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Learning to deal with life's ups and downs

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Abstract

A study shows that circadian glucocorticoid oscillations have dual roles in dendritic spine plasticity. Glucocorticoids control spine formation and elimination through distinct mechanisms, which together are important for motor learning and maintenance.

Chronic stress exposure and excessive glucocorticoid activation are known to cause deficits in learning accompanied by dendritic spine loss in the cortex and hippocampus, as well as changes in glutamate neurotransmission^{1,2}. But glucocorticoids function more broadly to control learning, with moderate transient elevations enhancing plasticity and performance³. Under normal conditions, stress hormones exhibit daily circadian oscillations, with a surge in adrenal glucocorticoid release early in the wake cycle followed by a trough at sleep⁴. These oscillations in stress hormones are maintained predictably in both rodents and humans⁴. Although previous studies have clearly demonstrated that disruptions of glucocorticoids in general can impair learning, we do not have a detailed understanding of how this diurnal rise and fall of glucocorticoids influences learning-related changes in spine synapses.

In this issue of *Nature Neuroscience*, Liston *et al.* show through molecular studies and time-lapse *in vivo* imaging with two-photon microscopy that circadian glucocorticoid oscillations influence spine plasticity following motor learning⁵. Mice trained in a rotarod motor learning task during the circadian glucocorticoid peak formed new spines through a non-transcriptional mechanism requiring the LIM kinase-1 (LIMK-1)–cofilin pathway and performed better on the rotarod task than mice trained during the circadian glucocorticoid trough. Interestingly, the trough was essential for elimination of spines present prior to learning and for maintenance of new spines, along with retention of the motor memory. Spine elimination, unlike formation, required mineralocorticoid receptor (MR) activation and gene transcription. These results provide the first mechanistic insight into how both the peak and trough phases of oscillating stress hormones are important for learning-dependent spine formation, stabilization, motor learning and maintenance.

Previous studies of glucocorticoid effects on spine plasticity focused on chronic high levels of corticosterone that cause dendritic spine loss in the hippocampus and prefrontal cortex, as well as cognitive decline¹. Consistent with the literature, Liston *et al.* found that 10 days of repeated high-dose corticosterone injections prevented both the formation of new learning-induced spines and the loss of pre-existing spines, leading to an overall net loss of spines. Although glucocorticoid oscillations resulted in loss of spines as well, the spine elimination seen with the normal circadian trough was balanced by stability of newly formed spines,

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maintaining a relatively constant net number of spines. Thus, the action of the acute, transient corticosterone rhythm appears fundamentally different from that of chronic exposure to the hormone (Figure 1).

To test potential underlying mechanisms for glucocorticoid-induced spine formation and elimination, Liston *et al.* examined the immediate time course of these events after intraperitoneal injection of corticosterone. Spine formation occurred rapidly, within 1 hour, and required a glucocorticoid receptor (GR)-dependent non-transcriptional mechanism, presumably through direct modulation of the local cytoskeleton. By contrast, spine elimination required at least 5 hours and continued for 24 hours after corticosterone injection. Application of corticosterone directly to the cortex along with the transcription inhibitor actinomycin D had no effect on spine formation but blocked spine elimination. Cotreatment with the GR antagonist mifepristone also blocked spine formation, whereas cotreatment with the MR antagonist spironolactone was needed to block spine elimination. Together these results support the notion that spine formation occurs locally through GR modulation of the actin cytoskeleton, but spine elimination requires a transcription-dependent mechanism involving MR activation.

As mentioned above, rapid formation of new spines occurs through a non-transcriptional mechanism, presumably through regulation of actin remodelers locally. Thus, Liston *et al.* examined acute changes in activity of the actin remodeling proteins. LIMK1 and cofilin in the cortex immediately after direct application of corticosterone. Activation of LIMK-1 leads to a phosphorylation-dependent inhibition of cofilin, which is known to stabilize actin polymers and contribute to spine formation⁶. The authors found that acute corticosterone increased phospho-cofilin, in line with previous studies showing that local GR activation at spines can modulate cofilin⁷. The authors then showed that RNA interference-mediated knockdown of GR in cultured cortical neurons prevented the increase in phospho-GR, phospho-cofilin and phospho-LIMK1. Corticosterone-induced spine formation was also reduced in LIMK1 knockout mice *in vivo*, which was associated with learning disability. Lastly, they showed that neither actinomycin D nor a membrane-impermeable glucocorticoid, which cannot access and bind to nuclear receptors, affected spine formation. Together, these data directly support a rapid, GR-dependent, non-transcriptional mechanism acting on local cytoskeletal machinery that is responsible for spine formation.

