

Glucocorticoid-Endocannabinoid Interactions in Influencing Memory for Emotionally Arousing Experiences

Benno Roozendaal

Department of Cognitive Neuroscience
Radboud university medical center
Donders Institute for Brain, Cognition and Behaviour
Radboud University Nijmegen
Nijmegen, The Netherlands



The formation of long-term emotional memories

“Of some experiences no memory survives the instance of their passage, others are recalled as long as life 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.

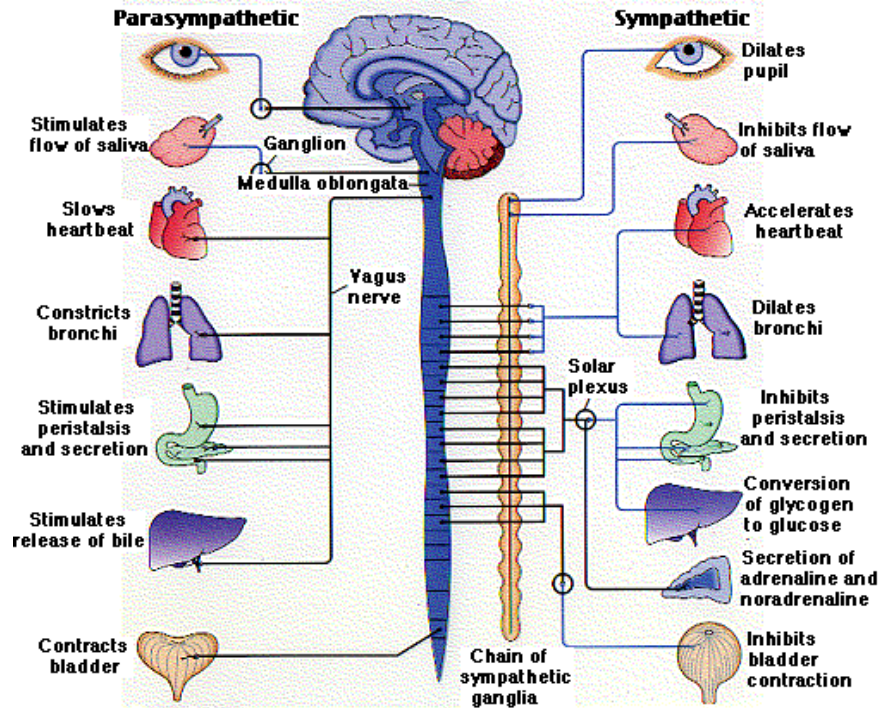


Emotionally arousing experiences induce the release of norepinephrine in the basolateral amygdala, inducing a hypervigilant state and promoting memory consolidation.

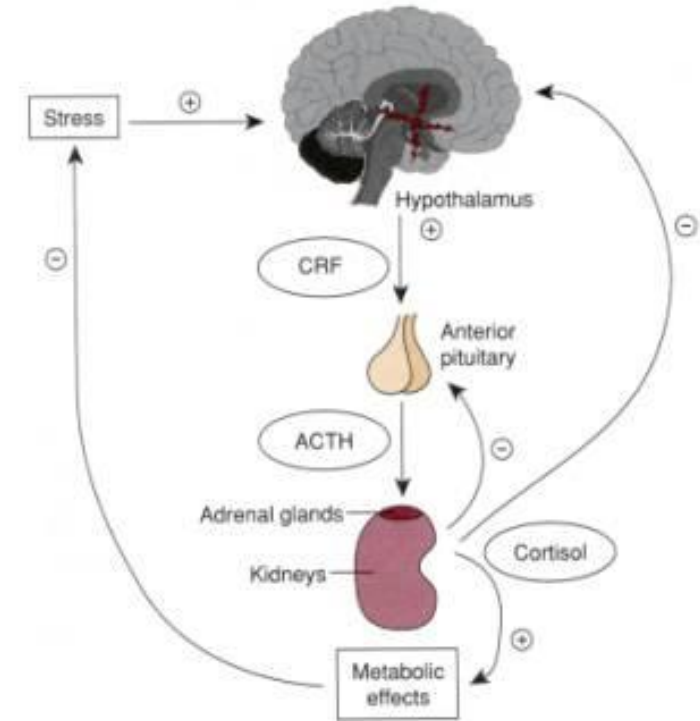
This mnemonic effect is enhanced when the situation is so stressful that glucocorticoid hormones are released and reach the basolateral amygdala.



Emotional arousal induces activation of stress hormone systems



Epinephrine from adrenal medulla



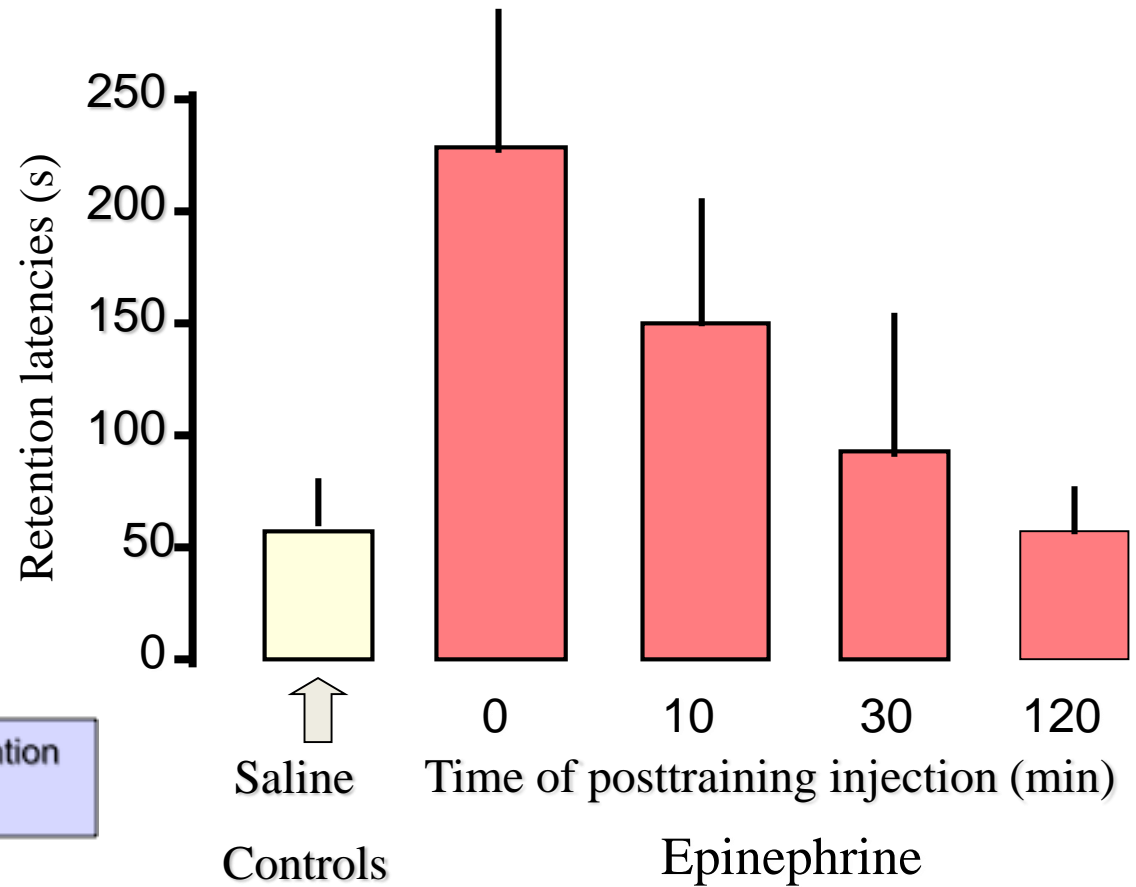
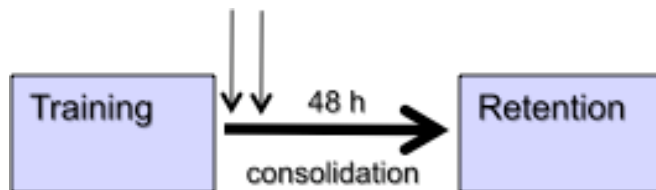
Glucocorticoids from adrenal cortex

