This Week in The Journal

● Cellular/Molecular

GluR1 Delivery in Mental Retardation

Hailan Hu, Yi Qin, Genrieta Bochorishvili, Yinghua Zhu, Linda van Aelst, and J. Julius Zhu

(see pages 7847–7862)

Fragile X mental retardation protein (FMRP) regulates many proteins, including Ras small GTPases, which are required for targeting of AMPA receptors to synapses during synaptic enhancement. Loss of FMRP causes mental retardation in humans, but experiments in which its gene, *FMR1*, was knocked out in mice have produced variable effects. Now Hu et al. have expressed mutant AMPA receptor subunits [glutamate receptors (GluRs)] in hippocampal and cortical neurons to track synaptic delivery in wild-type and *FMR1*-null mice. LTP was reduced by 50% in hippocampal slices from *FMR1* knock-outs, likely due to defective trafficking of GluR1. The neuromodulator histamine normally increases synaptic delivery of GluRs, in part via activation of a kinase pathway involving Ras, phosphoinositide 3-kinase, and protein kinase B, which phosphorylates GluR1. This signaling pathway is disrupted in *FMR1* knock-outs, but overexpression of Ras or reducing the activation threshold of its downstream kinases restored LTP and synaptic delivery of GluR1.

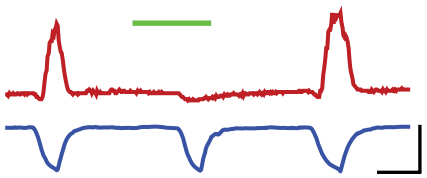
▲ Development/Plasticity/Repair

TRPA1-Mediated Cold Sensitivity

Otto Fajardo, Victor Meseguer, Carlos Belmonte, and Félix Viana

(see pages 7863–7875)

Although TRPA1 channels are activated by cold in cell lines, whether they have a physiologically relevant role in neurons has been questioned. Now the controversy appears to have been settled by Fajardo et al. Approximately half of visceral afferent neurons cultured from rat nodose ganglion responded to cold, as indicated by calcium imaging. Responses in the presence of specific agonists and antagonists of TRPA1 and TRPM8 (the main cold receptor in somatosensory neurons of the dorsal root ganglion) indicated that TRPA1 is responsible for most of the cold sensitivity in the nodose system. Interestingly, a subset of cold-sensitive nodose neurons were TRPA1 independent. Although mice had a smaller percentage of cold-sensitive nodose neurons than rats, TRPA1 knock-out eliminated most of the sensitivity, indicating that TRPA1 is also the main cold-responsive receptor in mouse visceral afferents. Some TRPA1-dependent cold-sensitive nodose neurons innervate the larynx, likely mediating reflexive responses to cold temperatures, such as coughing.



Response of a rat nodose neuron (red trace) to decreasing temperature (blue trace) is inhibited by application of a TRPA1 antagonist (green bar). Horizontal scale, 3 min; vertical scale, 200 nM Δ[Ca] or ~25°C. See the article by Fajardo et al. for details.

■ Behavioral/Systems/Cognitive

Dissociating Pain From Its Negative Affect

Satoshi Deyama, Takahiro Katayama, Atsushi Ohno, Takayuki Nakagawa, Shuji Kaneko, Taku Yamaguchi, Mitsuhiro Yoshioka, and Masabumi Minami

(see pages 7728–7736)

The negative affective states produced by pain can be reduced without eliminating the pain itself, according to Deyama et al. When formalin is injected into a rat's paw, the rat displays signs of pain (licking and biting the paw) and of aversion (the rat is conditioned to avoid the place where it experienced the pain). Deyama et al. found that formalin injection increased noradrenaline levels in the bed nucleus of the stria terminalis (BNST), a brain region implicated in negative affective states such as anxiety and fear. Injecting β_2-adrenoreceptor blockers into the BNST decreased the conditioned place aversion, but had no effect on paw licking and biting. Similarly, inhibiting protein kinase A (which normally increases after β-adrenoreceptor activation) reduced conditioned place aversion without altering pain behaviors. Conversely, injecting β-adrenoreceptor agonist into the BNST induced conditioned place aversion, indicating a prominent role for this pathway in producing the negative affective component of pain.

♦ Neurobiology of Disease

Dopamine and Noradrenaline Interactions in Learning

Liselijn A. B. Wisman, Gurdal Sahin, Matthew Maingay, Giampiero Leanza, and Deniz Kirik

(see pages 7797–7807)

This week, Wisman et al. describe interactions between dopaminergic and cholinergic pathways in modulating spatial memory. The authors used selective neurotoxins to lesion mesocorticolimbic dopaminergic neurons in the ventral tegmental area (VTA), septohippocampal cholinergic neurons in the medial septum, and/or basalocortical cholinergic neurons in the nucleus basalis magnocellularis. They then tested various forms of spatial learning using Morris water maze tasks. Reference memory—in which rats learned over several days to use extramaze navigational cues to find a stationary platform—was disrupted by dopaminergic lesions, but unaffected by cholinergic lesions. In contrast, performance on a working memory task—in which rats had to relearn the position of a platform that was moved daily—was not disrupted by dopamine or cholinergic lesions alone, but was disrupted when dopaminergic lesions were paired with septohippocampal cholinergic lesions. The results suggest that loss of dopaminergic neurons in the VTA contribute to cognitive decline in Parkinson's disease patients.