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) sub-type 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 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.

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References

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