Cortisol in humans

Corticosterone in rodents

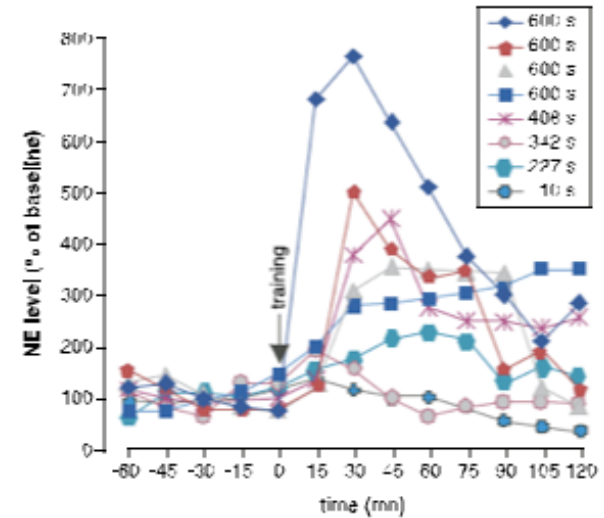
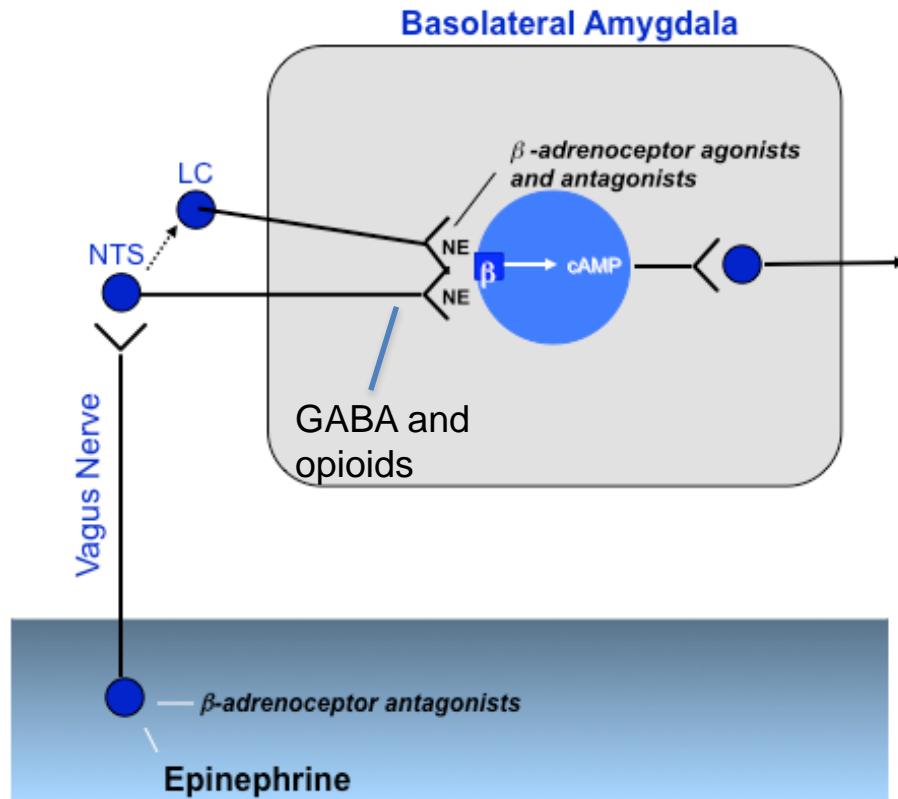


Epinephrine administered after training enhances memory of inhibitory avoidance training

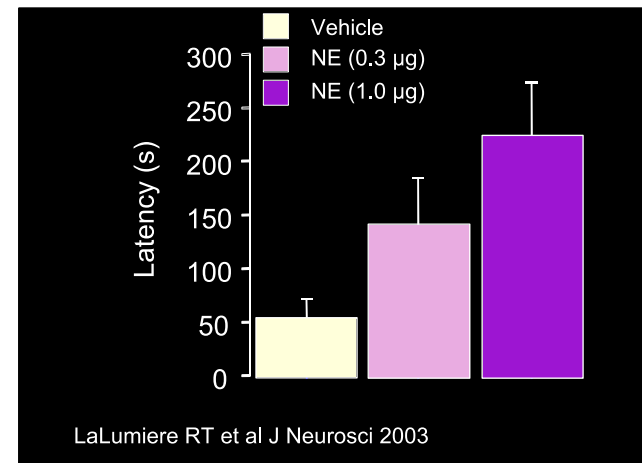




Role of the noradrenergic system in the basolateral amygdala in memory consolidation



McIntyre CK et al. Eur J Neurosci 2002, 16:1223-1226



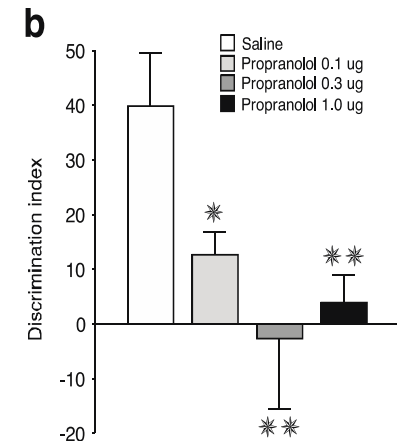
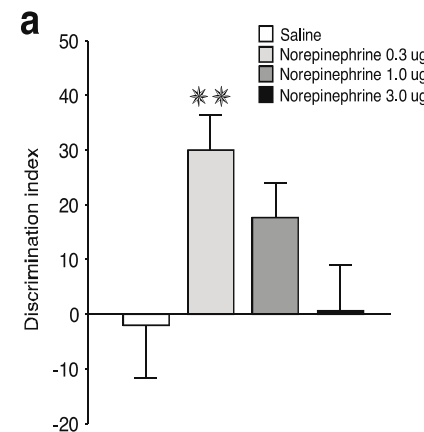
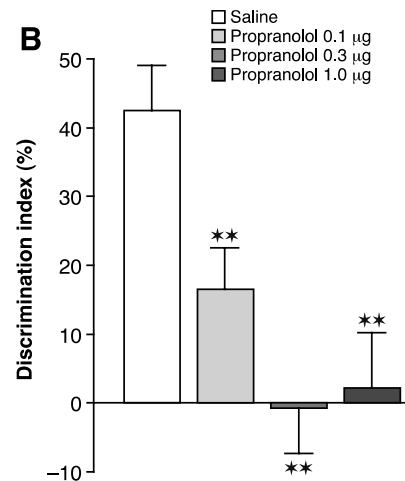
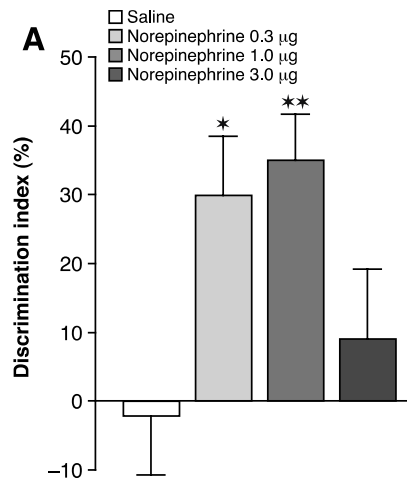
LaLumiere RT et al J Neurosci 2003



Norepinephrine in de basolateral amygdala enhances the consolidation of memory of object recognition training

