Three Ca^{2+} levels affect plasticity differently: the LTP zone, the LTD zone and no man's land

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A particularly interesting property of many glutamatergic synapses is that their strength can be bidirectionally modified; some patterns of stimulation make synapses stronger while others make them weaker. It is generally thought that these dual processes, referred to as long-term potentiation (LTP) and long-term depression (LTD), respectively, contribute to memory storage. Understanding the biochemical events that determine whether the synapse gets stronger or weaker has been an important goal.

It now appears likely that both LTP and LTD are triggered by the same second messenger, Ca^{2+}, and that what determines whether LTP or LTD occurs is the *level* of Ca^{2+}. Early experiments by Lynch *et al.* (1983) showed that LTP induction could be blocked by intracellular Ca^{2+} chelators, suggesting that an activity-dependent elevation of intracellular Ca^{2+} triggers LTP. But which second messenger triggers LTD? The proposal that LTD is also triggered by Ca^{2+} (Lisman, 1989) was based on the following line of reasoning. One form of LTD that works particularly well *in vivo* is a heterosynaptic process; the LTP induced by activating one set of synapses induces LTD (technically termed depotentiation) at inactive synapses. The weakened synapses can be quite distant, making it unlikely that what carries the message to them is a diffusible substance. It seemed more plausible that the message is carried by the spread of the depolarization produced by the active synapses. This depolarization could produce Ca^{2+} elevation at distant synapses by activating voltage-dependent Ca^{2+} channels. The resulting Ca^{2+} elevation would be smaller than at active synapses where Ca^{2+} entry through NMDA channels is a second source of Ca^{2+}. This line of reasoning suggests that high Ca^{2+} elevation might trigger LTP, whereas more moderate Ca^{2+} elevation might trigger LTD.

But how could different Ca^{2+} levels produce opposite effects? The following scheme (Lisman, 1989) was built on previous ideas about how the Ca^{2+}-activated kinase, CaMKII, might act as a molecular switch that was turned 'on' during LTP induction and that then strengthened the synapse (Miller & Kennedy, 1986; Lisman & Goldring, 1988). It was suggested that synaptic weakening might occur if moderate Ca^{2+} elevation activated a phosphatase cascade (involving calcineurin and protein phosphatase-1 (PP1)) and dephosphorylated CaMKII. In contrast, it was supposed that at the higher Ca^{2+} levels that occur during LTP induction, CaMKII would be switched to the 'on' state both because this kinase is itself activated by Ca^{2+} and because these higher Ca^{2+} levels would *inactivate* PP1 (through Ca^{2+}-dependent activation of adenylate cyclase and the known ability of PKA to inhibit PP1).

These hypotheses have received increasing experimental support. Early work by Mulkey & Malenka (1992) demonstrated that the weakening processes, like the strengthening processes, could be blocked by intracellular Ca^{2+} buffers. More recent work using the release of Ca^{2+} from caged compounds (Yang *et al.* 1999) demonstrated that Ca^{2+} is sufficient to trigger both LTP and LTD. Furthermore, there has come to be general agreement that LTP involves the activation of kinase processes whereas LTD involves activation of phosphatase processes. But what about the more specific idea that it is different levels of Ca^{2+} that determine whether LTP or LTD occurs? The first support for this came when it was shown that the same stimulus which induces LTP would instead induce LTD if the NMDA channels were *partially* blocked by an antagonist (Cummings *et al.* 1996). Presumably this lowered the Ca^{2+} elevation from the LTP zone to the LTD zone. A similar conversion of LTP to LTD can be achieved by simply damping Ca^{2+} elevation with moderate concentrations of Ca^{2+} buffers. For instance, in this issue of *The Journal of Physiology*, Cho *et al.* (2001) show that a stimulus that normally induces LTP will induce LTD if the intracellular Ca^{2+} buffer concentration is raised to 10 mM. Finally, the uncaging experiments mentioned above provided direct evidence that the level of Ca^{2+} can be an important determinant of the sign of synaptic modification.

The most surprising finding of Cho *et al.* (2001) suggests that there may actually be three important Ca^{2+} levels. Specifically, their data suggest a large 'no man's land' between the LTP and LTD Ca^{2+} zones. They found that elevating buffer concentration above normal can convert a stimulus from one that does not induce LTD to one that does. The most likely interpretation is that the stimulus normally elevates $[Ca^{2+}]$ into the 'no man's land' in which neither LTP nor LTD occurs. Apparently, this low frequency stimulation at −70 mV, which is considered a weak form of stimulation, is sufficient to raise $[Ca^{2+}]$ to this level. Presumably adding Ca^{2+} buffer leads to LTD induction because it lowers the $[Ca^{2+}]$ into the LTD zone. The existence of such a no man's land has important implications. It is well known that LTD can be finicky and there have been major controversies regarding whether it can or cannot be induced under given conditions (age, temperature, stress, *in vivo vs. in vitro*). Experimenters must now consider the possibility that failure to induce LTD may be because the Ca^{2+} elevation is so high that it reaches the no man's land.

Cho *et al.* (2001) make an advance in understanding what is occurring in no man's land. One possibility is that the kinase and phosphatase are balanced at this intermediate Ca^{2+} level and that this balance explains why there is no synaptic modification. Alternatively this Ca^{2+} level may be sufficient to inactivate the phosphatase but not sufficient to activate the kinase. Cho *et al.* (2001) provide evidence against the balance idea by showing that inhibiting the kinase does not lead to weakening. This conclusion must be considered preliminary since there are feedback loops by which Ca^{2+} entry and release mechanisms can themselves be affected by kinase inhibitors and buffers. However, their results are consistent with the increasing evidence that there is a Ca^{2+}-activated adenylate cyclase at synapses and a demonstrable importance of PKA-dependent inactivation of PP1 (Blitzer *et al.* 1998). Interestingly, the enzymatic control system necessary for this regulation is localized to the postsynaptic density by scaffolding proteins. Thus, the picture beginning to emerge is that detection of different Ca^{2+} levels and the transduction of these signals into bidirectional synaptic modification are done by a biochemical computation integral to the synapse.

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