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Synaptic Plasticity in an Altered State

In this issue of *Neuron*, Montgomery and Madison (2002) record from synaptically coupled pairs of CA3 neurons to closely examine the induction of synaptic depression at a small number of identified synapses. The authors provide convincing evidence that the activation history of a synapse determines both the ability of a synapse to depress and the mechanism of depression.

2002 marks the 10-year anniversary of the publications that launched the study of homosynaptic long-term depression (LTD) in the hippocampus. Over this decade, we have made remarkable progress in our understanding of the mechanisms of LTD, particularly the form that is triggered by activation of NMDA receptors (NMDARs) in area CA1. We now understand that LTD is induced by Ca^{2+}-dependent activation of a postsynaptic protein phosphatase cascade, followed by dephosphorylation and internalization of AMPA receptors (AMPARs) (see Linden and Bear, 2001, for review). Short of understanding what LTD actually does in the brain, one might surmise that most of the major mechanistic questions have been answered. However, an elegant study by Montgomery and Madison (2002) published in this issue of *Neuron* reminds us that there is still much to learn about LTD in the hippocampus. They show that the susceptibility to, and mechanism of, synaptic depression depends importantly on the state of the synapse at the time induction is attempted. Of equal importance, they show that AMPAR regulation is only part of the LTD story; we need to start considering the rapid regulation of NMDARs as well.

These advances were made possible by the innovative use of paired recordings from synaptically coupled CA3 neurons in slice culture. In a previous study, the authors used this preparation to demonstrate that induction of long-term potentiation (LTP) can convert "silent" connections, which possess NMDAR-mediated synaptic currents but lack detectable AMPAR-mediated currents, into "active" connections expressing a dual component EPSC (Montgomery et al., 2001). The obvious next step was to examine the flip side of the coin—LTD.

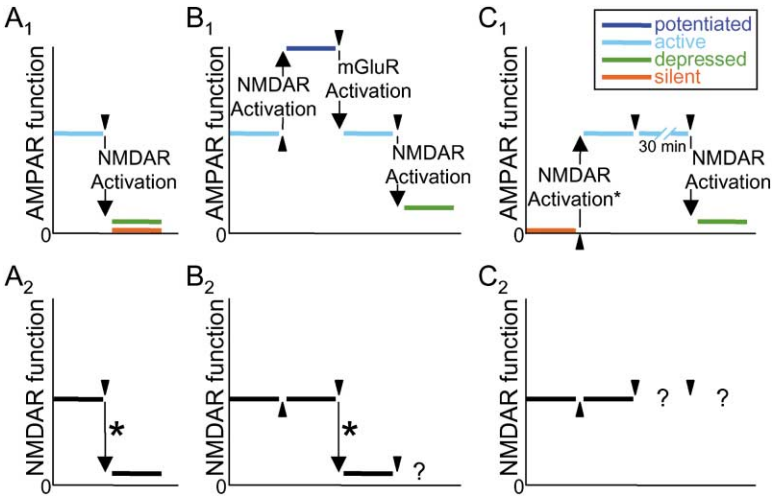
The authors first investigated the effects of a LTD induction protocol (low-frequency stimulation coupled with slight depolarization) on active synaptic connections. Not surprisingly, robust LTD of AMPAR-mediated transmission can be induced, and this depends on activation of NMDARs during the conditioning stimulation (see Figure, panel A_1). In some cases, AMPARs are completely silenced after LTD. But there are more intriguing twists to the story. One is that NMDAR-mediated transmission also undergoes LTD (see Figure, panel A_2). The parallel depression of AMPAR and NMDAR-mediated responses, previously described in slices of CA1 (Xiao et al., 1994), is consistent with a presynaptic mechanism for LTD expression. However, Montgomery and Madison show here that LTD reduces the sensitivity of the postsynaptic neuron to exogenously applied NMDA. Thus, postsynaptic NMDARs are modified during LTD. In this context, it is worth noting that another form of hippocampal LTD, induced by activation of group 1 metabotropic glutamate receptors (mGluRs), is associated with the rapid internalization of NMDARs (Snyder et al., 2001). Indeed, Montgomery and Madison's data do not rule out the possibility that the LTD of NMDARs might actually be triggered by activation of mGluRs during the conditioning stimulation (see below).

These findings are significant. First, they call into question the meaning of LTD saturation, which is usually interpreted as exhausting the expression mechanism of this type of plasticity. Instead, less LTD might result from repeated episodes of stimulation because fewer or less effective NMDARs reside postsynaptically. Second, the finding that both AMPARs and NMDARs are downregulated, and possibly internalized, supports the conjecture, based on work at the neuromuscular junction (Colman and Lichtman, 1993), that LTD could be a mechanism that ultimately leads to the elimination of synapses altogether (Bear and Rittenhouse, 1999).

