This Week in The Journal

Effects of Human mGluR7 Mutations on Rat Axon Outgrowth

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(see pages 2344–2359)

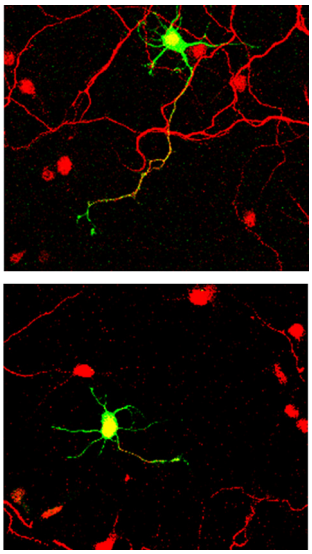
Metabotropic glutamate receptor 7 (mGluR7) is expressed throughout the brain, primarily in glutamatergic and GABAergic presynaptic terminals, where it inhibits neurotransmitter release. Mutations in *GRM7*, the gene encoding mGluR7, have been linked to several neurodevelopmental conditions in humans, including autism, intellectual disability, and seizure disorders. Knocking out *GRM7* in mice also causes seizures and cognitive and behavioral impairments, possibly by altering synaptic plasticity and impairing neuronal differentiation and neurite outgrowth.

To better understand how human variants of *GRM7* affect neuronal development, Song et al. asked whether particular variants could rescue the effects of *GRM7* knockdown in rat neurons in culture. Specifically, they tested the effects of wild-type *GRM7*, variant R622Q (which is linked to autism spectrum disorders), and variants I154T and R658W/T675K (both of which have been linked to developmental delay, intellectual disability, seizures, and reduced brain size).

Consistent with previous work, knocking down *GRM7* reduced axon growth and synapse formation in cultured neurons. These effects were rescued by expressing wild-type or R622Q *GRM7*, but not by expressing I154T or R658W/T675K variants. Notably, treating neurons that expressed *GRM7* I154T with a positive allosteric modulator of mGluR7 increased axon growth and synapse formation, whereas growth in neurons expressing R658W/T675K *GRM7* was unaffected by the modulator. This difference was attributable to the fact that R658W/T675K *GRM7* underwent proteasomal degradation and consequently was not expressed in the plasma membrane, whereas I154T *GRM7* was expressed on the cell surface, albeit at lower-than-normal levels.

The authors also sought to identify molecular mechanisms linking mGluR7 to axon growth. An mGluR7 agonist increased axonal growth, whereas an antagonist reduced growth. Somewhat surprisingly, however, preventing the interaction between mGluR7 and its partner $G_{i/o}$ had no effect on agonist-induced axon growth. Instead, the agonist effect was blocked by inhibiting protein kinase A, MAPK, or microtubule polymerization. Conversely, the effect of mGluR7 antagonist was reduced by a cAMP analog. Notably this analog also increased axon growth in neurons expressing I154T or R658W/T675K *GRM7*.

These results suggest that activation of mGluR7 promotes axon growth via MAPK-dependent increases in cAMP and downstream activation of protein kinase A and cytoskeletal reorganization. This function, as well as promotion of synapse formation, is disrupted in mGluR7 variants linked to intellectual disabilities and seizures. Whether these effects are directly related to cognitive and behavioral phenotypes remains to be tested.



Cortical neurons extend axons (red) by 3 d in culture (top). Knocking down mGluR7 (bottom) blunted axon growth. See Song et al. for details.

Contralateral Bias in Hippocampal Response to Visual Scenes

Edward H. Silson, Peter Zeidman, Tomas Knapen, and Chris I. Baker

(see pages 2382–2392)

People use their visual systems to interpret their surroundings, anticipate events that might occur in the current environment, and navigate within and between locations. These cognitive functions depend on the brain's ability to represent the spatial relationships between objects in a scene. The encoding of spatial relationships is likely facilitated by topographical organization, in which adjacent points in space are represented by adjacent clusters of neurons. Such topographical organization is present throughout the visual system, from the thalamic lateral geniculate nucleus and primary visual cortex to cortical areas involved in scene processing, such as the parahippocampal gyrus and the medial place area in the parietal cortex.

Scene-selective cortical areas provide input to the hippocampus, which contributes to both navigation and contextual memory formation. Silson, Zeidman, et al. show that a degree of retinotopographic representation persists even in the human hippocampus. The authors acquired functional magnetic resonance images as participants viewed fragments of scenes through an aperture that moved slowly across the visual field. Population receptive fields in both the left and right hippocampus showed a significant contralateral bias. This bias was detected in anterior and middle, but not posterior, portions of the hippocampus, and notably, the bias was strongest for voxels that were more responsive to scenes than to other visual stimuli, such as faces or objects. Importantly, these findings, based on data from 29 participants, were confirmed with data from 161 people obtained as part of the human connectome project initiative.

These results demonstrate the pervasiveness of retinotopy in the human brain by showing preferential representation of the contralateral visual field in the hippocampus, particularly in anterior regions that have a prominent role in representing scenes. The authors did not find evidence of systematic retinotopic organization within the hippocampus, however. Future work using higher-resolution fMRI with smaller voxel sizes should determine whether such retinotopic mapping exists and determine how this topography affects navigation and other hippocampal functions.

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