Cerebellar long-term potentiation: a synaptic candidate mechanism for forgetting

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Cerebellar Purkinje cells (PCs) receive two types of excitatory input: a) from parallel fibers (PFs) and b) from a single climbing fiber (CF). Over the last decades, long-term depression at PF-PC synapses (PF-LTD) has been studied as a cellular correlate of motor learning. In addition to PF activity, PF-LTD induction requires CF activation, contributing dendritic calcium (Ca) transients. Using patch-clamp recordings from slices of young adult rats (200 um), we can induce PF-LTD by paired PF and CF stimulation at 1Hz for 5 min (n=15). Stimulation of the PF alone (1 Hz, 5 min) induces long-term potentiation (PF-LTP; n=7). Thus, it seems that the absence or presence of CF activity provides a key factor determining the polarity of synaptic gain change. Both, PF-LTD and –LTP are postsynaptically expressed, as indicated by the absence of changes in the paired-pulse facilitation ratio. Sequential application of the LTP- and LTD-protocols shows that these phenomena can reverse each other (n=5). To examine whether the CF-evoked Ca signals determine whether LTD or LTP is induced, we applied the LTD-protocol with the Ca chelator BAPTA added to the internal saline (20 mM). Under these conditions, LTP is induced instead of LTD (n=11). Conversely, photolysis of the caged Ca compound DMNP-EDTA (8 mM) leads to LTD instead of LTP when the 'PF alone' protocol was co-applied (n=5). Finally, when CF-LTD was induced first and the PF-LTD protocol was applied 15 min later, the PF responses were potentiated. These observations suggest a novel, 'reversed' Ca threshold mechanism for the induction of LTD/LTP at PF-PC synapses that shows two novel features: a) the Ca amplitude threshold for LTD induction is higher than that for LTP induction (reverse to the BCM rule) and b) the probability to reach this threshold is dependent on the previous and current activity levels of the CF, a qualitatively different, heterosynaptic input.

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