses in response to changes in a few (Turrigiano and Nelson, 2004). In this issue of *Neuron*, Fonseca and colleagues now demonstrate a novel kind of heterosynaptic interaction between potentiated synapses, in which the maintenance of potentiation depends on competition between activated synapses for a protein synthesis-dependent factor (or factors) (Fonseca et al., 2004).

Generating persistent ($>$4 hr) hippocampal long-term potentiation (long, or L-LTP) requires transcription and protein synthesis, suggesting that signaling to the nucleus and generation of new proteins is essential for the long-term stabilization of synaptic modifications. Only strong activation of the postsynaptic neuron triggers such protein synthesis, so weak stimulation (or, by extension, activity of weak inputs) is not sufficient to generate L-LTP. It was demonstrated several years ago, however, that activation of a weak input in the few hours surrounding activation of a strong input leads to L-LTP of the weak input that can be induced even if the weak stimulation occurs in the presence of protein synthesis inhibitors (Frey and Morris, 1997). These and many similar observations at hippocampal synapses and at *Aplysia* sensorimotor synapses have led to the idea of a "synaptic tag" generated by active synapses that allows them to capture protein synthesis-dependent factors generated by a strong stimulus (Frey and Morris, 1998; Martin and Kosik, 2002). Such a mechanism avoids the necessity of routing proteins selectively to the potentiated synapses but generates some potential problems, because weak inputs can stabilize themselves by piggybacking on strong inputs. This spread of stabilization can occur both temporally (weak inputs need not be closely associated in time with activation of a strong input) and spatially (the weak input need not be located close to the strong input, since the stabilization factors are thought to be produced globally throughout the neuron) (Barco et al., 2002; Martin and Kosik, 2002). Such promiscuity would seem counterproductive for a memory storage device, as it could easily lead to stabilization of spurious associations. On the other hand, if the stimuli that normally produce protein synthesis-dependent stabilization are rare and precisely controlled, such a mechanism might serve to solidify a coordinated set of short-term synaptic changes that have accumulated over some interval of time.

The preceding studies have stressed the associative and cooperative nature of synaptic tagging. The surprising finding of Fonseca et al. is that there is also a competitive aspect to this process. One prediction of the synaptic tagging hypothesis is that if enough "factor" could be sequestered by one set of inputs, this should prevent other inputs from becoming stabilized in response to weak stimulation. To test this prediction, Fonseca et al. first initiated L-LTP on two independent pathways, and then limited the continued production of protein synthesis-dependent factors by applying protein synthesis inhibitors. They then stimulated one pathway a second time (still in the presence of protein synthesis inhibitors) to induce additional potentiation. In keeping with previous observations, the stimulated (or "reactivated") pathway underwent additional LTP. The surprising observation was that potentiation of the reactivated pathway was at the expense of the unstimulated (or test) pathway, which experienced a partial reversal of L-LTP. No depression of the test pathway was observed if the test pathway had not been potentiated initially, or if the reactivation was performed in the absence of protein synthesis inhibitors—suggesting that this effect was not due to heterosynaptic depression. Importantly, they were able to show that competitive maintenance can also be observed in the absence of protein synthesis inhibitors. They reasoned that fewer maintenance factors would be produced by a protocol that used paired weak stimulation of two pathways to induce L-LTP than by the standard tetanus protocol. Indeed, pairing of weak stimulation induced L-LTP, and they were able to observe competitive maintenance with this modified protocol without limiting protein synthesis. This suggests that the degree of competition for maintenance of L-LTP will depend on how strongly the postsynaptic neuron is activated during L-LTP induction—presumably because this will regulate the concentration of maintenance factors.