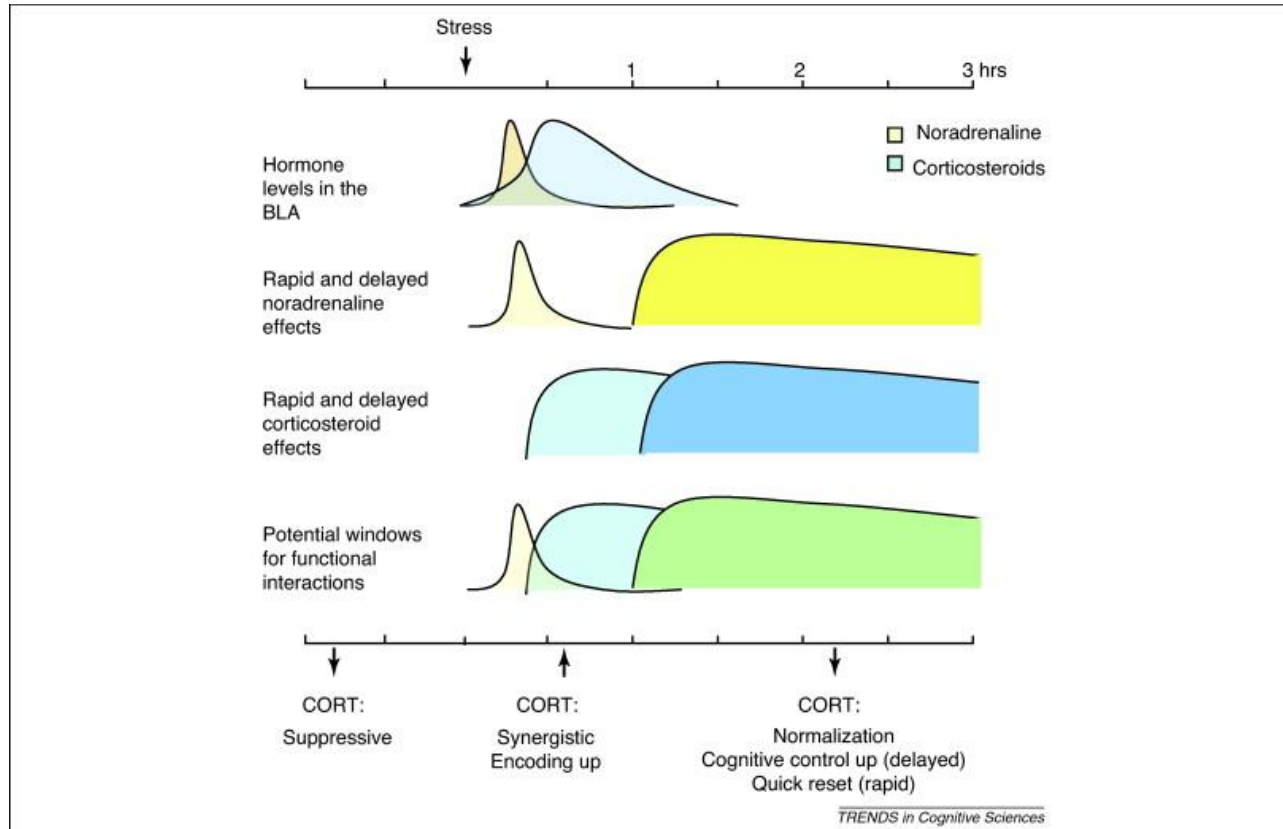


Object-in-Context



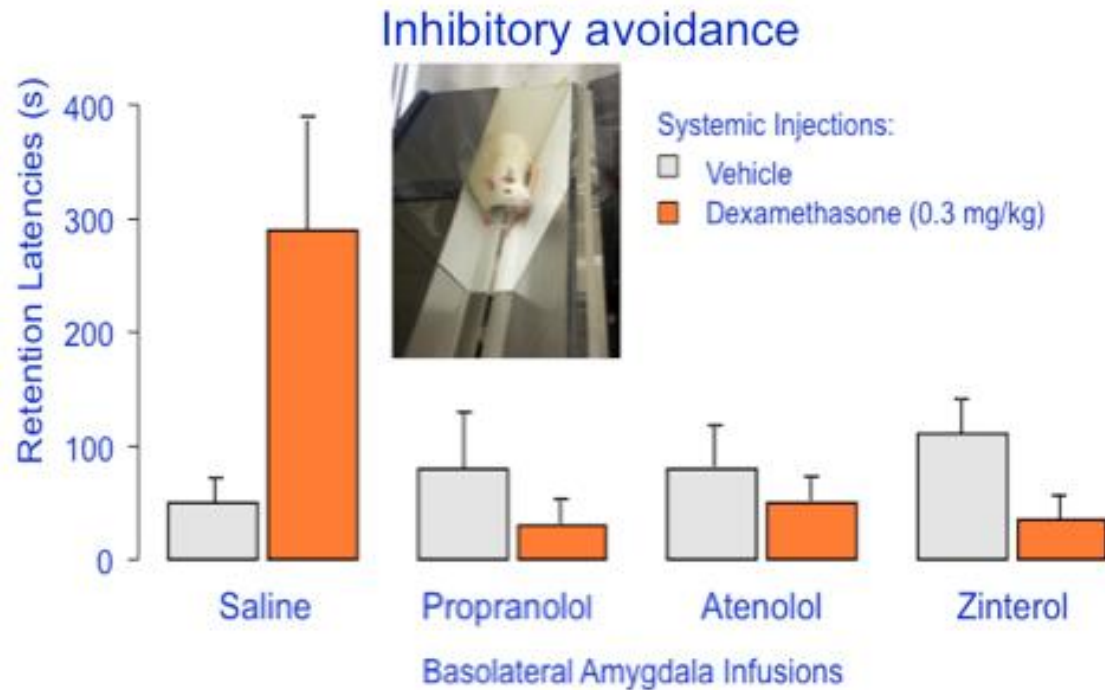


Norepinephrine and corticosterone are both present in the basolateral amygdala





Interaction between glucocorticoids and the noradrenergic system

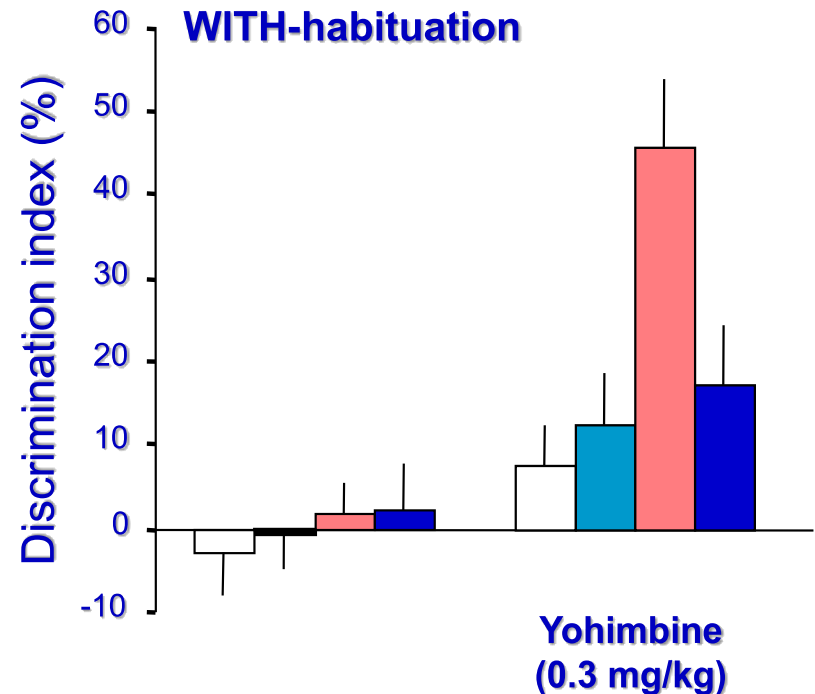
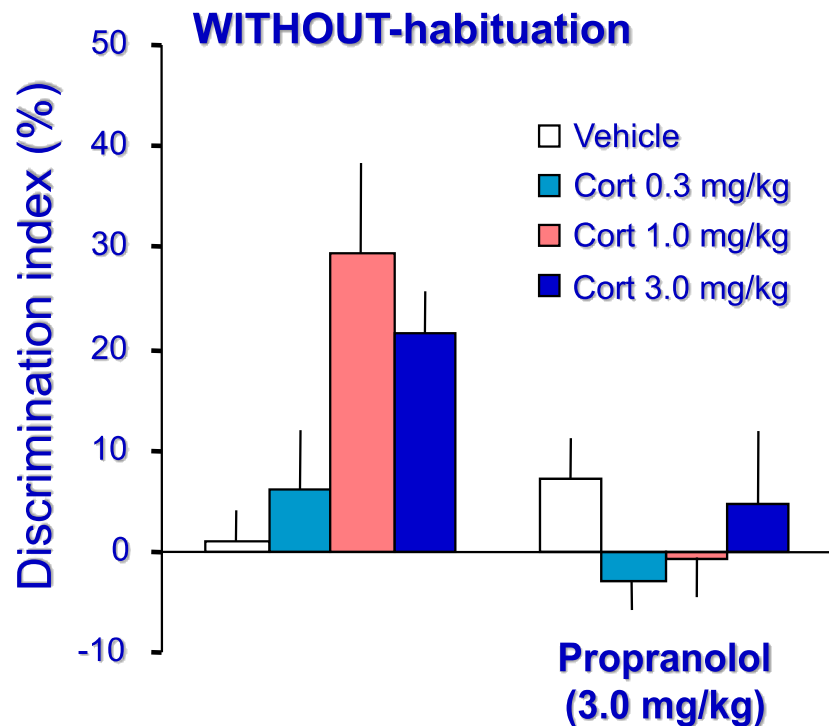
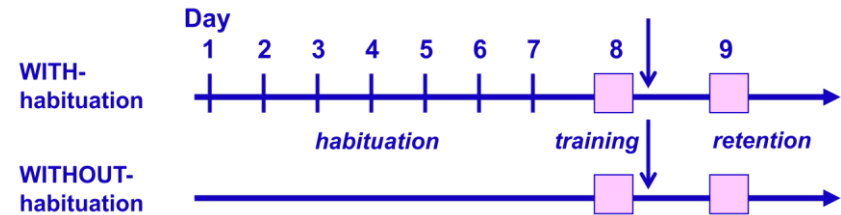
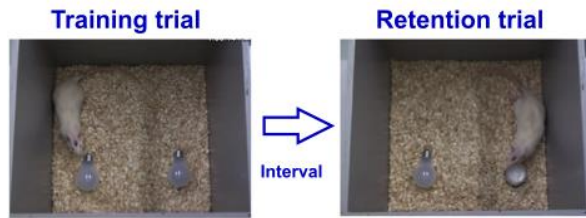


Emotional training induces the release of norepinephrine in the basolateral amygdala

Do glucocorticoid effects on memory interact with emotional arousal?

