This Week in The Journal

Reelin Modulates mGluR-Dependent Long-Term Depression

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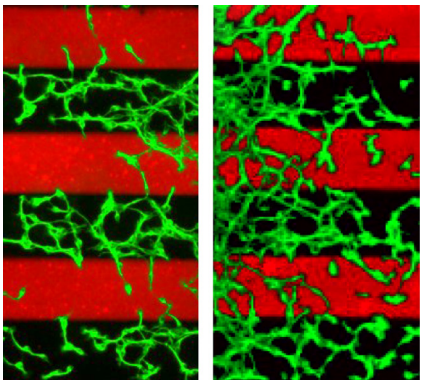
(see pages 7340–7349)

Long-term depression (LTD) of synaptic strength is an important component of synaptic plasticity and is required for certain types of learning and behavioral flexibility. LTD can be induced in multiple ways, including by activating metabotropic glutamate receptors (mGluRs). This form of LTD depends partly on mGluR-dependent increases in the tyrosine phosphatase $STEP_{61}$. $STEP_{61}$ dephosphorylates AMPA receptor (AMPAR) GluA2 subunits, leading to the internalization of GluA2-containing receptors. Notably, this process might be enhanced by β-amyloid peptides that accumulate in Alzheimer's disease. Durakoglugil et al. now show that mGluR-dependent LTD is dampened by the extracellular molecule Reelin.

Previous research has shown that Reelin activates Src family kinases, which can phosphorylate GluA2. Consistent with this, Durakoglugil et al. found that treating hippocampal slices with exogenous Reelin increased phosphorylation levels of GluA2. Importantly, Reelin also reduced basal levels of $STEP_{61}$, and this likely contributed to the reduced level of LTD seen after application of an mGluR5 agonist. In contrast, knocking out Reelin increased $STEP_{61}$ levels. Surprisingly, however, mGluR-dependent LTD was still impaired in Reelin-deficient mice. This effect appeared to result from a reduction in baseline surface expression of GluA2-containing AMPARs. Consistent with this, miniature and evoked AMPAR currents were larger in Reelin-deficient hippocampal neurons than in controls. In addition, comparing currents evoked at negative and positive holding potentials indicated that the proportion of inwardly rectifying, GluA2-lacking AMPARs was elevated in Reelin-deficient hippocampal neurons. Finally, a specific blocker of GluA2-lacking AMPARs greatly reduced AMPAR currents in Reelin-deficient neurons, but had no effect in wild-type neurons.

These results suggest that Reelin limits baseline expression of $STEP_{61}$ in adult hippocampus. Adding exogenous Reelin further reduces $STEP_{61}$ levels, thus inhibiting mGluR5-dependent LTD. In contrast, when Reelin is absent, $STEP_{61}$ levels increase, resulting in maximal dephosphorylation and internalization of AMPAR GluA2 subunits. Consequently, surface expression of GluA2-lacking receptors increases. This leads to an increase in basal AMPAR currents, and it occludes LTD because GluA2-lacking receptors are not subject to regulation by $STEP_{61}$.



Left, Migrating inhibitory interneurons (green) avoided substrate regions coated with the extracellular domain of FLRT3 (red). Right, The repulsive effect was lost when FLRT3 was mutated to prevent Unc5 binding. See Fleitas, Marfull-Oromí, et al. for details.

FLRTs Help Guide Migrating Cortical Interneurons

Catherine Fleitas, Pau Marfull-Oromí, Disha Chauhan, Daniel del Toro, Blanca Peguera, et al.

(see pages 7350–7362)

Unlike excitatory cortical neurons, which are born in the ventricular or subventricular zone (SVZ) just below the cortical layers they ultimately form and populate, inhibitory neurons are generated farther away, predominantly in the medial and caudal ganglionic eminences. Inhibitory neurons migrate tangentially to invade the developing neocortex in three streams: one in the marginal zone above the growing cortical plate, one along the border between the SVZ and the overlying intermediate zone (IZ), and one in the subplate between the IZ and the cortical plate. Later in development, inhibitory neurons change direction and migrate radially into the cortical plate. While migrating along these trajectories, neurons are guided by a combination of repulsive and attractive cues, few of which have been identified.

Fleitas, Marfull-Oromí, et al. hypothesized that members of the fibronectin- and leucine-rich transmembrane (FLRT) family of proteins, which contribute to guidance of excitatory cortical neurons, also help guide inhibitory neurons. Consistent with such a role, FLRT2 and FLRT3 were expressed in the IZ, which was avoided by inhibitory neurons migrating in the SVZ/IZ and subplate streams. Moreover, knocking out FLRT2 and FLRT3 (but not either by itself) led to a shortening of the subplate stream (but not the IZ/SVZ stream) and caused neurons that normally migrate in the subplate to spread into the IZ. In addition, migrating inhibitory neurons in explant cultures avoided stripes of substrate coated with FLRT2 and/or FLRT3. Notably, the repulsive effect of FLRT3 was diminished by mutating a domain that interacts with Unc5, a previously described FLRT3 receptor, and knocking out Unc5B and Unc5D mimicked the effect of FLRT2/3 knockout *in vivo*.

These results suggest that FLRT2 and FLRT3 have redundant functions in maintaining the subplate migratory stream of cortical inhibitory neurons. Examination of postnatal mice suggested that loss of FLRT2/3 selectively affected somatostatin-expressing neurons: there was a small but significant shift in the position of these neurons toward deeper cortical layers. But the marker used to identify interneurons, calbindin, was expressed in only ~40% of migrating GABAergic neurons, and previous work showed that few somatostatin-expressing neurons coexpress this protein. Therefore, FLRTs may affect inhibitory neuron migration even more profoundly than revealed by this study.

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