Why does the test pathway experience a decay of L-LTP? One possibility is that the reactivated pathway generates an inhibitory signal that causes decay of L-LTP on the test pathway. Because this decay is only seen in the presence of protein synthesis inhibitors (when tetanus is used to induce the initial L-LTP), this explanation would require that protein synthesis is normally protecting the test pathway from the deleterious effects of such an inhibitory factor. This is difficult to reconcile with the observation that competitive maintenance can occur in the absence of protein synthesis

inhibitors when paired weak stimuli are used instead of tetanus (see above). An alternative explanation, favored by the authors, is that synapses are actively and dynamically competing with each other for whatever factor or factors are required for L-LTP maintenance. The intriguing possibility raised by the data is that the reactivated pathway competes away factors already sequestered by the test pathway during the first round of stimulation, leading to decay of L-LTP in the test pathway. This interpretation presupposes that there is continued production of maintenance factors for many hours following a strong tetanus; in addition, either synapses need continuous replenishment of these factors, or else binding of factors to synaptic sites is reversible.

There are a few aspects of the data that are puzzling in the context of this competitive maintenance model. On the one hand, there was a nice correlation between the magnitude of additional LTP on the reactivated pathway and the magnitude of decay on the test pathway—as expected if greater LTP on the reactivated pathway sequesters more of a limiting factor that then generates more decay on the test pathway. However, this relationship broke down when the number of stimuli delivered to the reactivated pathway was systematically increased—this generated the same magnitude LTP on the reactivated pathway but increasing amounts of decay on the test pathway. This behavior suggests that the interactions between different synapses may be quite complex and depend intimately on the exact stimulation protocols used. Such complexity could arise, for instance, if there are multiple synaptic tags and multiple maintenance factors that can be differentially produced and/or sequestered by different activity regimes.

Whatever the mechanism ultimately proves to be, the observation that maintenance of some synapses comes at the expense of others significantly alters the way one must think about the process of long-term maintenance of synaptic strength. One functional implication of these data is that "reactivated" pathways will be stabilized at the expense of pathways that are not—a process that could help suppress some of the spurious associations generated by the long-lasting and neuron-wide production of maintenance factors (as long as one has a selective mechanism for "reactivation"). Although competitive maintenance of L-LTP is unlikely to account for homeostatic synaptic scaling (which can occur under conditions that do not allow expression of LTP, and at synapses that have not first been potentiated) (Turrigiano and Nelson, 2004), competitive maintenance could help mitigate the positive feedback nature of LTP (Abbott and Nelson, 2000) by ensuring that maintained potentiation of some inputs suppresses the maintenance of others and thus reduces overall potentiation. Finally, this study demonstrates that L-LTP of a given input is not stable and immutable but can be dynamically modified by the ongoing activity of both itself and other neighboring synapses. Because LTP maintenance has both cooperative and competitive aspects, the pattern of stabilized synaptic weights will ultimately be a highly complex function of the pattern of activity across a large number of a neuron's inputs.

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Selected Reading

Abbott, L.F., and Nelson, S.B. (2000). Nat. Neurosci. *3*, 1178–1183.

Barco, A., Alarcon, J.M., and Kandel, E.R. (2002). Cell *108*, 689–703.

Fonseca, R., Nägerl, U.V., Morris, R.G.M., and Bonhoeffer, T. (2004). Neuron *44*, this issue, 1011–1020.

Frey, U., and Morris, R.G. (1997). Nature *385*, 533–536.

Frey, U., and Morris, R.G. (1998). Trends Neurosci. *21*, 181–188.

Lynch, G.S., Dunwiddie, T., and Gribkoff, V. (1977). Nature *266*, 737–739.

Martin, K.C., and Kosik, K.S. (2002). Nat. Rev. Neurosci. *3*, 813–820.

Martin, S.J., Grimwood, P.D., and Morris, R.G. (2000). Annu. Rev. Neurosci. *23*, 649–711.

Royer, R.T., and Pare, D. (2003). Nature *422*, 518–522.

Scanziani, M., Malenka, R.C., and Nicoll, R.A. (1996). Nature *380*, 446–450.

Turrigiano, G.G., and Nelson, S.B. (2004). Nat. Rev. Neurosci. *5*, 97–110.