Next, Montgomery and Madison investigated the same type of stimulation on initially active synapses in an altered state—recently potentiated. As in the case of the naïve active connections, the low-frequency stimulation pairing protocol was effective in depressing transmission of synapses that had recently undergone LTP. However, depotentiation was not blocked by NMDAR antagonists; instead it was sensitive to a broad spectrum antagonists of mGluRs (see Figure, panel B_1). This mechanistic distinction between de novo LTD and depotentiation supports growing evidence that synapses temporarily visit a distinct molecular state following induction of LTP (Lee et al., 2000). Depotentiation apparently can reset the AMPARs, however. Once the synapse is depotentiated, additional low-frequency stimulation induces the familiar form of LTD requiring activation of NMDARs, although it is typically smaller in magnitude. These data serve as a potent reminder that, in addition to the pattern of inputs, we must carefully consider that the state in which a synapse resides, given by its activation history, can determine the properties of plasticity.

Of course, naïveté is a state that can only be occupied once, and the synapse is no exception. NMDARs, while unaffected by the initial LTP induction protocol, still undergo LTD as the AMPAR responses are depotentiated (see Figure, panel B_2). The reduced transmission through NMDARs is likely responsible for the reduced LTD magnitude when induction follows prior depotentiation.

A third experiment again reveals the state dependence of LTD. In this case, the initial state was silence—that is, NMDAR-mediated transmission without an AMPAR response. The paired recording techniques allowed Montgomery and Madison to examine the behav-



A Summary of the Consequences of Synaptic Conditioning on AMPA and NMDA Receptor Function in CA3→CA3 Collaterals

Synaptic states (potentiated, basal, depressed, and silent) are determined by the level of AMPA receptor function. Upward triangles indicate potentiation protocols, while downward triangles indicate depression protocols. The induction mechanisms (NMDAR or mGluR activation) are shown when known, while asterisks indicate where the induction mechanism has yet to be established. Question marks indicate gaps in knowledge.

ior of synapses that were "unsilenced" by inducing LTP (see Figure, panel C_1). Strangely, and in sharp contrast with LTP from the active state, the recently unsilenced synapses were found to be temporarily resistant to synaptic depression. Only after waiting 30 min after the "unsilencing" were the synapses again subject to depression, and this depression resembled that observed from the active state (i.e., the depression was NMDAR dependent).

The fact that newly inserted AMPA receptors are resistant to depression might lend insights to the mechanism of receptor insertion. Several possibilities exist. For example, newly inserted AMPA receptors might contain GluR1 subunits that are initially resistant to internalization (Shi et al., 2001). In time, these receptors might become associated with the endocytotic machinery (Passafaro et al., 2001). Alternatively, initially inserted AMPA receptors might be resistant to internalization, but receptors that can be rapidly recycled (e.g., - GluR2/3-containing AMPA receptors) might more slowly become incorporated into the synapse (Shi et al., 2001), and it is only when these receptors are inserted that depression can be observed. Finally, protection of newly inserted AMPA receptors from depression might involve phosphorylation mechanisms. For example, several studies suggest that phosphorylation of the GluR2 AMPA receptor subunit can alter the association of AMPA receptors with scaffolding proteins and might regulate endocytosis (Chung et al., 2000). Perhaps mechanisms for AMPA receptor phosphorylation/dephosphorylation only become competent after AMPA receptors gain association, over time, with an appropriate complement of postsynaptic scaffolding proteins. Although the mechanisms by which newly inserted AMPA receptors are protected from depression needs exploration, the protection of newly activated receptors might play an adaptive role in the formation of neural networks. Given that weak inputs are typically targeted for depression and elimination, temporary protection of newly activated synapses might allow them to acquire stable and responsive connections.

By studying synaptic depression of AMPA-mediated currents, Montgomery and Madison demonstrate that CA3 collateral synapses can occupy as many as seven distinct states—silent, active, depressed, recently potentiated, recently depotentiated, recently unsilenced, and remotely unsilenced—and that the lasting response to the same stimulation protocol differs among them. In reality, synapses likely exist along an infinite continuum of synaptic states, for which there may exist great heterogeneity in the properties of synaptic plasticity. Understanding the meaning and mechanisms behind this diversity should keep synaptic physiologists busy for years to come.

