THE CONTRIBUTION OF INVERSE PLASTICITY MECHANISMS TO CEREBELLUM-DEPENDENT LEARNING

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Many plasticity mechanisms have been characterized *in vitro* in circuits important for learning. We are beginning to parse out the dependence of motor learning upon different plasticity mechanisms in the cerebellum and related structures. The most influential model of cerebellum-dependent learning has focused on a single plasticity mechanism, long-term depression (LTD) at parallel fiber to Purkinje cell (pf-Pk) synapses (Albus 1971, Marr 1969), but our studies of the vestibulo-ocular reflex (VOR) suggest that multiple plasticity mechanisms are involved. Applied to motor learning in the VOR, the Marr-Albus model attributes both increases and decreases in VOR gain to pf-Pk LTD (Ito 1982). Here we present two lines of evidence that increases and decreases in VOR gain depend upon different plasticity mechanisms.

First, increases in VOR gain are reversed more readily than decreases in VOR gain. This difference in reversal properties suggests that increases and decreases in VOR gain are mediated by different plasticity mechanisms. Furthermore, the behavioral asymmetry suggests that these plasticity mechanisms reverse each other with unequal efficacy (Boyden & Raymond 2003). The plasticity mechanisms at the pf-Pk synapse (LTD and two forms of LTP) seem to possess such an asymmetric reversal property. Thus we propose a new model in which pf-Pk LTD contributes primarily to increases in VOR gain, whereas pf-Pk LTP contributes primarily to decreases in VOR gain. We are testing this model with mutant mice deficient in either pf-Pk LTD or one of the forms of pf-Pk LTP. Mice lacking Ca^{+2}/CaM-kinase IV (CaMKIV), a molecule required for the late phase of pf-Pk LTD are selectively impaired in retention of an increase in VOR gain. Acquisition of increases and decreases in VOR gain is normal, as is retention of a decrease in VOR gain (Boyden et al 2003). Therefore, long-term memory for an increase in VOR gain relies upon a CaMKIV-dependent process (such as pf-Pk LTD), whereas long-term memory for a decrease in gain does not. Our results suggest that models of cerebellum-dependent motor learning should be revised to consider the role of inverse plasticity mechanisms at pf-Pk synapses.

