



Figure 1. Schematic Representation of Spike Timing-Dependent Plasticity of a GABA Synapse in a CA1 Pyramidal Cell

A train of back propagating action potentials (triggered at a frequency of 5 Hz by somatic current injections) invades the apical dendrites of a pyramidal cell, thus activating nifedipine-sensitive (L-type) voltage-dependent Ca^{2+} channels (VDCC). When a GABAergic synapse (e.g., that formed by interneuron #1 in the figure) is stimulated such that individual synaptic events occur within 20 ms of the postsynaptic action potentials, the resulting influx of Ca^{2+} (dark cloud on lower right panel) suppresses the activity of neighboring K^+/Cl^- cotransporters (KCC2). As the recordings were made at a membrane potential hyperpolarized from the Cl^- reversal potential (E_{Cl}), the diminished KCC2 mediated Cl^- extrusion leads to a local intracellular accumulation of Cl^- resulting in larger GABAergic postsynaptic potentials. Remarkably, this spike timing-dependent plasticity of the E_{Cl} and hence of GABAergic transmission, is synapse specific. Only the function of the synapse formed by interneuron #1 in the figure is altered because it is the only one that fulfills the following two requirements. (1) It is active (indicated by red in the figure) within 20 ms of each postsynaptic action potential and (2) is located on a KCC2-rich apical dendrite of a pyramidal cell. Another dendritic GABA synapse, that formed by interneuron #2, does not display the plasticity, because it was not active during the firing of the action potentials. Because of the paucity of KCC2 on pyramidal cell somata (Gulyás et al., 2001), the somatic synapse formed by interneuron #3 will not display spike timing-dependent plasticity, even if it were active during the train of action potentials.

Selected Reading

Abbott, L.F., and Nelson, S.B. (2000). *Nat. Neurosci. Suppl.* 3, 1178–1183.
 Collin, C., Devane, W.A., Dahl, D., Lee, C.J., Axelrod, J., and Alkon, D.L. (1995). *Proc. Natl. Acad. Sci. USA* 92, 10167–10171.

DeFazio, R.A., Keros, S., Quick, M.W., and Hablitz, J.J. (2000). *J. Neurosci.* 20, 8069–8076.
 Ganguly, K., Schinder, A.F., Wong, S.T., and Poo, M. (2001). *Cell* 105, 521–532.
 Gulyás, A.I., Sik, A., Payne, J.A., Kaila, K., and Freund, T.F. (2001). *Eur. J. Neurosci.* 13, 2205–2217.
 Markram, H., Lübke, J., Frotscher, M., and Sakmann, B. (1997). *Science* 275, 213–215.
 Payne, J.A. (1997). *Am. J. Physiol.* 273, C1516–C1525.
 Payne, J.A., Rivera, C., Voipio, J., and Kaila, K. (2003). *Trends Neurosci.* 26, 199–206.
 Rivera, C., Voipio, J., Payne, J.A., Ruusuvuori, E., Lahtinen, H., Lamsa, K., Pirvola, U., Saarma, M., and Kaila, K. (1999). *Nature* 397, 251–255.
 Stein, V., and Nicoll, R.A. (2003). *Neuron* 37, 375–378.
 Woodin, M.A., Ganguly, K., and Poo, M.-m. (2003). *Neuron* 39, this issue, 807–820.

Making Space for Rats: From Synapse to Place Code

The formation of spatial memories is believed to depend on long-term potentiation (LTP) of synapses within the hippocampal network. In this issue of *Neuron*, Dragoi et al. demonstrate that LTP can cause changes in the hippocampal representation of space without disrupting network dynamics. These results help define the elusive relationship between cellular-level synaptic plasticity and systems-level neural coding.

For 30 years, hippocampal researchers have known that high-frequency stimulation of hippocampal projections produces immediate and long-lasting changes in synaptic strength. This hours-long increase in potentiation of synaptic weights is known as long-term potentiation (LTP) (Bliss and Lomo, 1973). For about 30 years, we have also known that the principal cells of the rat hippocampus have the nifty property of firing robustly when the rat is in a particular location and being essentially silent when the rat is walking around outside of that place (O’Keefe and Dostrovsky, 1971). The development of these “place fields” happens within minutes of exposure to a new location (Wilson and McNaughton, 1993).

It seems likely that the changes in synaptic strength associated with LTP underlie the rapid formation of place fields, but a direct link has not been established. We know that LTP is particularly easy to induce at hippocampal synapses and that pharmacological or genetic disruption of LTP causes spatial learning impairments (Morris et al., 1986; Nakazawa et al., 2003). Thus, while it is clear that LTP plays an essential role in spatial processing in rodents, the precise nature of that role is not known. In order to link mechanisms of synaptic strengthening and mechanisms of spatial learning, Dragoi et al. (2003 [this issue of *Neuron*]) investigated the effects of LTP on the place-related firing of hippocampal cells.