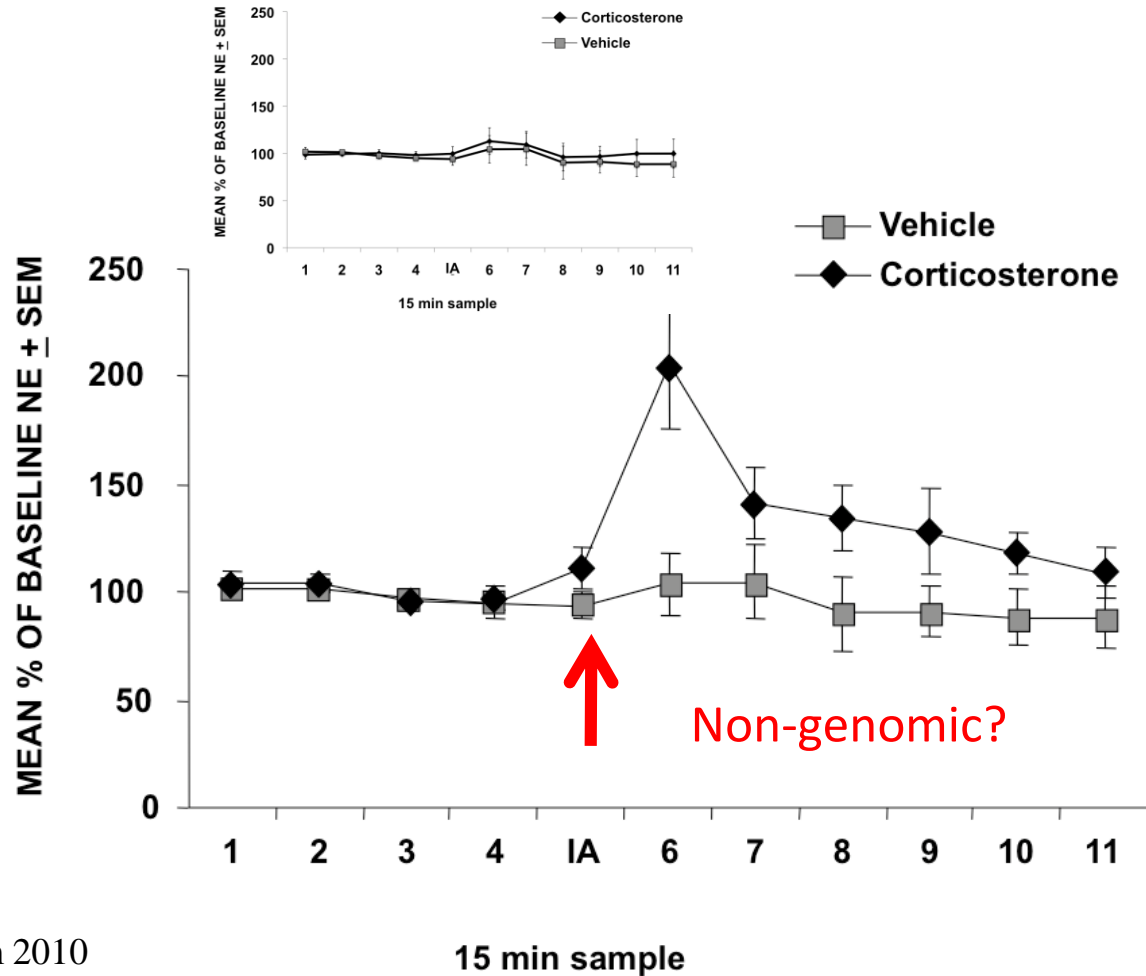
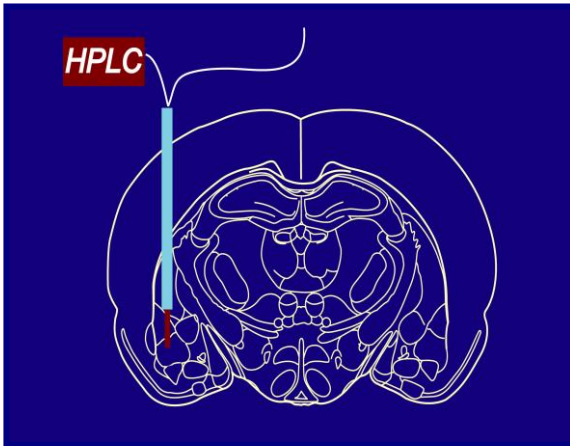


Glucocorticoid effects on memory consolidation require noradrenergic activation





Corticosterone rapidly interacts with noradrenergic system

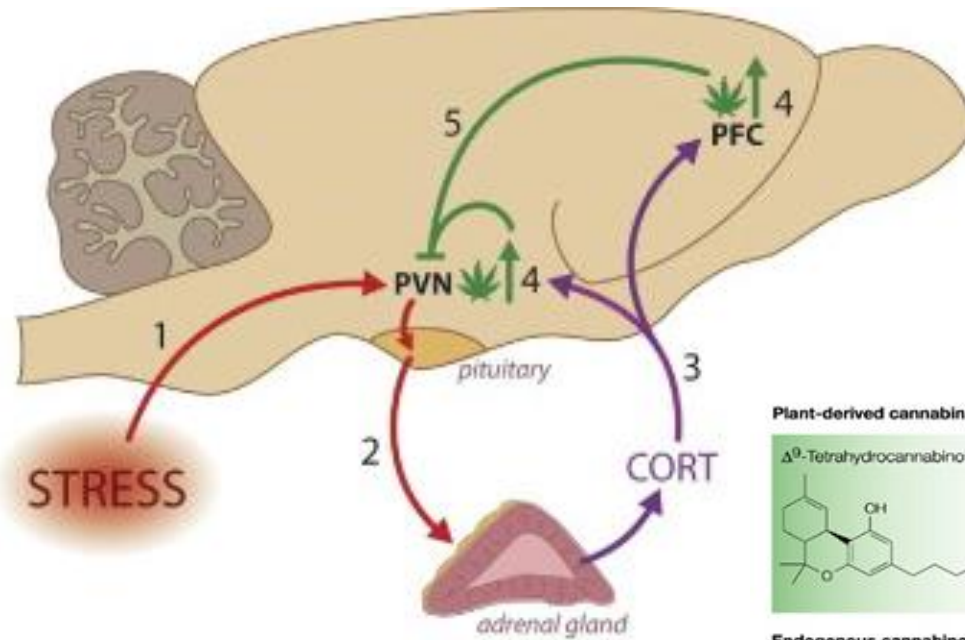




- Glucocorticoids synergistically interact with noradrenergic transmission within the basolateral amygdala to induce optimal strengthening of memory formation.
- This effect requires a rapid, nongenomically mediated action of glucocorticoids.
- The neural mechanism of how glucocorticoids might rapidly alter noradrenergic signaling is unknown.

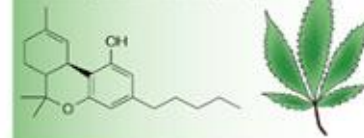


The endocannabinoid system



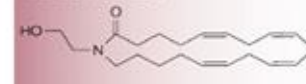
Plant-derived cannabinoid

Δ^9 -Tetrahydrocannabinol (THC)

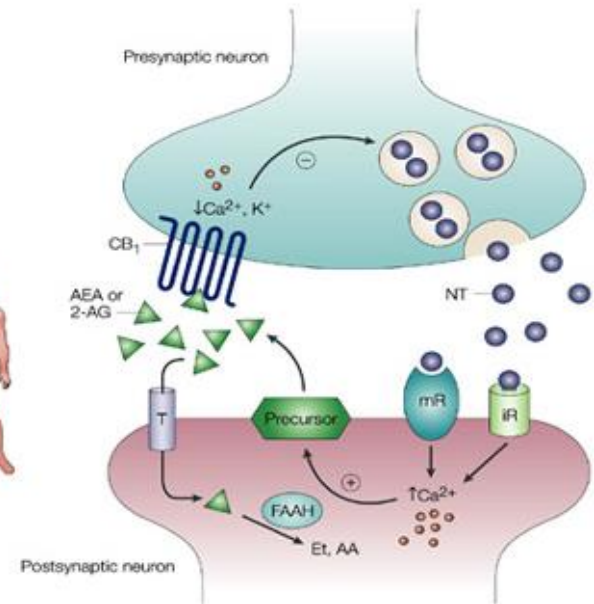


Endogenous cannabinoids

Anandamide (AEA)

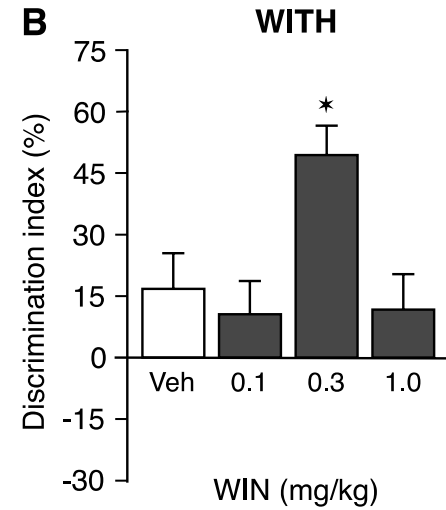
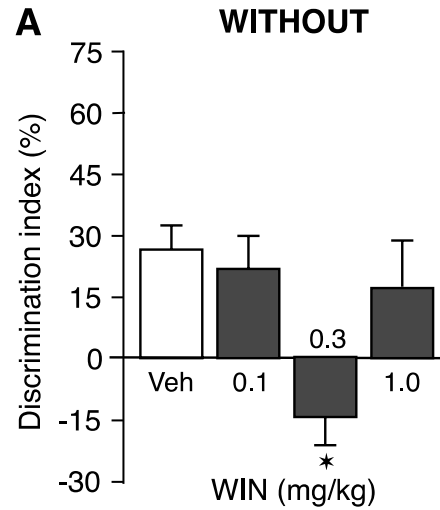
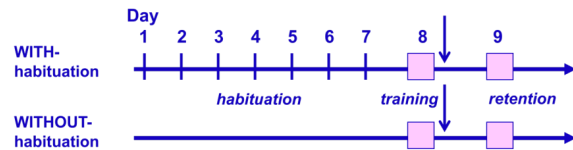
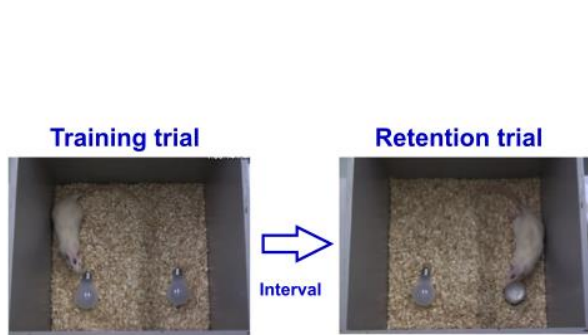


