This Week in The Journal

Neither GluN2A nor GlunN2B Is Required for LTD

Jonathan M. Wong and John A. Gray

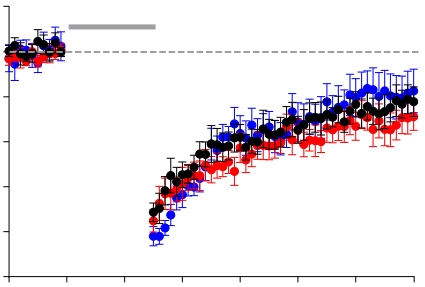
(see pages 4462–4470)

Activation of postsynaptic NMDA receptors (NMDARs) induces either long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength depending on stimulation parameters. For example, high-frequency stimulation of hippocampal CA3 afferents to CA1 pyramidal neurons induces LTP, whereas low-frequency stimulation of the same afferents induces LTD. How NMDAR activation can produce opposite effects remains unknown.

One appealing hypothesis is that the subunit composition of NMDARs influences the direction of plasticity. Most hippocampal neurons express NMDARs containing two GluN1 subunits along with two GluN2A and/or GluN2B subunits. GluN2A-containing receptors have a higher probability of opening and have faster kinetics than GluN2B-containing receptors; consequently, the charge transfer and calcium elevation resulting from activation of the two types of receptors differs. In addition, differences in the intracellular domains of GluN2A and GluN2B enable them to interact with different proteins. For example, GluN2B binds to CaMKII, an essential mediator of LTP induction. Such differences in receptor properties might favor LTP or LTD. In fact, there is good evidence that GluN2B-containing NMDARs are necessary for LTP induction. One might expect, then, that GluN2A-containing receptors promote LTD. Previous tests of this hypothesis have produced conflicting results, however (Shipton and Paulsen, 2014 Philos Trans R Soc Lond B Biol Sci 369:20130163).

Wong and Gray now provide strong evidence that neither GluN2A nor GluN2B is required for LTD at CA3–CA1 synapses. Whereas knocking out the obligatory GluN1 subunit in a sparse population of rat CA1 neurons prevented the induction of LTD in these neurons, knocking out either GluN2A or GluN2B had no effect on LTD. Moreover, LTD was induced in GluN2A-lacking and GluN2B-lacking neurons in both the presence and absence of a glycine-site antagonist that blocks channel opening, suggesting that NMDARs containing either subunit can support LTD regardless of current flux.

These results suggest that the subunit composition of NMDARs does not determine the direction of plasticity produced by receptor activation, at least in CA3–CA1 synapses in 2- to 3-week-old rats. What does allow NMDARs to induce opposite effects on synaptic strength remains unclear. The answer might lie in the GluN1 subunit and its interaction partners.



Low-frequency stimulation (gray bar) induces similar amounts of LTD in control neurons (black), neurons lacking GluN2A (red), and neurons lacking GluN2B (blue). See Wong and Gray for details.

How Neuropeptide Y Reduces Future Excitability in Amygdala

Heika Silveira Villarroel, Maria Bompolaki, James P. Mackay, Ana Pamela Miranda Tapia, Sheldon D. Michaelson, et al.

(see pages 4505–4520)

Excessive stress can cause long-term psychological problems, including depression and anxiety. Not all people who experience intense or prolonged stress develop these disorders, however. Social support, experience dealing with mild stressors, and genetic factors help make people resilient. Neuropeptide Y (NPY) is thought to play a major role in this resilience.

NPY is released during stressful experiences and it helps terminate stress responses initiated by corticotropin releasing factor (CRF). For example, whereas CRF enhances I_h (a depolarizing inward current that is activated at hyperpolarized membrane potentials) in neurons from rat basolateral amygdala (BLA), NPY inhibits I_h, thus limiting depolarization and reducing neuronal excitability. Moreover, injection of NPY into the BLA lessens the reduction in social interaction seen in rats after they are exposed to restraint stress, and this effect persists for up to 8 weeks (Sajdyk et al., 2008 J Neurosci 28:893).

Whether the long-term effects of NPY on social interactions involve I_h has been unknown. To address this, Silveira, Bompolaki, et al. injected NPY into BLA and recorded neurons in slices 2 or 4 weeks later. After 2 weeks, NPY-exposed neurons had a more hyperpolarized resting membrane potential than control neurons. Furthermore, whereas CRF increased I_h in control neurons, it did not affect I_h in neurons from NPY-treated rats. Nonetheless, I_h amplitudes were similar in control and NPY-exposed neurons, and acute NPY application hyperpolarized neurons regardless of prior treatment. At 4 weeks after injection, NPY-exposed neurons were still more hyperpolarized than normal and remained insensitive to CRF. But baseline I_h was significantly reduced at this time, and acute NPY had no effect. The reduction in I_h was attributable at least in part to reduced levels of HCN1, the channel that carries this current. Notably, knocking down HCN1 in BLA mimicked the effect of NPY injection, increasing social interaction for at least 8 weeks.

These results suggest that NPY produces long-term reductions in the excitability of BLA neurons by reducing expression of HCN1 channels. This not only results in a more hyperpolarized resting membrane potential, but also blunts the effect of CRF. The reduction in HCN1 levels appears to contribute to increases in social interaction induced by NPY treatment, and may thus help counter the effects of stress.

This Week in The Journal was written by Teresa Esch, Ph.D.