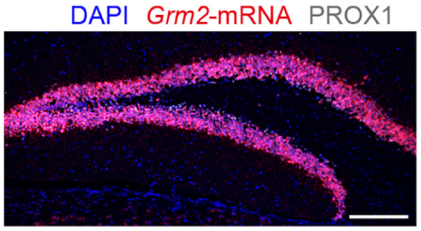
This Week in The Journal

Metabotropic Glutamate Receptors in Developing Adult-Born Neurons

Jiao Ma, Zhechun Hu, Huimin Yue, Yujian Luo, Chao Wang, et al.

(see pages 2822–2836)

Adult-born dentate granule cells (DGCs) are generated throughout adulthood and integrated into existing circuits in the hippocampal dentate gyrus—but how? The neurons are required for certain types of memory encoding and mood regulation; abnormal integration is associated with pathologies including schizophrenia, epilepsy, or Alzheimer's disease. This week, Ma et al. investigate the molecular requirements for the development and integration of the adult-born neurons in mice. The axon terminals of DGCs, called mossy fibers, contain the inhibitory metabotropic glutamate receptors GRM2/3, which, when activated, suppress the release of neurotransmitter by activating potassium ion channels and inhibiting calcium channels. GRM2 is expressed in mature DGCs, but their role in development remains unclear. Aberrant expression of GRM2 has also been implicated in neuropathological conditions, so the authors focused on their role in the DGCs. GRM2 expression was high in mature DGCs but not in newborn cells; expression increased over the first 3 weeks of development. When the authors knocked down expression of GRM2 using a small hairpin RNA, neurons produced fewer and shorter dendritic branches and had altered membrane and electrophysiological properties. Knockdown also led to a reduction in dendritic spine density and smaller axon boutons in newborn DGCs and decreased synaptic activity, suggesting that both axonal and dendritic integration had been impaired. Downstream of GRM2, the researchers interrogated the level of the signaling proteins cAMP response element-binding protein and extracellular signal-regulated protein kinases 1/2 (ERK1/2). Knockdown of GRM2 resulted in elevated phosphorylated ERK1/2 and its upstream effector, mitogen-activated protein kinase kinase (MEK), in developing neurons. Activation of ERK1/2 led to impaired neuronal development similar to that in GRM2 knock-down mice, indicating that GRM2 normally suppresses MEK/ERK1/2 activity, which is activated by the signaling protein b/cRaf. Viral expression of a dominant negative gene for ERK2, which leads to inhibition of MEK, rescued the developmental defects seen with GRM2 knockdown. In behavioral tests, GRM2 knockdown led to impaired object-to-place recognition. Finally, suppressing the activation of the MEK/ERK1/2 pathway in the knock-down mice rescued that cognitive deficit, leading the authors to speculate that such a manipulation of neurons lacking GRM2 might theoretically provide therapeutic benefits.



Fluorescently labeled GRM2 in the hippocampus.

Tangles of Tau: Maybe Not So Bad After All

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(see pages 2988–3006)

Neurodegenerative diseases that cause dementia, such as Alzheimer's disease, feature the aggregation of Tau, an essential microtubule-associated protein, which is thought to eventually contribute to neurotoxicity and neurodegeneration. But whether such neurofibrillary tangles contribute to the cognitive defects that emerge earlier in such tauopathies remains contested. This week, Vourkou et al. use a *Drosophila* model of tauopathy with pan-neuronal expression of human Tau to investigate. Flies expressing $hTau^{0N4R}$ for 12 d developed marked deficits in learning and protein synthesis-dependent memory (PSD-M). Learning was recovered, however, with an intensive conditioning paradigm, indicating that the deficits did not arise from neuronal loss. Protein synthesis-independent learning was not compromised by $hTau^{0N4R}$ expression, suggesting that Tau aggregation impaired protein translation but did not cause widespread neurotoxicity. Suppression of the hTau gene resulted in reduced transcript but not protein, demonstrating the stability of the aggregates. Remarkably, the deficits in PSD-M were rescued by hTau suppression, providing further evidence that the memory loss arose from specific neuronal dysfunction rather than widespread neurodegeneration. Transcriptional suppression increased rather than decreased insoluble hTau, suggesting that aggregates do not lead to neuronal dysfunction, and in fact may even be protective. But did the benefit arise from the increase in insoluble Tau or a decrease in soluble Tau? To find out, the authors fed the flies methylene blue (MetBlu), a drug that prohibits Tau aggregation, which did not change the level of soluble Tau but decreased insoluble Tau. MetBlu-treated $hTau^{0N4R}$ flies had impaired PSD-M compared with untreated animals, suggesting that aggregates of Tau are not harmful, but that soluble protein is. Together the results of the study paint a surprising picture of the role of Tau aggregates as a protective, rather than destructive, preserving and promoting PSD-M, whereas soluble Tau may play a more insidious role in disrupting learning and memory.

This Week in The Journal was written by Stephani Sutherland

https://doi.org/10.1523/JNEUROSCI.twij.43.16.2023