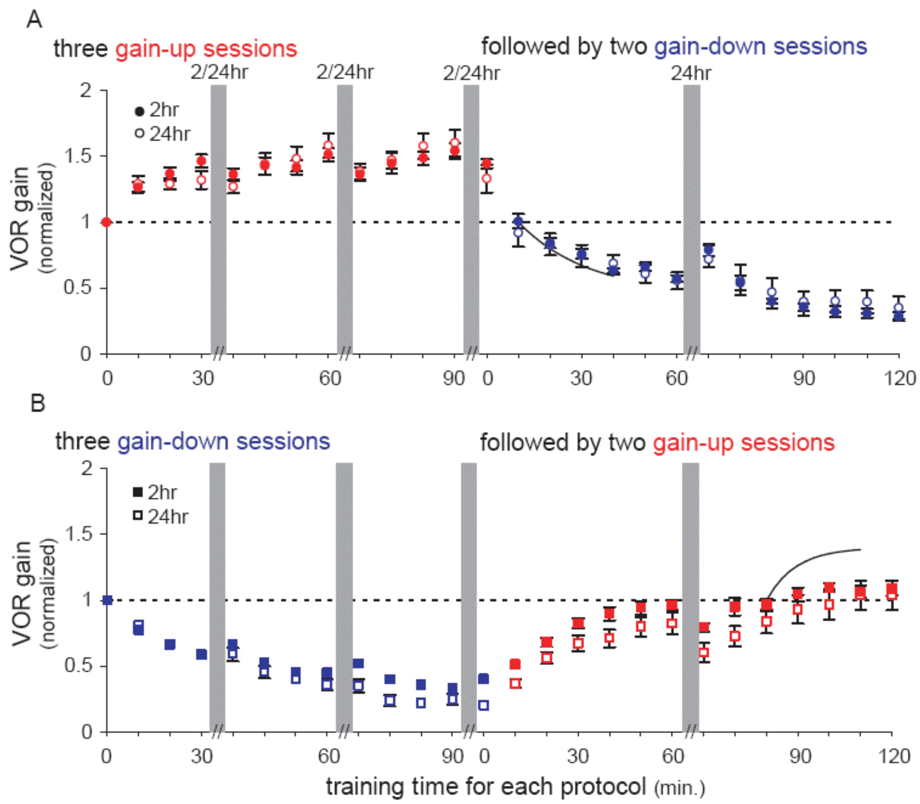

Figure 1. Increases in VOR gain are more readily reversed than decreases in VOR gain.
(A) Mice were trained with three 30-minute gain-up training sessions (red symbols), followed by two 1-hour gain-down training sessions (blue symbols). Between training sessions, there were either 2-hour (filled circles) or 24-hour (open circles) rest periods in darkness, indicated by shaded bars. The x-axis time is reset to zero when the gain-down protocol begins. The solid curve starting at the 10-minute point in gain-down training is the exponential fit to gain-down training from the naïve state, for comparison to the timecourses shown here. During reversal, the decrease in VOR gain parallels that seen in naïve mice, consistent with complete reversal of changes induced by prior gain-up training.
(B) Mice were trained with three 30-minute gain-down training sessions (blue symbols), followed by two 1-hour gain-up training sessions (red symbols). The solid curve beginning at the 80-minute point in gain-up training is the exponential fit to gain-up training from the naïve state. Even after VOR gain is restored to normal, the mice are not capable of learning normally in response to the gain-up stimulus. Thus the changes induced by the initial gain-down training were not fully reversed.

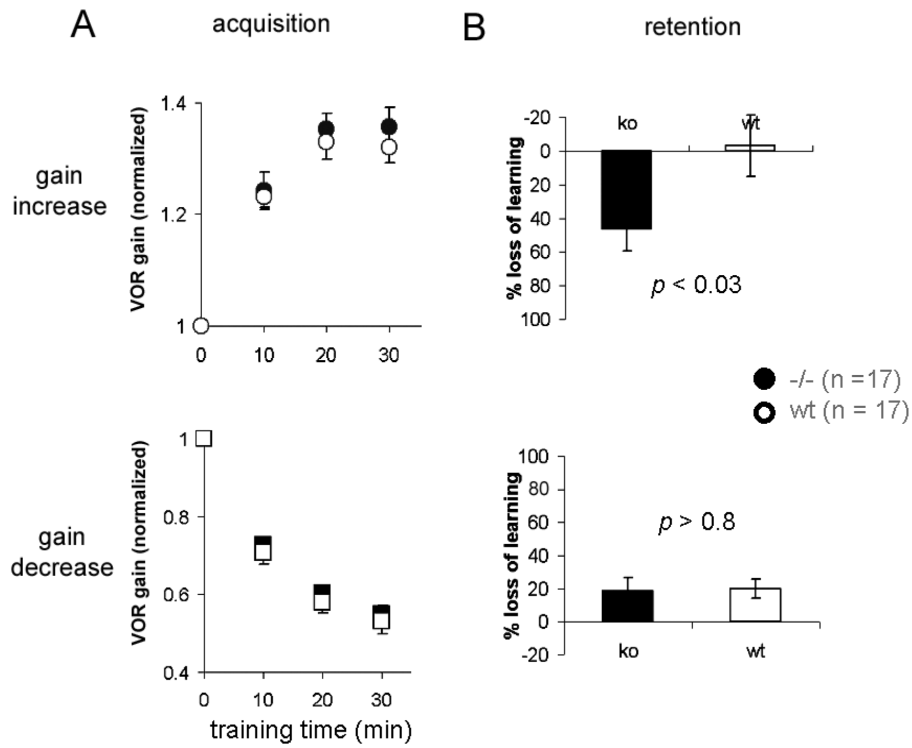

Figure 2. CaMKIV knockout mice have impaired retention of increases but not decreases in VOR gain.
(A) Normal acquisition of learning in the CaMKIV KO. CaMKIV KO (filled symbols) and wild-type (open symbols) mice were trained with 30 minutes of gain-up (top) or gain-down (bottom) training. There was no difference between wt and KO mice, for gain-up or gain-down training.
(B) Impaired retention of an increase in VOR gain in the CaMKIV KO. CaMKIV KO (filled bars), but not wild-type (open bars) mice forget increases (top) but not decreases (bottom) in VOR gain, when measured 24 hours after a 30-minute training session. This shows that the mechanisms mediating increases and decreases in VOR gain are different.

References

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