An equal challenge is to understand the activity-dependent regulation of NMDARs. Although Montgomery and Madison found that depotentiation and LTD of AMPA-mediated responses are accompanied by a depression of NMDA-mediated responses, less is known about the requirements for the loss of NMDA responses (e.g., see Figure, panel C_2). Future studies are needed to explore the mechanism for depressing NMDA receptors. Furthermore, it is curious that Montgomery and Madison found that NMDA receptor responses are readily depressed, yet there is little evidence to suggest that NMDA responses can be potentiated in CA3 collaterals. But in an essential variation of Newton's law, it seems to us that what goes down must come up—at least if further NMDAR-dependent plasticity is to be possible in the synapse's lifetime. Clearly, a synaptic mechanism must exist to increase NMDA receptor responses, or synapses would lose all NMDA receptors as their synaptic strength fluctuates over time. Currently, an induction mechanism for increasing NMDA receptor responses remains to be discovered. We know little about how NMDAR-mediated transmission undergoes LTD, and we know virtually nothing about how NMDAR responses can be potentiated on a short time scale. The 1990s were the decade of progress on bidirectional AMPAR regulation (Malenka and Nicoll, 1999); perhaps the next decade will provide as much illumination for the NMDAR.

The work by Montgomery and Madison is a much needed step toward an appreciation that synapses can exist in multiple states for which the induction and mechanisms of plasticity might differ, but like most seminal experiments, many more questions are raised for future studies.

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The Nature of Illusory Contour Computation

Neural correlates of illusory contour perception have been found in both the early and the higher visual areas. But the locus and the mechanism for its computation remain elusive. Psychophysical evidence provided in this issue of *Neuron* shows that perceptual contour completion is likely done in the early visual cortex in a cascade manner using horizontal connections.

An organizing principle underlying many visual computations is postulated to be the need for producing a parsimonious and simple description of the visual scene. The process for fulfilling this need is called perceptual organization. The perception of illusory contour in Kanizsa figures (Figure, panel A) underscores the workings of this principle. Rather than describing the picture as an accidental arrangement of four pacmen in some peculiar orientations, it is much simpler to interpret it as a diamond in front of four circular discs. This interpretation implies a surface or depth discontinuity between the diamond and the background. The vivid perception of illusory contour suggests this surface or depth discontinuity may be represented in the visual system explicitly, even at locations where there is no direct physical evidence for it. Psychophysical and neurophysiological studies of illusory contour perception are therefore important for understanding the neural mechanisms responsible for contour completion, in particular, and perceptual organization, in general.

Single unit neurophysiology, in recent years, has provided direct evidence that the early visual areas (V1 and V2) are involved in representing illusory contour. Since only the early visual areas contain neurons with small receptive fields for encoding information with high spatial precision and feature resolution, these areas are ideal for representing the perceived sharp contours explicitly. In their ground-breaking experiment, von der Heydt et al. (1984) found that a moving illusory bar could excite V2 neurons in monkeys even when there was nothing inside the receptive field of the neurons. Lee and Nguyen (2001) studied the temporal evolution of neuronal activities in V1 and V2 in response to the static display of Kanizsa figures. They found that the response to illusory contour emerged in V1 at about 100 ms, significantly later than the emergence of illusory contour response in V2. Other single unit and optical imaging studies involving the illusory contour defined by abutting gratings, as shown in the Figure, panel B, also implicated V1 and V2 in the representation of illusory contour (Grosof et al., 1993; Sheth et al., 1996; Ramsden et al., 2001).

However, a recent functional imaging experiment by Mendola et al. (1999) found Kanizsa figures elicited significant responses in the lateral occipital (LOC) region, but only weak, if any, response in the human early visual areas. This finding, along with the observation by Huxlin et al. (2000) on the impairment of a monkey's ability to see illusory contours as a result of a lesion in the inferotemporal cortex (IT), ignited a debate on whether the illusory contour computation is an early or a late process. While single unit studies have confirmed that the early visual cortex participates in the representation of illusory contour, they did not pinpoint the locus or the mechanism of the illusory contour computation. Computational models on illusory contour completion offered several possible solutions. Some suggested an intracortical mechanism within the early visual cortex through algorithms based on horizontal interaction (Geiger et al., 1996). Others argued for a computation that is based on successive feedforward conjunctions of elementary features (Heitger and von der Heydt, 1993). Grossberg and Mingola's (1985) model involved both intracortical and intercortical interaction.

Pillow and Rubin (2002), in this issue of *Neuron*, reported a series of careful psychophysical experiments to dissect these issues. They asked observers to discriminate the shapes of slightly deformed Kanizsa-type illusory figures. They found that, if the stimuli is exposed only for 97 ms, followed by a blank screen and then a mask, the subjects are more sensitive to the curvature of the illusory contour when the inducers (pacmen) are within a visual hemifield than when the inducers are on opposite sides of the vertical meridian. This asymmetry in sensitivity increases dramatically with an increase in gap size between the inducers. Crossing the hemispheric divide through the corpus callosum apparently has incurred an extra cost that is gap size dependent. If the computation is purely feedforward and completed in IT, one would expect the extra cost for interhemispheric transfer to be more or less fixed, independent of the gap size. The finding that the cost of interhemi-