LTP ≠ learning: lessons from short-term plasticity

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A commentary on

Differing presynaptic contributions to LTP and associative learning in behaving mice.
by Noelia Madroñal, Agnès Gruart and José M. Delgado-Garcia

Memory and other kinds of long-term adaptive changes in the brain rely on the plasticity of neuronal communication, including mechanisms of synaptic plasticity. Diverse lines of evidence from molecular and biochemical studies of synapses, structural imaging and electron microscopy, pharmacological and genetic manipulations, and electrophysiology overwhelmingly support a role for synaptic plasticity in learning processes in a wide variety of invertebrate and vertebrate species. In terms of synapse physiology, however, we still know relatively little about the changes that occur during learning and memory and their functional impact. This applies foremost to synaptic transmission in the mammalian brain, which remains difficult to study at the single-synapse level in behaving animals.

Electrophysiological studies have revealed numerous forms of activity-dependent synaptic plasticity, including mechanistically distinct kinds of long-term potentiation (LTP) and depression (LTD), spike-timing dependent plasticity, homeostatic plasticity, and metaplasticity (Abraham, 2008; Nelson and Turrigiano, 2008; Sjostrom et al., 2008; Feldman, 2009; Bramham et al., 2010). LTP, a lasting increase in synaptic efficacy triggered by high-frequency stimulation (HFS) of afferent fibers, has long been considered a potential mechanism for memory; LTP follows Hebbian rules, it can be induced in excitatory pathways throughout the forebrain, and its expression is synapse-specific. *In vivo* studies of synaptic efficacy typically depend on stimulation of fiber tracts and extracellular recording of the evoked population (field) response. Elegant application of field potential recording has now provided compelling evidence for LTP-like enhancement of synaptic transmission at Schaffer collateral synapses between CA3 and CA1 neurons of the hippocampus following classical conditioning of the eye-blink reflex in mice in the Delgado-Garcia lab (Gruart et al., 2006; Madronal et al., 2007) and inhibitory avoidance learning in rats in the Bear lab (Whitlock et al., 2006). Combined, these studies showed that learning-associated synaptic potentiation prevents (occludes) LTP, while prior induction of LTP blocks learning and learning-induced potentiation. It would therefore appear that synaptic potentiation induced by learning and HFS have a common mechanism of expression at CA3-CA1 synapses. Probing the issue further, both labs sought to identify a putative shared mechanism for synaptic potentiation (Whitlock et al., 2006; Madronal et al., 2009).

The recent study of Madronal and colleagues in Frontiers in Behavioural Neuroscience specifically asked whether synaptic potentiation during eye-blink conditioning has a presynaptic locus of expression. They exploited a well-known form of short-term plasticity known as paired-pulse facilitation (PPF). PPF is the enhancement of an evoked excitatory postsynaptic potential in response to the second pulse in a stimulus pair (within a range of less than 1 s). Quantal analysis of synaptic transmission at hippocampal CA3–CA1 synapses as well as classical studies of the crayfish neuromuscular junction indicate that PPF is a presynaptic phenomenon springing from an enhanced probability of neurotransmitter release. Madronal and colleagues could therefore use PPF to detect changes in short-term plasticity as well as presynaptic contributions to synaptic potentiation during learning. They used a trace conditioning paradigm in which the unconditioned stimulus (US; shock to the supraorbital nerve) is presented 500 ms after the end of a conditioned stimulus (CS) tone. Sixty CS–US pairings were given per day over 10 days and evoked transmission at CA3-CA1 synapses was monitored during the CS–US pairing in response to a stimulus pulse applied 300 ms after CS presentation. For comparison with the learning group, another set of mice received HFS to induce LTP.

HFS produced an immediate potentiation of the field EPSP and a concomitant decrease in PPF, consistent with a presynaptic component to LTP. Interestingly, whereas LTP decayed to baseline over 7 days, depression of PPF was still detectable 13 days later. In the behavioural experiments, acquisition of the conditioned response was present from day 1 of CS–US pairing, yet PPF was increased, not decreased, as seen during LTP. Learning performance improved each day over 10 days of training, yet, instead of increasing as might be predicted, the PPF ratio declined back to preconditioning levels. Furthermore, in sharp contrast to the rapid and transient effects of learning on PPF, enhancement of synaptic transmission was not detected until day 5 of CS–US pairing.

The study thus turned up a host of intriguing surprises. For one, the divergent effects on short-term potentiation suggest that HFS-induced LTP and learning-induced potentiation involve at least partly distinct mechanisms of expression. These mechanisms have distinct onset kinetics (LTP is rapid, learning-induced potentiation is delayed), though both are long-lasting. To my mind the most interesting finding is the decline in PPF prior to completion of the learning trials and synaptic potentiation. This could mean that changes in paired-pulse plasticity have nothing to do with the development of a long-term change in synaptic efficacy. Alternatively, alterations in short-term plasticity could reflect a learning-specific shift in the processing state of the CA3–CA1 network (e.g. a change in hippocampal sharp wave/ripple activity) which declines over time as performance improves but is essential for

memory formation and development of synaptic potentiation. The authors raise the possibility that learning triggers homeostatic plasticity in CA1. If learning-induced synaptic potentiation at a small subpopulation of synapses coincides with transient homeostatic depression of a large population, this might explain both the inability to detect synaptic potentiation during the early training sessions and the presence of enhanced PPF. In studies of plasticity in the somatosensory cortex, whisker deprivation converts normal paired-pulse depression at L4–L2/3 synapses into facilitation by a presynaptic mechanism involving cannabinoid 1 receptor-dependent LTD (Feldman, 2009).

In the paper of Whitlock et al. (2006), increases in synaptic efficacy appeared immediately after one-trial inhibitory avoidance learning and were confined to a small subset of synapses as detected using a multielectrode recording array. Biochemical measurements of glutamate receptor subunit phosphorylation and subcellular localization and the absence of changes in PPF were consistent with a known postsynaptic mechanism of LTP expression (membrane insertion of AMPA-type glutamate receptors). However, the biochemical changes were gone by 2 h. Trace eye-blink conditioning and avoidance learning may therefore engage distinct synaptic mechanisms, including component mechanisms known from LTP studies. While presynaptic

mechanisms do not figure prominently in avoidance learning, such effects may emerge over time, and perhaps this is what occurs in classical conditioning. It should also be noted that the validity of PPF as a test of presynaptic function has been called into question by evidence for a strong postsynaptic component to PPF at CA3–CA1 synapses. More direct imaging approaches to monitor presynaptic function, including use of the pH-sensitive fluorescent indicator synaptopHluorin, indicates that the presynaptic component of LTP is slow to develop (Blundon and Zakharenko, 2008) and the relative contribution of pre- and postsynaptic sides is itself variable, depending on the initial functional state and molecular composition of the synapse (Ward et al., 2006). The work of Madronal and colleagues elegantly demonstrates learning-specific changes in short-term plasticity in mice. Application of advanced imaging techniques and genetically-encoded reporters will ultimately be needed resolve distinct forms of plasticity on a synapse-by-synapse basis within the CA3–CA1 network.

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