Comment on “Role of NMDA Receptor Subtypes in Governing the Direction of Hippocampal Synaptic Plasticity”

Liu et al. (1) recently showed that blockade of N-methyl-D-aspartate (NMDA) subtype glutamate receptors containing either NR2A or NR2B subunits leads to a selective defect in either long-term potentiation (LTP) or long-term depression (LTD), respectively. Their report provides an elegant demonstration of complementarity of function of the receptor subtypes (2). We would like to draw attention to a potentially important implication of the results for network behavior. NR2A-containing receptors, unlike NR2B-containing receptors, are located almost exclusively within synapses (3–5). Therefore, the balance of LTP and LTD in a cell could reflect the degree to which synaptic, as opposed to extrasynaptic, receptors are activated. Liu et al. modestly omitted reference to a previous study from the same group supporting precisely this principle (6).

Taken together with recent evidence that extrasynaptic spillover of glutamate is detected exclusively by NR2B-containing NMDA receptors (7–9), these findings provide a novel mechanism for homeostatic regulation of excitatory transmission (10) and for sharpening pattern storage in the neuronal network. An elevation in ambient glutamate, released from multiple synapses and sensed by extrasynaptic NR2B-containing receptors, should trigger widespread LTD if accompanied by neuronal depolarization (Fig. 1). This does not preclude induction of LTP at synapses where glutamate is released and opens synaptic NR2A-containing receptors. The higher affinity of NR2B- than NR2A-containing receptors for glutamate (11) is well suited to their proposed role in weakening transmission as a function of heterosynaptic activity.

Differential activation of NR2A- and NR2B-containing receptors by synaptic and extrasynaptic glutamate also has distinct consequences for gene transcription (12). Finally, because the relative density of synaptic and extrasynaptic NR2A- and NR2B-containing receptors changes with age (3, 13, 14), their complementary roles in synaptic plasticity may be developmentally regulated.

Dmitri A. Rusakov*  
Annalisa Scimemi  
Matthew C. Walker  
Dimitri M. Kullmann*  
Institute of Neurology  
University College London  
Queen Square  
London WC1N 2BG, UK  
*To whom correspondence should be addressed.  
E-mail: d.kullmann@ion.ucl.ac.uk (D.M.K); d.rusakov@ion.ucl.ac.uk (D.A.R.)

References

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Fig. 1. NR2B-containing receptors (unlike NR2A-containing receptors) occur in the extrasynaptic membrane. Glutamate escaping from synapses selectively activates NR2B-containing receptors (dotted arrows). The selective coupling of NR2A- and NR2B-containing receptors to LTP and LTD, respectively (1), provides a mechanism for homeostatic plasticity if homosynaptic LTD is accompanied by heterosynaptic LTD. The model also implies that LTP induction overrides or precludes LTD at the same synapse, indicated by the question mark.
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