2-Arachidonoylglycerol (2-AG)

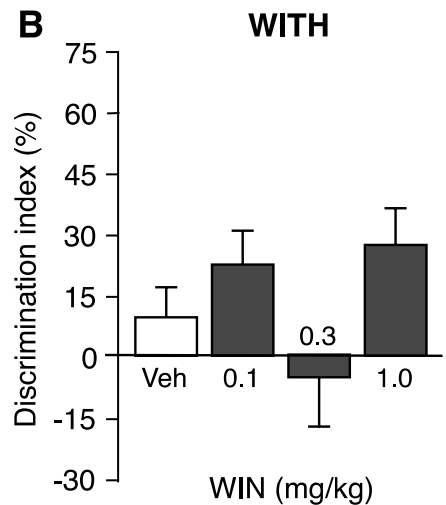
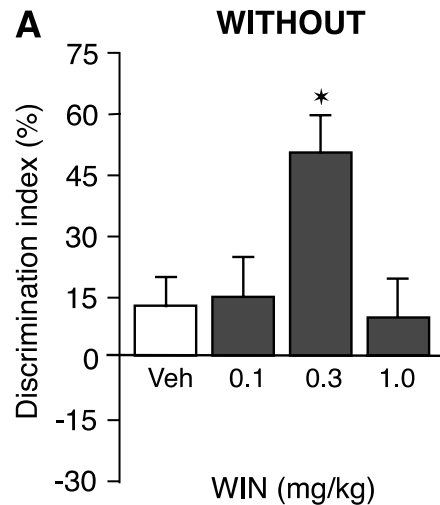




Cannabinoid effects on short- and long-term memory depend on level of emotional arousal



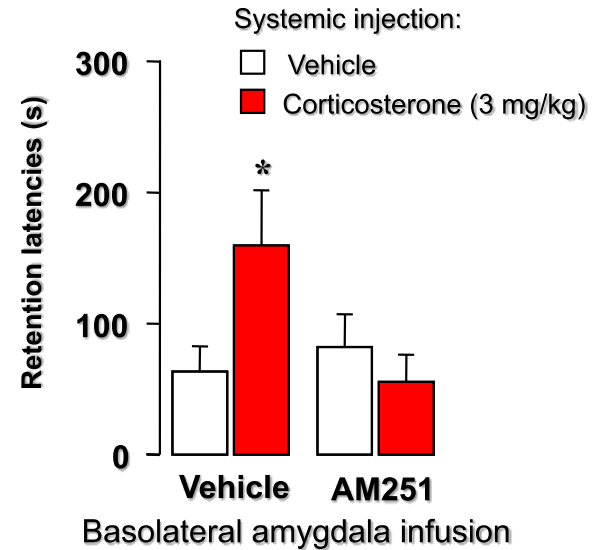
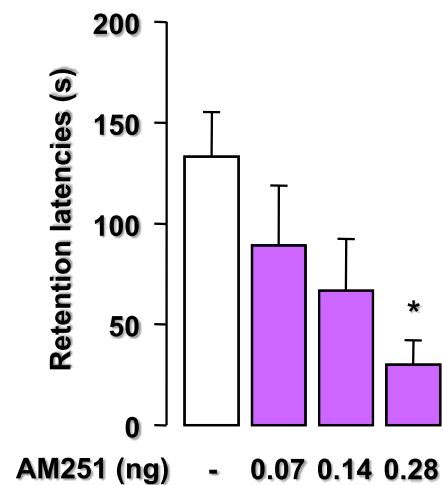
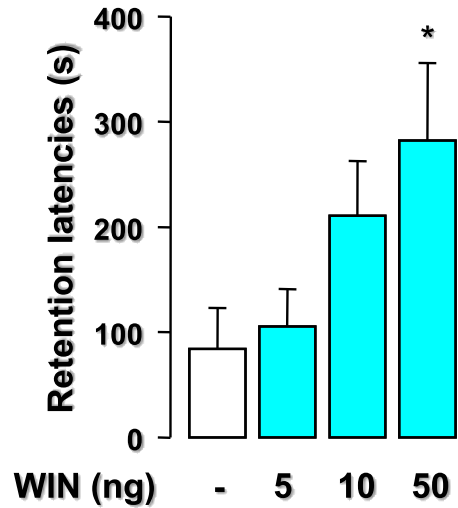
1 hour



24 hour

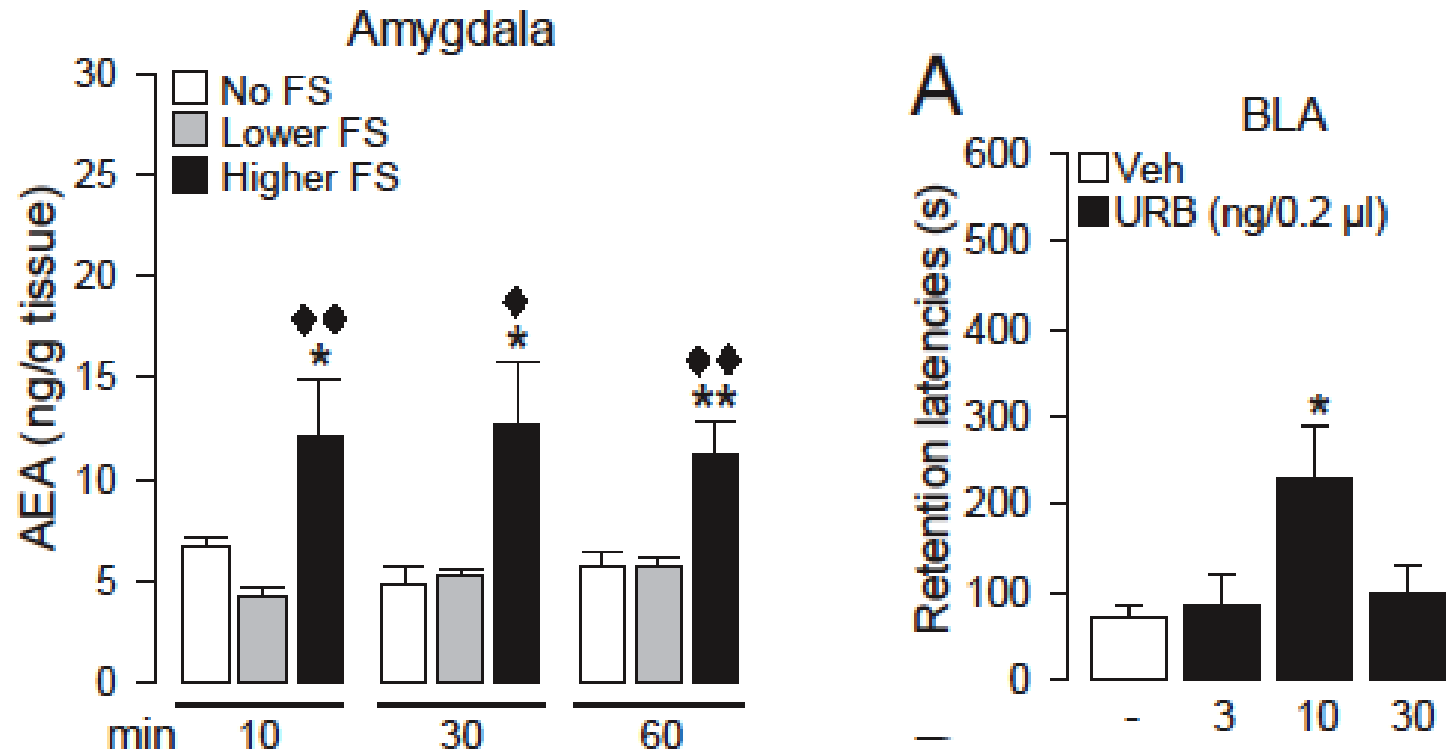


Glucocorticoids interact with endocannabinoids in the basolateral amygdala in influencing memory consolidation



