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LTP: GluN2B on the go

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LTP, the lasting increase in synaptic transmission following heightened activity, is viewed as the physiological basis of learning. In this issue of *The EMBO Journal*, Dupuis *et al* find that certain NMDARs diffuse away upon LTP. Antibodies against the NMDAR from patients with autoimmune synaptic encephalitis prevent this redistribution and LTP.

See also: **JP Dupuis *et al*** (April 2014)

During basal neurotransmission, glutamate activates Na^+ influx through AMPA receptors (AMPARs) to depolarize postsynaptic sites. Bursts of high-frequency neurotransmission induce Ca^{2+} influx through NMDA receptors (NMDARs) to stimulate the Ca^{2+} and calmodulin-dependent kinase CaMKII (Lisman & Hell, 2008; Nicoll & Roche, 2013). These events can cause LTP, that is, permanently enhance the strength of a synapse, by increasing postsynaptic AMPAR content (Lisman & Hell, 2008; Nicoll & Roche, 2013).

Most AMPARs consist of two GluA1 and two GluA2 subunits and NMDARs of two GluN1 and two GluN2A or GluN2B subunits (Gray *et al*, 2011). PSD-95 anchors AMPAR and NMDAR at postsynaptic sites (Lisman & Hell, 2008; Nicoll & Roche, 2013). Dupuis *et al* (2014) now find that in immature neurons, lateral diffusion of GluN2B (but not GluN2A) increases 1–4 min after LTP, which they induced by brief glycine application to temporarily increase NMDAR activity. The result is a reduction in postsynaptic GluN2B. These findings mirror electrophysiological work showing that in young (P2-9) rats, GluN2B is swiftly replaced by GluN2A following LTP (Bellone & Nicoll, 2007). Dupuis *et al* now provide a cellular mechanism for this GluN2B/2A switch.

The GluN2B mobilization requires two kinases, CaMKII and the casein kinase CKII (Fig 1A). Activation of CaMKII upon Ca^{2+} influx leads to its autophosphorylation on T286. The dodecameric CaMKII then binds simultaneously to GluN2B and CKII linking the two together (Sanz-Clemente *et al*, 2013). CKII subsequently phosphorylates S1480 in the C-terminal SXV motif of GluN2B to disrupt its binding to PSD-95, which otherwise docks GluN2B at postsynaptic sites, allowing GluN2B to diffuse away (Fig 1A, center and right). An alternative, perhaps parallel mechanism is suggested by the finding that the GluN2B mobilization (Dupuis *et al*, 2014) as well as the GluN2B/2A switch during synapse maturation (Matta *et al*, 2011) also requires the activity of mGluR5, a Gq protein-coupled metabotropic glutamate receptor that activates PKC. PKC can stimulate the tyrosine kinase Pyk2, which then stimulates the tyrosine kinase Src to augment NMDAR activity and to promote LTP (Fig 1B, center and right) (Bartos *et al*, 2010).

To define a functional role of this GluN2B mobilization, the authors impair NMDAR diffusion with antibodies against the extracellular N-termini of GluN1 or GluN2B plus secondary, cross-linking antibodies. This manipulation does not affect basal GluA1 mobility, synaptic GluA1 or GluN1 content or NMDAR-mediated mEPSCs. It does, however, prevent the glycine-induced increase in postsynaptic GluA1 and GluA2 content in cultured neurons and LTP induced by electric stimulation in acute hippocampal slices, suggesting that GluN2B diffusion plays a role in LTP.

Autoantibodies against the N-terminus of GluN1 can cause autoimmune synaptic encephalitis, which impairs cognition and memory. Dupuis *et al* find that IgG from sera of such patients prevent NMDAR diffusion and glycine-induced LTP. This effect does not require secondary, cross-linking antibodies raising the question how these autoimmune antibodies do impair NMDAR diffusion or whether effects other than impaired diffusion are responsible for the LTP block. The antibodies could have structural effects potentially preventing metabotropic signaling by NMDARs, which occurs independent of ion flux apparently via conformational changes in NMDARs (Nabavi *et al*, 2013). Although the antibodies do not affect CaMKII binding to GluN2B under basal conditions, they prevent the accumulation of CaMKII in spines that is otherwise seen upon Ca^{2+} influx via NMDAR and requires binding of CaMKII to the C-terminus of GluN2B, as needed for LTP (Halt *et al*, 2012). Lateral mobility of GluN2B might be necessary for capturing CaMKII and perhaps moving CaMKII to locations such as perisynaptic sites. However, it seems more likely that GluN2B and with it CaMKII diffusing away from the central postsynaptic sites would impair rather than promote LTP. Alternatively, the antibodies could prevent a conformational change in the C-terminus upon glutamate binding to GluN2B, which in turn prevents CaMKII binding or phosphorylation by Src and with it coincidentally LTP and lateral diffusion (Fig 1, left panels). Such a conformational model would also address the issue that within the time frame of GluN2B diffusion of 1–4 min after LTP induction, NMDAR activation at least by evoked transmission is no longer required for the maintenance of LTP (Adesnik & Nicoll, 2007). Further supporting allosteric mechanisms, only CaMKII binding to GluN2B, but not CaMKII activity, is required beyond initial induction of LTP for LTP to be stable (Sanhueza *et al*, 2011). It is thus quite conceivable that the NMDAR antibodies prevent LTP by

