This Week in The Journal

Do Hippocampal $\alpha 5$ -GABA_A Receptors Regulate Anxiety?

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(see pages 788–801)

Information processing in hippocampal circuits is shaped by a diverse population of inhibitory interneurons that target different regions of pyramidal cells, influencing the integration of inputs or gating output. Oriens-lacunosum moleculare cells (OLMs) target the apical tufts of pyramidal cells, thus regulating input from entorhinal cortex. The activity of OLMs, in turn, is shaped by inputs from local pyramidal cells, septal afferents, and other interneurons, particularly type 3 interneuron-specific interneurons (IS3s). Recent work has suggested that OLMs in mouse ventral hippocampus regulate fear and anxiety-like behaviors: activating OLMs increased exploration near a predator odor, whereas inhibiting the neurons reduced exploration (Mikulovic et al., 2018 Nat Commun 9:917).

Work by Magnin, et al. complicates this picture. These authors were interested in the role of hippocampal GABA receptors containing the $\alpha 5$ subunit ($\alpha 5$ -GABA_ARs), because previous studies showed that these receptors are expressed widely in the hippocampus, including in OLMs, and inverse agonists of the receptors increase anxiety-like behaviors. $\alpha 5$ -GABA_ARs were indeed present near GABAergic terminals on the dendrites of presumptive OLMs in hippocampal CA1, and when channelrhodopsin was expressed selectively in neurons that express vasoactive intestinal peptide (a marker of IS3s), light-mediated activation of these neurons produced short-latency inhibitory currents in cells that expressed somatostatin (a marker of OLMs). These currents were partially suppressed by an inverse agonist of $\alpha 5$ -GABA_ARs, indicating that the $\alpha 5$ -GABA_AR inverse agonist might increase anxiety by reversing inhibition of OLMs by IS3s. If this is true, however, suppressing IS3 activity with designer receptors exclusively activated by designer drugs (DREADDs) should increase anxiety; it did not. Nevertheless, when IS3 activity was suppressed, the inverse agonist no longer

promoted anxiety-like behaviors in an elevated plus maze.

These and previous results might be reconciled by supposing that the $\alpha 5$ -GABA_AR inverse agonist affects anxiety primarily by disinhibiting IS3s. This would do nothing if the IS3s were silenced by DREADDs, but without such silencing, the inverse agonist would increase IS3 activity, and thus increase inhibition of OLMs (despite partial suppression of this inhibition by the inverse agonist). This would increase anxiety as observed by Mikulovic et al. (2018). Future work using more restricted targeting of neuronal subtypes in the ventral hippocampus should further elucidate this pathway.

Three months after transplantation of cells from dorsal epithelium, new ventral OSNs have been generated, as indicated by similar patterns of expression of dorsal (red) and ventral (green) markers in olfactory epithelia from damaged (right) and control (left) nasal cavities. See Coleman et al. for details.

Spatial Cues Shape Neuron Fate in Mature Olfactory Epithelium

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(see pages 814–832)

Mammals possess ~1000 odorant receptor genes, but each olfactory sensory neuron (OSN) expresses only one. Although the choice of receptor by a given OSN is somewhat stochastic, it is not entirely random: the olfactory epithelium is divided into zones in which only a particular subset of

odorant receptors is expressed. These zones, which also differ in expression of proteins other than odorant receptors, are thought to be induced during development by gradients of molecular cues. Nonetheless, the zones of receptor expression persist throughout life, even as OSNs are continually regenerated from olfactory stem cells. How the zones are maintained is unclear. One possibility is that environmental cues that guide receptor choice by OSNs persist throughout adulthood. Another is that during development, the cues induce epigenetic modifications in stem cells, restricting the set of odorant receptors that can be expressed by their progeny.

To test these hypotheses, Coleman et al. chemically ablated OSNs in the ventral olfactory epithelium of adult mice, then implanted cells harvested from the dorsal epithelium of donors. After 3 weeks, OSNs generated from donor stem cells populated the hosts' ventral epithelium; ~85% of these OSNs expressed normal ventral proteins, including the olfactory cell adhesion molecule. Moreover, these OSNs extended axons into the appropriate region of the olfactory bulb. Although many newly generated OSNs expressed multiple olfactory receptors, this is not unusual in immature OSNs and nearly all expressed at least one ventral receptor. Notably, treating donor cells with an inhibitor of histone deacetylases—which remove a particular type of epigenetic modification—significantly reduced the number of donor-derived OSNs that expressed ventral markers. This suggests that donor stem cells were partially restricted to a dorsal fate by histone acetylation and that these modifications had to be removed for the cells to acquire a ventral fate.

These results suggest that environmental cues that drive regional gene expression patterns in developing OSNs persist into adulthood and can shape appropriate development of transplanted stem cells. This is fortunate because it means that stem-cell therapies developed to replace damaged olfactory epithelia might not require the harvesting or production of region-appropriate precursors.

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