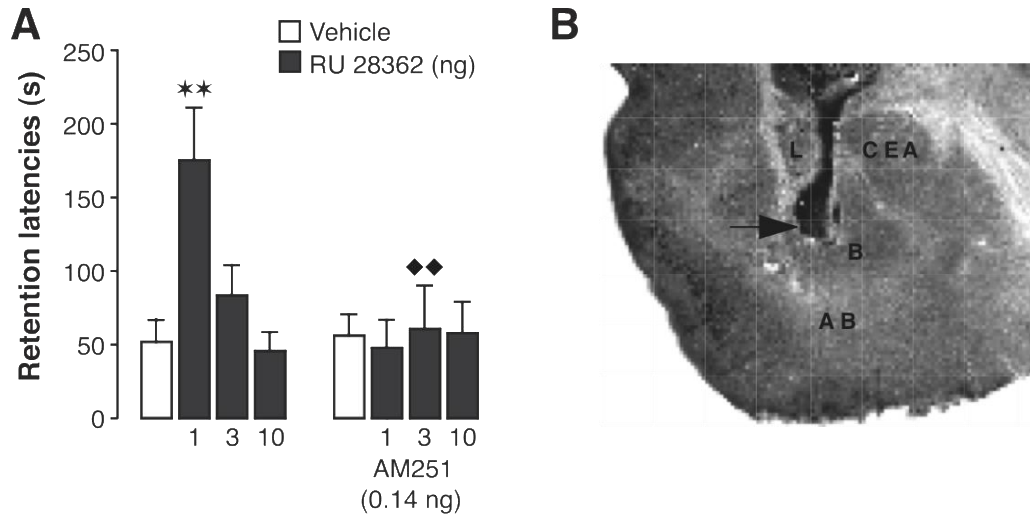


Emotionally arousing training and corticosterone increase endocannabinoid levels in the amygdala



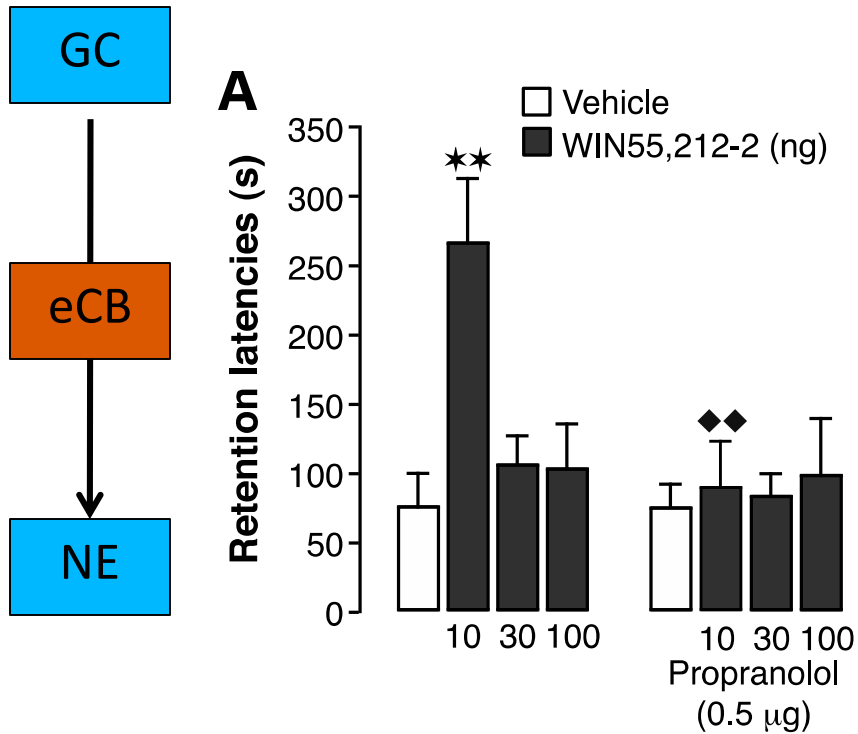
Corticosterone injection also increases endocannabinoid levels in the amygdala (Hill et al., 2010)

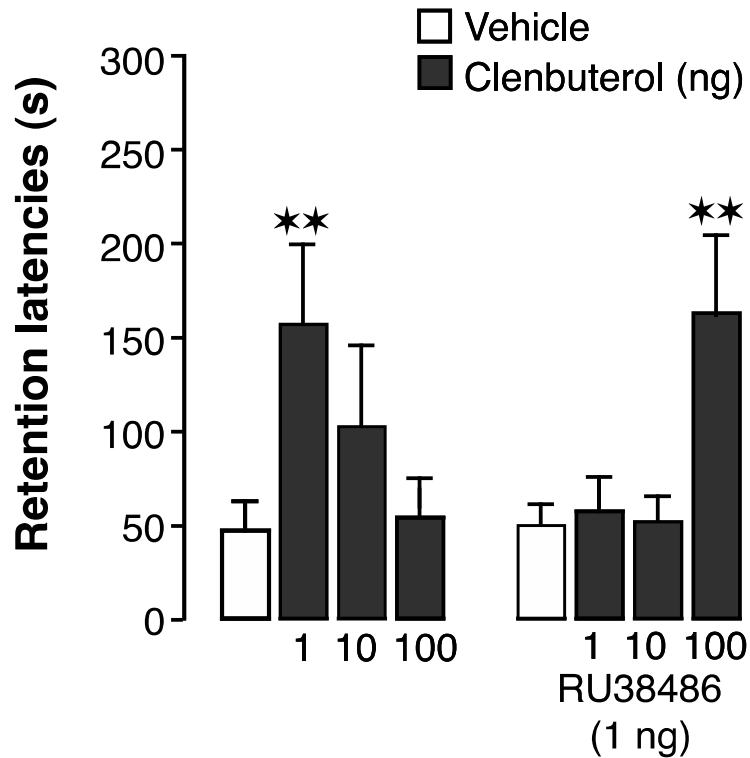
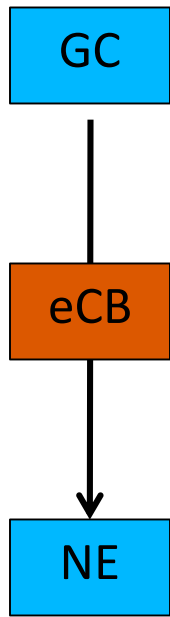
Glucocorticoids interact with the endocannabinoid system in the basolateral amygdala in enhancing memory consolidation





Endocannabinoids interact with noradrenergic system of the basolateral amygdala

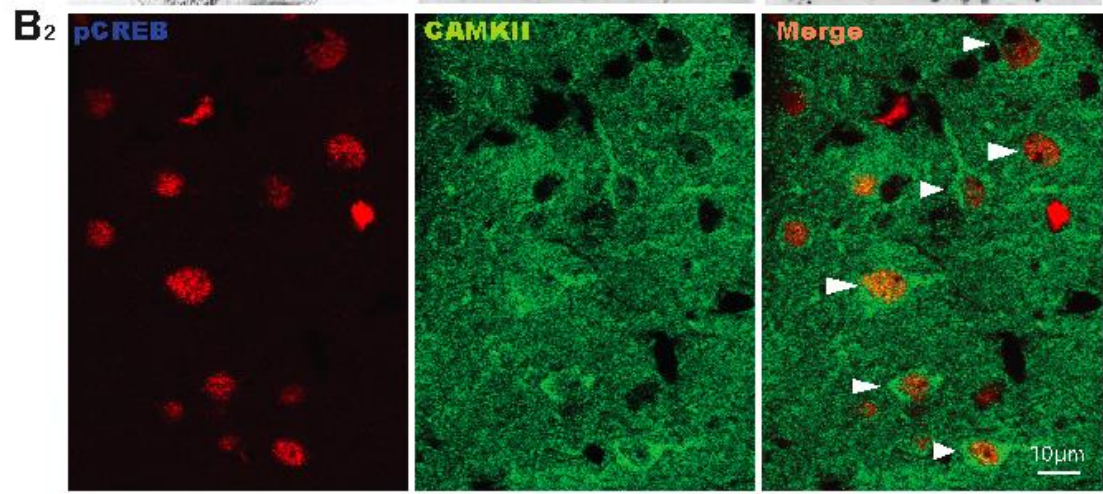
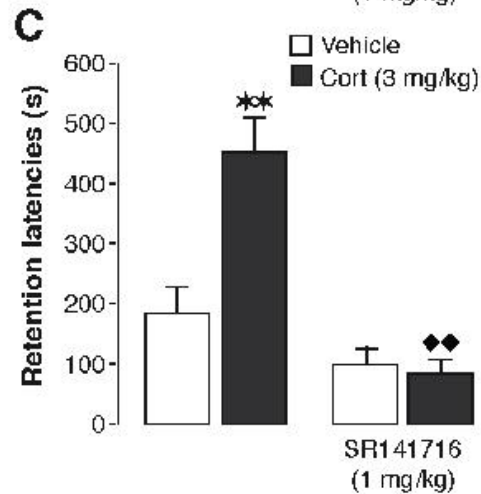
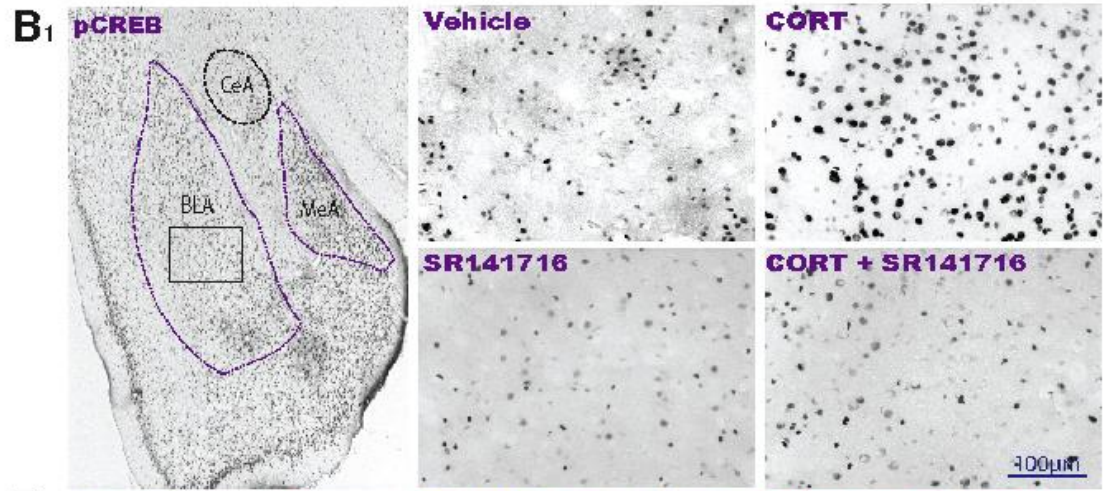
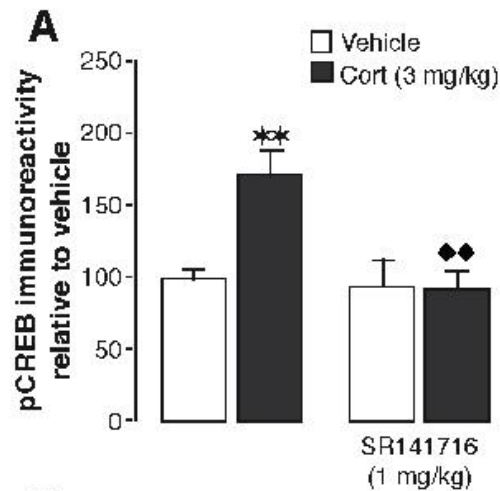




