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Reappearance of astrocytic mGluR5 assembles cortical networks in induction of neuropathic pain

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Astrocytes play essential roles for the modulation of neural networks, but also have critical roles for the pathogenesis of neural disorders. Recently, we revealed that astrocytes in the primary somatosensory cortex (S1) have a critical role for neuropathic pain after partial sciatic nerve ligation (PSNL). In brief, PSNL generated Ca²⁺ excitation in S1 astrocytes, induced synaptogenesis, thereby resulting in cross-wiring of innocuous and nocuous circuits. Reappearance of mGluR5 correlated with neuropathic pain, but we still do not know whether astrocytic mGluR5 is required or not. Here, we show that mGluR5 in S1 astrocytes is a cause of cortical rewiring and neuropathic pain. Firstly, we found that mGluR5 is almost absent but reappeared in S1 astrocytes after PSNL. Secondly, we made brain astrocyte-specific mGluR5 knockout mice (astro-mGluR5-KO) and validated them. PSNL-induced mechanical allodynia was abolished in astro-mGluR5-KO mice, suggesting that upregulation of mGluR5 in S1 astrocytes should be required for mechanical allodynia. Third, mechanisms underlying astrocytic mGluR5-mediated allodynia were; (1) increase in Ca²⁺ activity, (2) expression of synaptogenic molecules such as glypican4 and hevin, (3) synaptogenesis, (4) persistent rewiring of incorrect S1 circuits. Hence, we conclude that astrocytic mGluR5 is a crucial molecule that triggers synaptogenesis in S1 after PSNL, which is the causative event for the pathogenesis of neuropathic pain.