Glucocorticoid-Endocannabinoid Interactions in Influencing Memory for Emotionally Arousing Experiences

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The formation of long-term emotional memories

“Of some experiences no memory survives the instance of their passage, others are recalled as long as live endures. How can we explain this?”

William James (1890)

Emotionally arousing experiences are well retained. This is a highly adaptive process, but could also result in traumatic memories and PTSD.

Emotionally arousing experiences induce the release of norepinephrine in the basolateral amygdala, inducing a hypervigilant state and promoting memory consolidation.

This mnemonic effect is enhanced when the situation is so stressful that glucocorticoid hormones are released and reach the basolateral amygdala.
Emotional arousal induces activation of stress hormone systems

Epinephrine from adrenal medulla
Glucocorticoids from adrenal cortex
Cortisol in humans
Corticosterone in rodents
Epinephrine administered after training enhances memory of inhibitory avoidance training

Gold PE & van Buskirk R, 1975
Role of the noradrenergic system in the basolateral amygdala in memory consolidation


LaLumiere RT et al J Neurosci 2003
Norepinephrine in the basolateral amygdala enhances the consolidation of memory of object recognition training.
Norepinephrine and corticosterone are both present in the basolateral amygdala
Interaction between glucocorticoids and the noradrenergic system

Emotional training induces the release of norepinephrine in the basolateral amygdala

Do glucocorticoid effects on memory interact with emotional arousal?

Quirarte GL et al. Proc Natl Acad Sci USA 1997, 94:14048-14053
Glucocorticoid effects on memory consolidation require noradrenergic activation

Roozendaal B et al. Proc Natl Acad Sci USA 2006, 103:6741-6746
Corticosterone rapidly interacts with noradrenergic system

McReynolds JR et al. Neurobiol Learn Mem 2010
• Glucocorticoids synergistically interact with noradrenergic transmission within the basolateral amygdala to induce optimal strengthening of memory formation.

• This effect requires a rapid, nongenomically mediated action of glucocorticoids.

• The neural mechanism of how glucocorticoids might rapidly alter noradrenergic signaling is unknown.
The endocannabinoid system
Cannabinoid effects on short- and long-term memory depend on level of emotional arousal

Campolongo P et al Neuropsychopharmacol 2013, 38: 1276-1286
Glucocorticoids interact with endocannabinoids in the basolateral amygdala in influencing memory consolidation

Emotionally arousing training and corticosterone increase endocannabinoid levels in the amygdala

Corticosterone injection also increases endocannabinoid levels in the amygdala (Hill et al., 2010)

Morena M et al. Proc Natl Acad Sci USA 2014, 111:18333-18338
Glucocorticoids interact with the endocannabinoid system in the basolateral amygdala in enhancing memory consolidation

Atsak P et al. Neuropsychopharmacology 2015, 40:1484-1494
Endocannabinoids interact with noradrenergic system of the basolateral amygdala

Atsak P et al. Neuropsychopharmacology 2015,40:1484-1494
A blockade of glucocorticoid signaling in the BLA attenuates the memory-enhancing effect of noradrenergic stimulation

If this GR effect is mediated by reduced endocannabinoid levels, then a small Increase in cannabinoid signaling should overcome this attenuating effect

Atsak P et al. Neuropsychopharmacology 2015, 40:1484-1494
CB1 receptor blockade prevents corticosterone effects on pCREB phosphorylation in the basolateral amygdala

Atsak P et al. Neuropsychopharmacology 2015, 40:1484-1494
The endocannabinoid system is necessary for regulating rapid glucocorticoid effects on the noradrenergic system

Atsak, Roozendaal & Campolongo, Neuroscience 2012, 204:104-116
A model of basolateral amygdala-induced memory modulation
Long-term memory

Consolidation

Retrieval

Norepinephrine

Glucocorticoids

Acute stress

- de Quervain et al., *Nat Neurosci* (2000)
Memory retrieval

Water maze task

Training

Probe-trial Retention test

Time in training quadrant Latency to platform location Total swim distance
Stress induces a time-dependent impairment in memory recall

Glucocorticoids interact with the hippocampal endocannabinoid system in impairing memory retrieval

Summary

- Acute glucocorticoid administration enhances the formation of emotional memories and impairs memory retrieval. These effects depend on rapid (nongenomic) interactions with the noradrenergic system.

- The present findings show that the endocannabinoid system is critically involved in mediating these rapid glucocorticoid effects on noradrenergic function.

- The model suggests that glucocorticoids stimulate the synthesis of endocannabinoids, reducing GABAergic inhibitory tone, rendering neurons more sensitive to the memory-modulatory effects of norepinephrine.
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