A blockade of glucocorticoid signaling in the BLA attenuates the memory-enhancing effect of noradrenergic stimulation

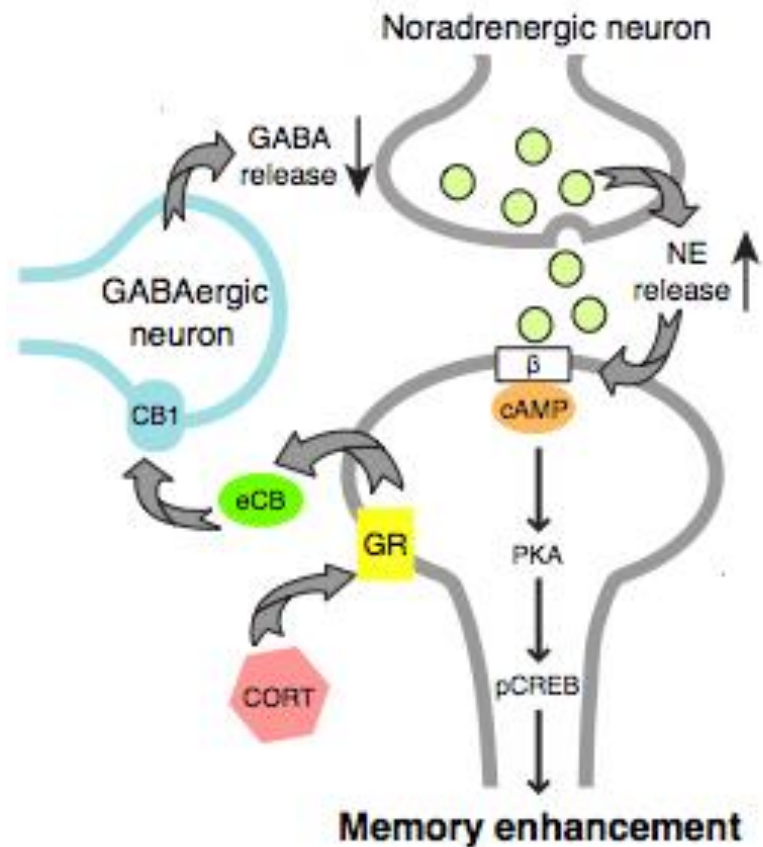
If this GR effect is mediated by reduced endocannabinoid levels, then a small Increase in cannabinoid signaling should overcome this attenuating effect

CB1 receptor blockade prevents corticosterone effects on pCREB phosphorylation in the basolateral amygdala



