This Week in The Journal

Effects of Stress, NR4A1, and AMPK on Spine Density

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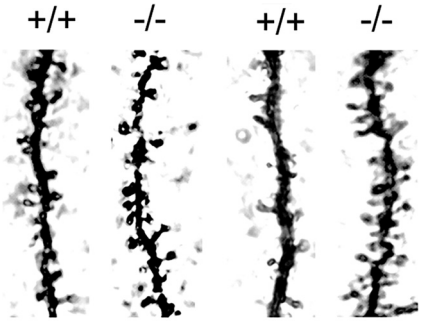
(see pages 1335–1350)

Exposure to stressors triggers release of glucocorticoids, such as corticosterone, from the adrenal glands. Glucocorticoids act on receptors in the brain to alter neural activity and circuitry, thus shaping behavioral and physiological responses to the stressor. The effects of glucocorticoids differ depending on the brain region, as well as on the intensity and duration of the stressful event. For example, acute exposure to moderate stressors increases glutamate release and the expression of glutamate receptors in the prefrontal cortex (PFC), and this is associated with enhanced working memory. In contrast, chronic stress leads to loss of dendritic spines and branches in the PFC, and it impairs PFC-dependent functions. These effects are thought to underlie stress-related psychiatric conditions. Nonetheless, loss of dendritic spines and branches might be beneficial, because it may protect neurons from glutamate-induced excitotoxicity (Popoli et al. 2012 Nat Rev Neurosci 13:22).

Little is known about the molecular pathways leading to dendritic atrophy during chronic stress, but Jeanneteau et al. provide evidence that the transcription factor NR4A1 is involved. Chronic stress or corticosterone administration increased nuclear localization and activity of NR4A1 in PFC. Furthermore, overexpression of wild-type NR4A1 reduced spine density in PFC, whereas knocking down or overexpressing a dominant-negative form of NR4A1 prevented spine loss resulting from chronic stress or corticosterone. Finally, whereas corticosterone normally increases immobility in the tail-suspension test, this effect was reduced in NR4A1-deficient mice.

Investigating how NR4A1 might affect spine density, Jeanneteau et al. focused on mitochondrial genes. They found that NR4A1 overexpression altered expression of genes that uncouple the electron transport chain from ATP synthesis. Consistent with this, NR4A1 overexpression exacerbated ATP depletion produced by glutamate, and thus increased activation of AMP kinase (AMPK). Notably, reducing or increasing AMPK activation rescued spine density changes associated with increasing or decreasing NR4A1 activity, respectively.

Together, these results suggest that chronic stress leads to spine loss at least in part through activation of NR4A1 and downstream activation of AMPK. The authors suggest that AMPK acts as a sensor of cellular energy levels and triggers spine loss to reduce neural activity and thus conserve energy when ATP levels are low. Future work should test this hypothesis.



Compared with control conditions (left two images), chronic treatment with corticosterone (right two images) reduces spine density in wild-type (+/+) cortical pyramidal neurons but not in neurons lacking NR4A1 (−/−). See Jeanneteau et al. for details.

Timing Cortical Stimulation to Maximize Plasticity

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(see pages 1396–1407)

Some functions lost after stroke can be restored through rehabilitative therapies that promote nervous system plasticity. Recovery of motor function, for example, is enhanced by movement exercises, which may be assisted by robotic devices. Electrical stimulation of muscles or peripheral nerves can further improve function by inducing activity-dependent plasticity. Still further improvement might be achieved with noninvasive stimulation of motor cortex in conjunction with other therapies. For such stimulation to be helpful, however, the timing must be controlled to ensure that plasticity mechanisms strengthen rather than weaken circuits. Moreover, the stimulation must selectively target those neurons that promote production of the intended movement: stimulating all neurons in a region can increase noise and degrade performance. When using inherently indiscriminate techniques such as transcranial magnetic stimulation (TMS), specificity can be achieved by controlling the activity state of neuronal populations through performance of relevant tasks (Romei et al. 2016 Trends Neurosci 39:782).

Kraus et al. examined how the timing of motor cortical stimulation relative to ongoing brain activity and proprioceptive input from the hand affected corticospinal output, as reflected by the size of motor-evoked potentials (MEPs) recorded in the hand extensor muscle. Healthy subjects were asked to imagine opening their hand without actually doing so. Successful motor imagery causes desynchronization of β-frequency oscillations in motor cortex, which was detected with electroencephalography and used to trigger passive hand opening by a robotic brace. TMS was applied to the hand region of motor cortex either when desynchronization occurred or 80 ms later. Persistent increases in MEP amplitude and area were produced only when cortical stimulation was applied concurrently with desynchronization. In contrast, when TMS was applied simultaneously with passive hand opening in the absence of motor imagery, MEP amplitudes decreased.

These results demonstrate that TMS can increase, decrease, or have no effect on motor corticospinal output depending on the state of cortical activity when stimulation is administered. The fact that the MEP area increased when stimulation was paired with motor imagery suggests that additional corticospinal neurons were recruited as a result of the stimulation. This type of plasticity might be especially important for recovery of function after stroke. Therefore, such stimulation protocols might improve rehabilitative therapies.

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