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mGluR5 is a central regulator of synaptic function and plasticity in the developing mouse barrel cortex

Glutamate, the main excitatory neurotransmitter in the vertebrate brain, acts both on ligand-gated ion channels as well as on metabotropic receptors (mGluRs), which engage an array of biochemical regulatory pathways via activation of G-proteins. mGluRs have been shown to exert central roles in the regulation of neuronal excitability by both pre- and post-synaptic mechanisms, and consequently have been implicated in a variety of central nervous system functions that include, but are not limited to, learning, pain perception and anxiety. There exists three groups of mGluRs (types I, II and III), accounting for a total of eight different mGluR types (mGluR1-8) (Hollmann and Heinemann 1994).

Group I mGluRs, which encompass mGluR1 and mGluR5, engage Gq-dependent second messenger systems which, in turn, regulate post-synaptic activity and local protein synthesis. Abnormal signalling through group I mGluRs have been associated with a series of neurological disorders including Fragile X syndrome and schizophrenia (Dolen and Bear 2008; Krivoy *et al*. 2008). Importantly, group I mGluRs have been shown to regulate synaptic plasticity both in developing and adult organisms. Noteworthy, genetic or pharmacological manipulations directed at mGluR5-containing receptors significantly impair learning and memory formation (Lu *et al*. 1997; Chiamulera *et al*. 2001). These roles for mGluR5 correlate with marked experience-dependent changes in synaptic strength, including long-term potentiation and depression (Eckert and Racine 2004).

The impact of mGluR5 activity on synaptic function and plasticity suggested that activation of this receptor may constitute a central molecular component underlying the developmental establishment and/or experience-dependent refinement of sensory maps found in primary sensory cortex of mammals. Such a role for mGluR5 was recently confirmed in an elegant study by She and colleagues (2009) recently published in the *European Journal of Neuroscience*. These authors report that mice devoid of the mGluR5 receptor expression (mGluR5$^{-/-}$) lack the normal arrangement of thalamocortical afferents and layer IV cell bodies associated with the rostral smaller whiskers of the facial vibrissal system, commonly referred to as the barrel cortex. Interestingly, the anatomical organisation of the thalamocortical afferents carrying information from the caudal and larger vibrissae was preserved in mGluR5$^{-/-}$ mice. These animals, however, lack the aggregation of the cortical layer IV cell bodies into clusters that would, in wild-type or heterozygous mice (mGluR5$^{+/-}$), exclusively represent each vibrissa. In addition, it was found that mGluR5-null mice exhibit a striking mis-alignment of the dendritic fields of spiny stellate neurons, which contribute to the formation of the classic columnar neuronal arrangements typical of the barrel cortex. In particular, in intact mice, dendritic fields of layer IV neurons are normally oriented towards the barrel center, an organisation that putatively oversamples inputs from the dominant vibrissae to sharpen the perceptual experience of sensory drive from each whisker (Harris and Woolsey 1981). In mGluR5-deficient mice, dendritic fields are more dispersed suggesting that pruning or mobility may be mal-adaptive in these animals, and may ultimately compromise the resolution at which sensory input can be processed. It was found that at post-natal weeks 2–3, mGluR5$^{-/-}$ mice failed to show the expected polarisation of dendritic fields towards the barrel center and that this abnormal pattern persists into adulthood. Interestingly, the anatomical patterning of axonal terminations from thalamocortical afferents was appropriate for barrel formation, and functional synaptic transmission for sensory-driven responses was spared. Malformation of the barrel cortex in mGluR5$^{-/-}$ therefore appears to result from abnormalities in intra-cortical properties and localised to post-synaptic neurons targeted by the thalamocortical afferents.

Consistent with abnormalities in the formation of the barrel cortex in mGluR5$^{-/-}$ mice, these mutant animals show reduced latency to the surround whisker responses. This feature is shared with *barrelless*

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mice, which carry a mutation in the gene that encodes adenylyl cyclase type I and that lacks the barrel-like segregation of thalamocortical axons and layer IV neurons. These findings suggest that mGluR5-deficient mice may exhibit reduced ability to distinguish deflections occurring in the principle whiskers versus those generated by surround stimulation.

Using *in vivo* single-unit electrophysiological recordings, She and colleagues were also able to show that the response magnitude of neurons responding to the principal whisker is not different between control and mGluR5 knock-out mice. Interestingly, however, it was found that the latency of the dominant surround whisker (within the surround receptive field) was markedly shorter in mGluR5$^{-/-}$ mice versus those observed in controls, suggesting that deletion of mGluR5 decreases the temporal discrimination of center to surround whiskers.

Finally, She and co-workers explored if and how the properties of synaptic transmission and plasticity in may be affected following genetic deletion of mGluR5. Using an *in vitro* barrel cortex preparation, these authors found that signalling mediated by AMPA-type glutamate receptors appeared normal. Conversely, NMDA currents with significantly faster kinetics were observed in mGluR5$^{-/-}$ mice. Unlike *barrelless* mice, however, mGluR5$^{-/-}$ mice exhibited intact or enhanced thalamocortical LTD, and attenuated LTP, suggesting that experience-dependent changes in synaptic strength are altered in mutant animals and appear to rely on mGluR5-containing receptors under normal conditions. Taken together with findings from *barrelless* mice, these data suggest that activity of mGluR5 is required for the adequate experience-dependent orientation of dendritic fields and that mGluR5-dependent LTP may be required for normal development of the barrel cortex.

In summary, the findings obtained by She and colleagues illustrate a central contribution of mGluR5 to the development of the barrel cortex in the rodent brain, and further our understanding of how specific receptor compositions contribute to shaping the anatomical and functional organisation of sensory maps in the vertebrate brain. Moreover, the partial disruption of barrel cortex formation observed in mGluR5$^{-/-}$ mice highlights the synergistic interaction of developmentally-guided and activity-dependent processes in the development of mammalian sensory maps. Future studies should focus on investigating whether such mechanisms are specific to the somatosensory system or generalise to other sensory systems.

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