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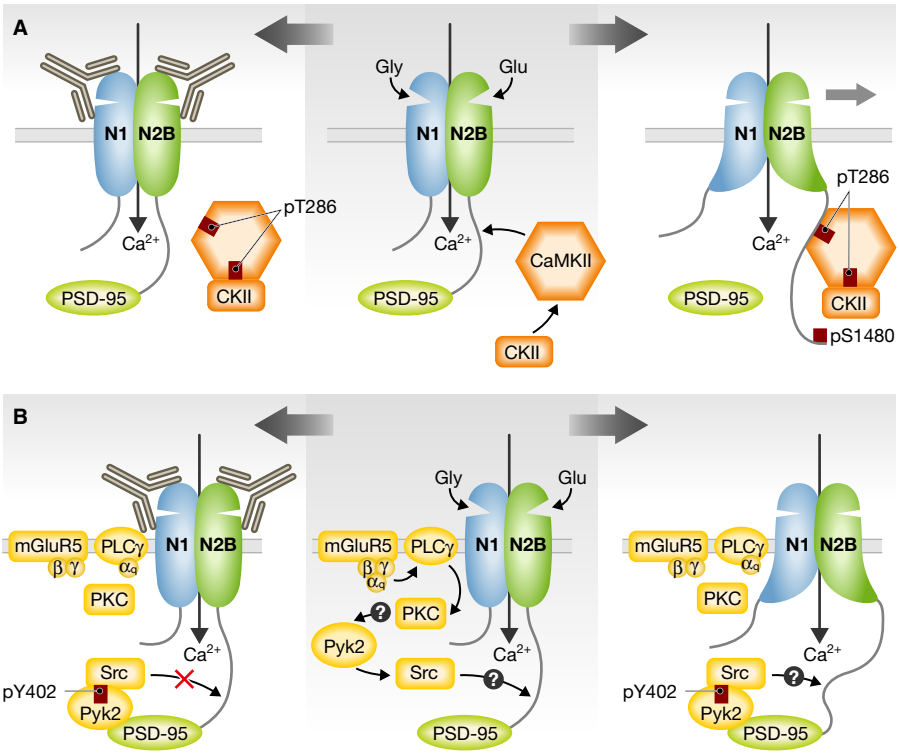

Figure 1. Hypothetical model of allosteric mechanisms upon binding of glutamate to GluN2B and the co-agonist glycine to GluN1.
(A) The Ca^{2+} influx triggers autophosphorylation of the dodecameric CaMKII on T286 (center) for the recruitment of CKII to GluN2B, S1480 phosphorylation, displacement of PSD-95, and GluN2B mobilization (right). (B) Activation of mGluR5 stimulates PKC, which, via unknown mechanisms, induces Pyk2 autophosphorylation on Y402. Src binds to pY402 and increases NMDAR activity via unknown mechanisms that might be important for the stabilization of LTP during its first 2–3 min (Bartos *et al*, 2010). In the models to the left, without affecting Ca^{2+} influx, antibodies are hypothesized to prevent a conformational change in the GluN2B C-terminus, which in turn prevents binding of the CaMKII/CKII couple (A) or regulation of NMDAR by Pyk2/Src (B).

blocking the required activity-induced binding of CaMKII to GluN2B. Changes in postsynaptic GluN2B content could then be important during later phases of LTP and, more generally, synaptic development. Clearly, Dupuis *et al* raise many interesting open questions, which will inspire future work.

Conflict of interest

The authors declare that they have no conflict of interest.

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