LEARNING AND MEMORY

Reelin' in clues to memory

Reelin is well known to regulate neuronal migration in embryonic development. More recently, it has been implicated in long-term potentiation in the adult hippocampus. New work, reported in *The Journal of Neuroscience*, shows that this dual role for Reelin in development and memory involves a shared signalling pathway that influences memory through its regulation of NMDA (*N*-methyl-D-aspartate) receptor function.

During embryonic development, Reelin regulates the proper positioning of neurons by triggering a cascade of events, starting with its binding to the very low-density lipoprotein (VLDL) receptor (VLDLR) and apolipoprotein E receptor 2 (APOER2), which, in turn, induces tyrosine phosphorylation of the adaptor protein disabled 1 (DAB1).

NMDA receptors (NMDARs) modulate synapse formation and long-term changes in synaptic strength through their control of Ca^{2+} entry into neurons. Phosphorylation and dephosphorylation of tyrosine residues on NR2 subunits of NMDARs is necessary for NMDAR gating activity. It turns out that DAB1 activates Src family kinases (SFKs), which are crucial for phosphorylation of NMDAR subunits. This suggests the intriguing possibility of a relationship between the Reelin-activated developmental signalling pathway and the regulation of synaptic ion channels.

To test this possibility, Chen and colleagues investigated the effects of Reelin on Ca^{2+} influx through NMDARs in primary cortical neurons of rats and mice. In the presence of Reelin, glutamate stimulation led to a striking increase in Ca^{2+} influx through NMDARs, whereas Reelin or glutamate stimulation alone led to no such increase. Blocking Reelin binding to VLDLR and APOER2 prevented the enhancing effects of glutamate-mediated Ca^{2+} influx. A similar effect was observed in neurons that were deficient in DAB1, and, therefore, unable to respond to Reelin. Pharmacological inhibition of SFKs also abolished the enhancing effects of Reelin on Ca^{2+} influx.

Increases in intracellular Ca^{2+} induce long-term changes in synaptic strength through the activation of CREB (cyclic AMP responsive element (CRE) binding protein), which triggers changes in gene transcription and expression. In the presence of Reelin, glutamate induced phosphorylation of CREB, whereas glutamate or Reelin alone had only minor effects. This indicates that Reelin might, ultimately, influence long-term synaptic plasticity by modulating activity-dependent gene transcription through its influence on intracellular Ca^{2+} concentrations.

This work draws together several lines of evidence to support a modulatory role for Reelin in long-term synaptic plasticity in adulthood through its effects on NMDAR gating. Moreover, results indicate that the same Reelin-activated developmental signalling pathway that supports neuronal migration is central to its role in learning and memory.

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ION CHANNELS

The comfort of camphor

The analgesic properties of camphor, a plant-derived product with a long history of medical use, might reflect its effects on at least two types of TRP (transient receptor potential) ion channel, according to a recent report from David Clapham's laboratory.

The six subfamilies of TRP ion channels have diverse roles as cellular sensors. Thermosensitive TRP channels detect a wide range of temperatures, including cool and warmth, and noxious cold and heat. In addition, all thermoTRP channels seem to be chemosensitive. For example, the vanilloid receptor TRPV1 is stimulated by heat and by capsaicin (the 'hot' ingredient in chilli peppers), the analgesic effects of which are probably due, at least in part, to channel desensitization.

Camphor is commonly applied to the skin for analgesic, antipruritic and counter-irritant purposes, but its molecular and cellular targets are largely unknown. Camphor was recently shown to activate TRPV3 in epithelial keratinocytes, and is known to produce a warm sensation, in keeping with the thermal activation range of this thermoTRP. But repeated applications of camphor led to TRPV3 sensitization, apparently contradicting camphor's analgesic role.

Xu and colleagues now report that camphor activates TRPV1 in a manner that is independent of the vanilloid (capsaicin) binding site, and inhibits ankyrin-repeat TRP 1 (TRPA1). Both of these thermoTRPs are abundant in nociceptive dorsal root ganglion (DRG) neurons. Camphor-evoked TRPV1-like currents recorded from rat DRG neurons were strongly potentiated after a manipulation that mimicked peripheral sensitization, which suggests that the use of camphor to treat irritated or inflamed skin might be related to its increased efficacy in these states.

Among TRPV1 agonists, Xu *et al.* showed that camphor has exceptionally strong desensitizing properties. The combined desensitization of TRPV1 and inhibition of TRPA1 provides a new explanation for the analgesic properties of this age-old remedy.

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