An astrocytic generation gap

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It has become somewhat of a cliché to say that glial cells are more than ‘brain glue’ and have important functions in the brain. However, the idea that glial cells, specifically astrocytes, respond to neuronal glutamate release with increases in intracellular Ca^{2+} levels and the subsequent release of ‘gliotransmitters’ has remained controversial. Nedergaard and colleagues now show that contradictory data could be explained by their new finding that astrocytes in developing brains express metabotropic glutamate receptor 5 (mGluR5), whereas astrocytes in adult brains express only mGluR3, and that the former, but not the latter, respond to glutamate with a Ca^{2+} increase.

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Studies that showed evidence of mGluR5-dependent increases in intracellular Ca^{2+} in astrocytes in response to neural activity have mainly been performed in slices taken from young animals or from astrocyte cultures obtained from fetal brain tissue. Among other issues, these approaches raised the question of whether the effect could be limited to the developing brain, and the authors set out to address this question.

They used an antibody directed against the astrocyte-specific glutamate transporter excitatory amino acid transporter 2 (also known as GLT1) or ALDH1L1 protein to specifically label astrocytes and then measured the expression of different mGluRs on astrocytes. Microarrays and quantitative PCR showed that astrocytes from adult human cortex almost exclusively expressed *GRM3*, the gene encoding mGluR3. Similarly, cortical and hippocampal astrocytes from adult mice mainly expressed *Grm3*. By contrast, astrocytes from 1-week-old mice showed high expression of both *Grm3* and *Grm5*, and, importantly, *Grm5* expression fell sharply from week 2 onwards.

mGluR5 is a G_q -coupled receptor that mobilizes intracellular Ca^{2+} when activated. Accordingly, in acute slices taken from the cortex or hippocampus of 12–15-day-old mice, treatment with several mGluR5 agonists evoked a clear increase in astrocytic intracellular Ca^{2+} . Similarly, in mice pups *in vivo*, intracellular Ca^{2+} levels increased in cortical

astrocytes in response to injections of an mGluR5 agonist. By contrast, in adult mice, astrocytes did not respond to the mGluR5 agonist. This was not due to an inability of adult astrocytes to mobilize Ca^{2+} , as Ca^{2+} levels did increase in response to ATP injections. Injections of an mGluR3 agonist also did not induce a Ca^{2+} rise in astrocytes in adult mice — this was expected, as mGluR3s are G_i -coupled receptors, which are linked to cyclic AMP (cAMP) signalling rather than Ca^{2+} signalling.

The finding that astrocytic Ca^{2+} signalling in response to neural activity is restricted to astrocytes in (or harvested from) developing cortex and hippocampus, which express mGluR5, could explain the absence of such signalling in some studies. Adult astrocytes may instead respond to neural activity by mGluR3-induced suppression of intracellular cAMP signalling. Together, these data point to distinct forms of neuron–astrocyte signalling in developing and adult brains. Future studies may explore whether astrocytic mGluR3 and mGluR5 expression is altered in disease states that have been associated with changes in gliotransmitter release.

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ORIGINAL RESEARCH PAPER Sun, W. et al. Glutamate-dependent neuroglial calcium signaling differs between young and adult brain. *Science* **339**, 197–200 (2013)
FURTHER READING Hamilton, N. B. & Attwell, D. Do astrocytes really exocytose neurotransmitters? *Nature Rev. Neurosci.* **11**, 227–238 (2010)