A fine balance exists between spine formation and spine elimination needed for long-term motor learning and retention on the rotarod task. Though there is no net change in spines during glucocorticoid oscillations, it seems that the right spine at the right time is critical for fine-tuning learned motor responses. Yet several questions remain. How does the brain determine which pre-existing spines should be eliminated in the face of new motor learning, while still maintaining a representation of past motor memories? Pruning and stabilization of spines is a common phenomenon occurring at various rates throughout the lifespan of an organism, to consolidate and maintain long-term memories^{8,9}. How can the lifetime of memories be encoded by this very dynamic system? It would be interesting to determine whether training animals in a second motor task prunes and stabilizes a distinct set of spines to answer the critical questions of whether individual spines are a proxy for specific memories or whether the overall reorganization of brain circuitry is key for memory maintenance.

Lastly, deficits in cognition and abnormalities in cortical plasticity are extensively shown in patients suffering from a host of stress-related psychiatric illnesses¹⁰. For example, patients with major depressive disorder show deficits in performance on cognitive tasks¹¹, along with a loss of cortical synapses¹². Thus, it would be important to test whether chronic stress impairs cognition and spine stability by simply changing absolute levels of corticosterone or

whether shifts in the oscillatory nature of its release drive pathological spine turnover. In addition, given that stress disorders, such as major depressive disorder, are generally caused by a pathology in deeper structures such as the hippocampus¹ and nucleus accumbens¹³, it will be important for future studies to establish whether these synaptic rules apply to these other brain structures and whether they control different aspects of depression symptomatology. In the end, a better understanding of the normal physiologic response to stress hormone oscillations in the context of learning might pave the way for improved approaches to the treatment of chronic stress disorders. Therapies aimed at not just reducing overall stress but also at restoring the normal, diurnal oscillation in glucocorticoid secretion might promote enhanced performance important for the rehabilitation of these patients.

References

1. McEwen BS, Eiland L, Hunter RG, Miller MM. *Neuropharmacology*. 2012; 62:3–12. [PubMed: 21807003]
2. Popoli M, Yan Z, McEwen BS, Sanacora G. *Nature Reviews Neuroscience*. 2011; 13:22–37.
3. Krugers HJ, Hoogenraad CC, Groc L. *Nature Reviews Neuroscience*. 2010; 11:675–681.
4. Kalsbeek A, et al. *Molecular and Cellular Endocrinology*. 2012; 349:20–29. [PubMed: 21782883]
5. Liston C, Cichon JM, Jeanneteau F, Jia Z, Gan WB. *Nat. Neurosci.* 2013; 16
6. Sarmiere PD, Bamburg JR. *Journal of Neurobiology*. 2004; 58:103–117. [PubMed: 14598374]
7. Jafari M, Seese RR, Babayan AH, Gall CM, Lauterborn JC. *Molecular Neurobiology*. 2012; 46:304–315. [PubMed: 22717988]
8. Segal M. *Nature Reviews Neuroscience*. 2005; 6:277–284.
9. Yang G, Pan F, Gan WB. *Nature*. 2009; 462:920–924. [PubMed: 19946265]
10. Millan MJ, et al. *Nat Rev Drug Discov*. 2012; 11:141–168. [PubMed: 22293568]
11. Goeldner C, et al. *Neuropharmacology*. 2013; 64:337–346. [PubMed: 22992331]
12. Kang HJ, et al. *Nature Medicine*. 2012; 18:1413–1417.
13. Golden SA, et al. *Nature Medicine*. 2013; 19:337–344.

Figure 1.

Two-photon *in vivo* imaging of the mouse motor cortex before and after motor learning on the rotarod task. Acquisition of learning requires an intact circadian peak and activation of glucocorticoid receptors (GR), which results in phosphorylation of cofilin and increased spine formation through a rapid, nontranscriptional mechanism. Retention of learning requires the circadian trough, leading to spine elimination through a transcriptional mechanism requiring activation of mineralocorticoid receptors (MR).