LEARNING AND MEMORY

Learning with peaks and troughs

Although perhaps best known as a marker of stress, glucocorticoids are continually released, and their baseline levels fluctuate in a circadian manner. Gan and colleagues now show that in mice, these circadian fluctuations are important for learning and memory by promoting learning-associated spine formation and elimination.

The authors trained mice on a rotarod during the circadian peak of glucocorticoid (specifically, corticosterone) release on 2 consecutive days and found that this increased spine formation in layer 5 pyramidal cells of the motor cortex 5 days later. Enhancing and inhibiting endogenous corticosterone release during the circadian peak increased and prevented this effect, respectively. By contrast, training during the circadian trough did not increase spine formation, but corticosterone injections at this time mimicked the effect of training at the circadian peak. Survival of the newly formed spines was also greater in mice trained at high corticosterone levels

than in mice trained during the circadian corticosterone trough, and the number of surviving spines predicted motor performance on the rotarod.

These findings indicated that the daily corticosterone peak increases the long-term retention of a motor memory by promoting dendritic spine formation and survival. But the daily corticosterone trough is also important, as disrupting it (by administering corticosterone during the nadir on the 3 days following training) reduced the survival of newly formed spines and impaired rotarod performance in mice that had been trained during the circadian peak. This suggests that the daily trough supports the stabilization of newly formed spines. The authors showed that it is also required for the pruning of pre-existing spines. Indeed, spine elimination correlated with rotarod performance 5 days after training.

Ex vivo studies showed that the effect of corticosterone on spine formation was rapid, mediated by

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the glucocorticoid receptor and independent of gene transcription. By contrast, the effect on spine elimination was slower, required the mineralocorticoid receptor and was dependent on gene transcription and translation. Moreover, corticosterone application induced rapid expression of activated LIM kinase 1 (LIMK1) and its substrate cofilin. This effect was prevented by the application of a glucocorticoid receptor-specific small interfering RNA. Thus, corticosterone-induced spine formation may be mediated by activation of the LIMK1-cofilin pathway.

Many studies have shown effects of excessive, stress-induced glucocorticoid release on learning and memory. The new findings reveal that circadian glucocorticoid fluctuations are important for these processes as well.

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