Dragoi et al. induced LTP in awake, freely behaving

rats. They implanted the animals with adjustable electrodes targeting the CA3 and CA1 subregions of the hippocampus, areas in which place-related firing is robust and well characterized. The rats were trained to run around a square track for chocolate wafer rewards, and neural data were collected both during rest sessions in the animals' home cages and run sessions on the track. During the rest between two run periods, either LTP-inducing stimulation or low-frequency control stimulation (LFS) was delivered to the ventral hippocampal commissure (VHC), a fiber bundle of projections to CA3 and CA1. The place-related firing of individual cells was then analyzed during run sessions before and after LTP/LFS. Test stimuli delivered to the animals during rest periods allowed the authors to assess the degree of potentiation at each recording site, measured as a change in the slope of stimulus-triggered EPSPs in the local field potential at each electrode tip.

Dragoi et al. found that LTP induction changed the hippocampal place responses without disrupting characteristic network features. The degree of LTP correlated with the degree of change in place-related firing such that LTP produced much greater potentiation at some recording sites than at others, and neurons recorded from sites with greater potentiation were more likely to change their place representations. These new representations involved shifts of the original field, loss of the field, or appearance of a new field. The new place fields were indistinguishable from the endogenous representations: place fields of the changed cells were similar to the original fields in size and shape; the average firing rate of the population did not change; and characteristic small time scale correlations of the hippocampal ensemble were preserved. LTP-induced place firing showed the directional specificity typical of place cells (McNaughton et al., 1983), such that a new field might appear when the animal traveled clockwise around the track but not counterclockwise. They also fired with a normal relationship to the theta rhythm, a 4–12 Hz oscillation observed in the hippocampal EEG of awake behaving rats.

There was, however, an important difference between the LTP-driven place representation and the animal's own place representation: permanence. Once a rat forms a place map (a process that is well underway after 10 or so minutes of exploring a new spot [Wilson and McNaughton, 1993]), each neuron's place response is generally stable for as long as the neuron can be recorded (Thompson and Best, 1990). In contrast, the place responses generated by LTP disappeared as the potentiation faded over a period of about 6 hr. This result is quite elegant, as it strongly suggests a causal relationship between LTP and place cell coding, but it leaves the question: if an LTP-like mechanism is driving place field formation, what signal maintains the changed synaptic weights across days and weeks? Or in the parlance of the hippocampal community, how are changes in synaptic weights "consolidated"?

One possibility is that synaptic changes are consolidated when the animal is in a particular attentional state, such as when it perceives an experience as novel. Hippocampal consolidation requires protein synthesis (McGaugh, 2000), and it may be that protein synthesis is triggered by a systemic learning/novelty/error signal.

In this case, we would predict that the place representation driven by Dragoi et al. would have been permanent if it were generated when the animal was in a novel place.

Dragoi et al.'s findings provide an important link between the cellular processes associated with synaptic plasticity and the hippocampal representation of space. The authors showed that altering the synaptic weights in the hippocampal network correspondingly alters the hippocampal representation of space without disrupting the network dynamics. This strong connection between long-term potentiation and modification of the hippocampal place code outlines a possible causal relationship between plasticity and spatial memory.

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Selected Reading

- Bliss, T.V., and Lomo, T. (1973). *J. Physiol.* 232, 331–356.
- Dragoi, G., Harris, K.D., and Buzsáki, G. (2003). *Neuron* 39, this issue, 843–853.
- McGaugh, J.L. (2000). *Science* 287, 248–251.
- McNaughton, B.L., Barnes, C.A., and O'Keefe, J. (1983). *Exp. Brain Res.* 52, 41–49.
- Morris, R.G., Anderson, E., Lynch, G.S., and Baudry, M. (1986). *Nature* 319, 774–776.
- Nakazawa, K., Sun, L.D., Quirk, M.C., Rondi-Reig, L., Wilson, M.A., and Tonegawa, S. (2003). *Neuron* 38, 305–315.
- O'Keefe, J., and Dostrovsky, J. (1971). *Brain Res.* 34, 171–175.
- Thompson, L.T., and Best, P.J. (1990). *Brain Res.* 19, 299–308.
- Wilson, M.A., and McNaughton, B.L. (1993). *Science* 261, 1055–1058.

Can't Learn without You: Predictive Value Coding in Orbitofrontal Cortex Requires the Basolateral Amygdala

Basolateral amygdala and orbitofrontal cortex are implicated in cue-outcome learning. In this issue of *Neuron*, Schoenbaum et al. show that, following basolateral amygdala lesions, cue-selective neurons in orbitofrontal cortex are more sensory driven and less sensitive to the motivational value of an outcome, suggesting that predictive value coding in orbitofrontal cortex is dependent on input from basolateral amygdala.

In order to survive, most animals require the ability to predict when and where in the environment rewarding or punishing stimuli will occur and adapt behavior accordingly. Research in affective neuroscience over the