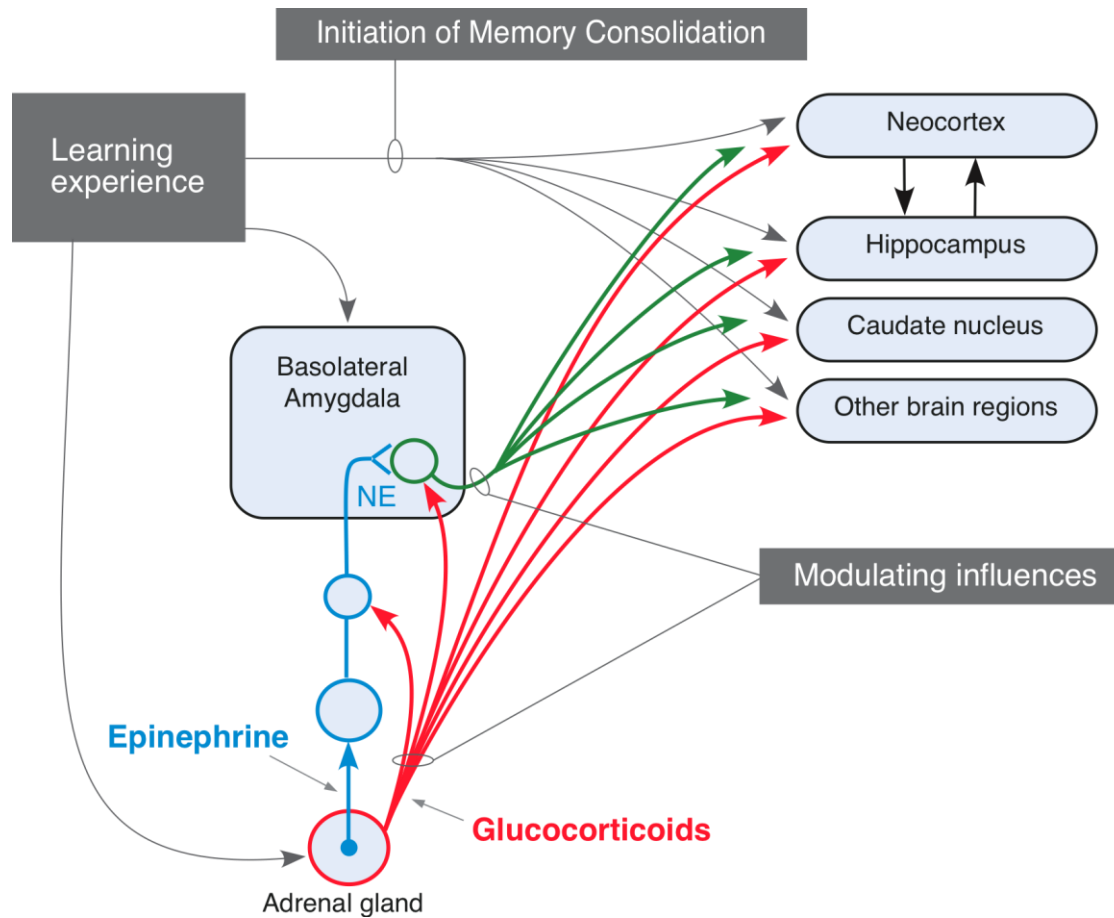


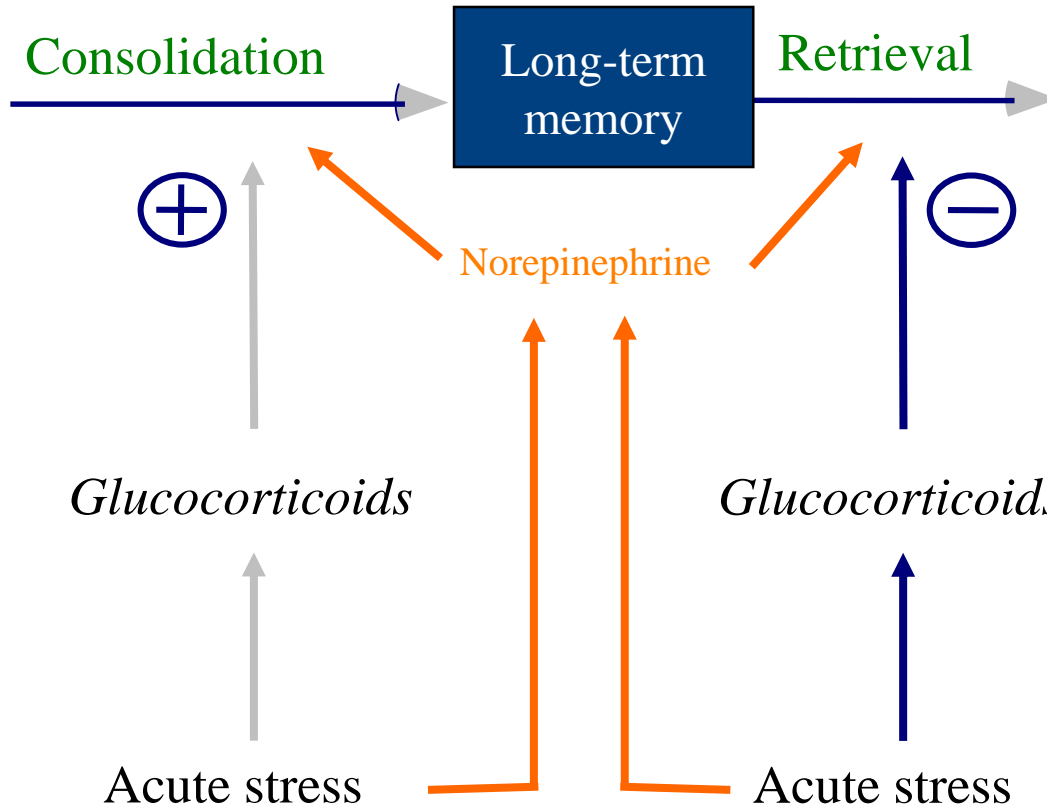
The endocannabinoid system is necessary for regulating rapid glucocorticoid effects on the noradrenergic system





A model of basolateral amygdala-induced memory modulation





- de Quervain et al., *Nature* (1998)
- de Quervain et al., *Nat Neurosci* (2000)
- Kuhlmann et al., *J. Neurosci* (2005)

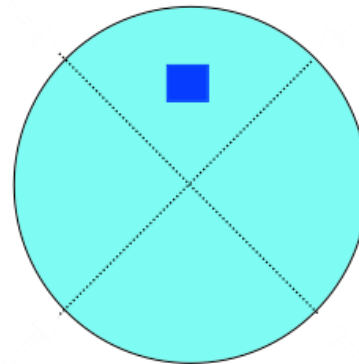


Memory retrieval

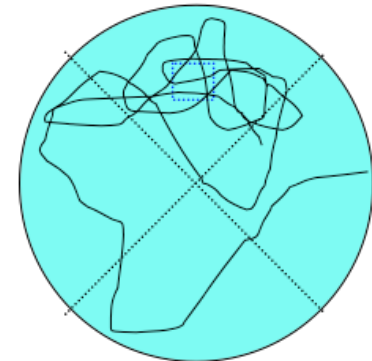


Water maze taak

Training



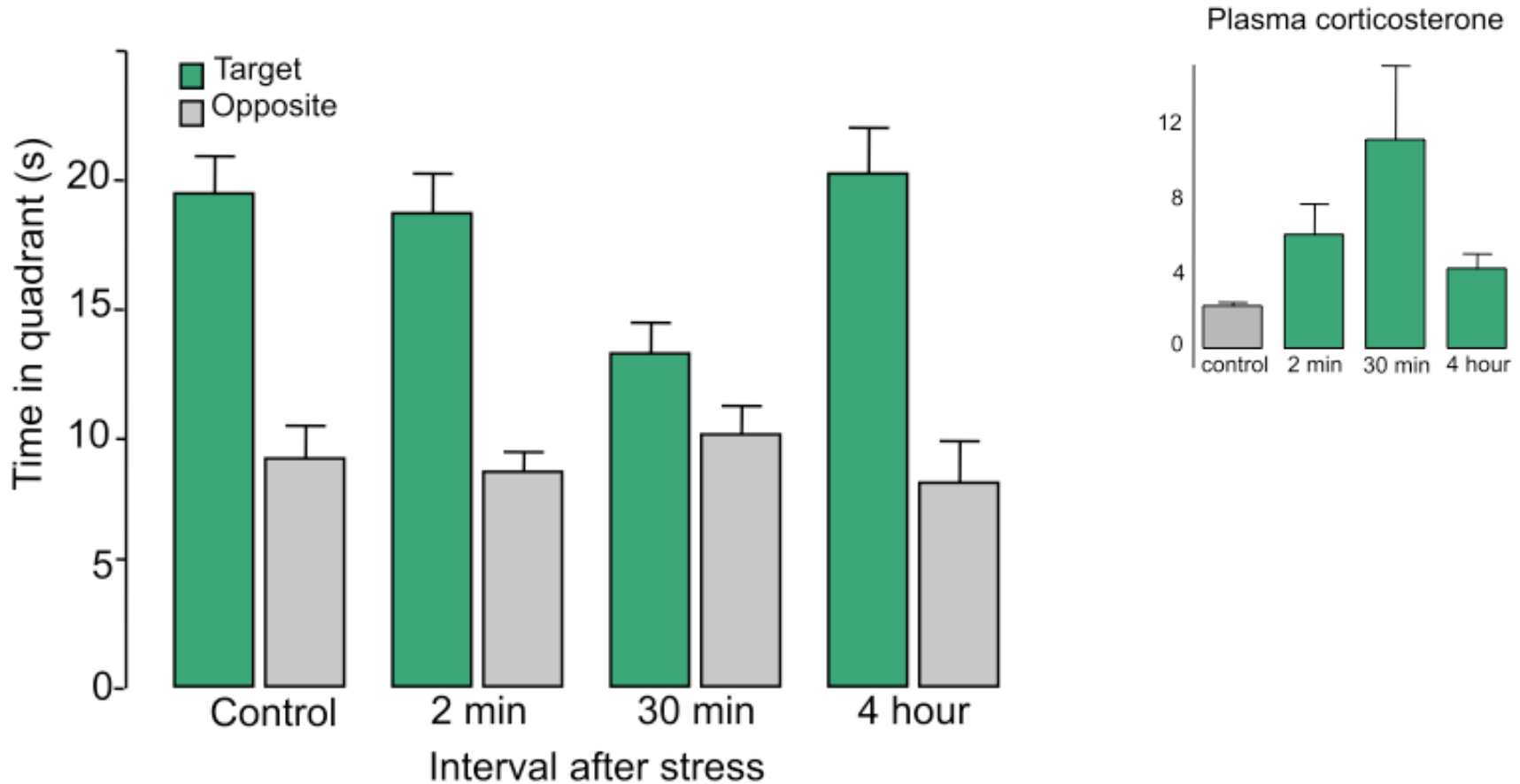
Probe-trial
Retention test



Time in training quadrant
Latency to cross platform location
Total swim distance

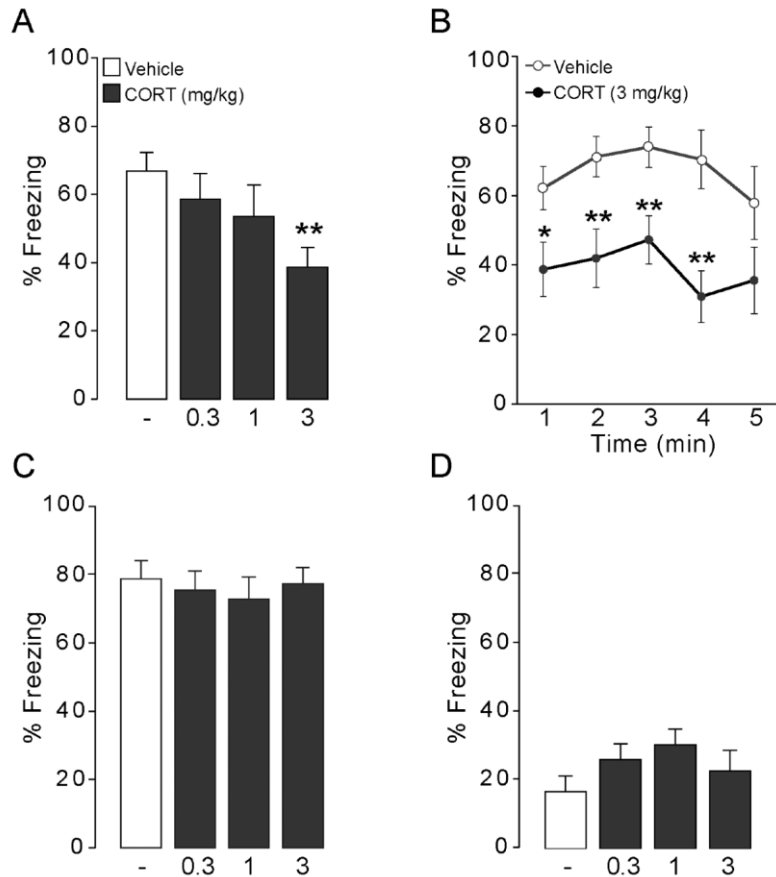


Stress induces a time-dependent impairment in memory recall





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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