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Amygdala Depotentiation and Fear Extinction

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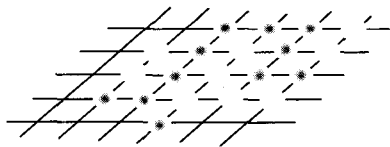
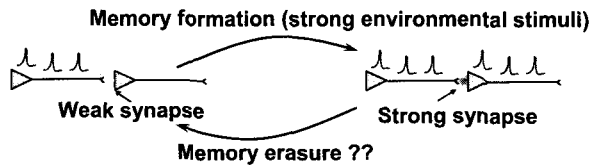
Auditory fear memory is thought to be maintained by fear conditioning-induced potentiation of synaptic efficacy. The conditioning-induced potentiation has been shown to be maintained, at least in part, by enhanced expression of surface AMPA receptor (AMPA) at excitatory synapses in the lateral amygdala (LA). Depotentiation, reversal of conditioning-induced potentiation, has been proposed as a cellular mechanism for fear extinction. However, a direct link between depotentiation and extinction has not yet been tested. To address this, we applied both *ex vivo* and *in vivo* approaches to rats in which fear memory had been consolidated. We found a novel form of *ex vivo* depotentiation: the depotentiation reversed conditioning-induced potentiation at thalamic input synapses onto the LA (T-LA synapses) *ex vivo*, and it could be induced only when both NMDA and metabotropic glutamate receptors were co-activated. Extinction returned the enhanced T-LA synaptic efficacy observed in conditioned rats to baseline and occluded the depotentiation. Consistently, extinction reversed conditioning-induced enhancement of surface expression of AMPAR subunits in LA synaptosomal preparations. A GluR2-derived peptide that blocks regulated AMPAR endocytosis inhibited depotentiation, and microinjection of a cell-permeable form of the peptide into the LA attenuated extinction. Our results are consistent with the use of depotentiation to weaken potentiated synaptic inputs onto the LA during extinction, and they provide strong evidence that AMPAR removal at excitatory synapses in the LA underlies extinction. The results described here are in line with previous findings. Neural activity in the LA has been shown to decrease after extinction in the rat and human. The NMDAR dependency of the depotentiation fits nicely with a large body of evidence that fear extinction depends upon amygdala NMDARs. Similarly, blockade of metabotropic glutamate receptors in the LA has recently been shown to attenuate fear extinction.

Amygdala Depotentiation and Fear Extinction

최석우, 서울대 생명과학부



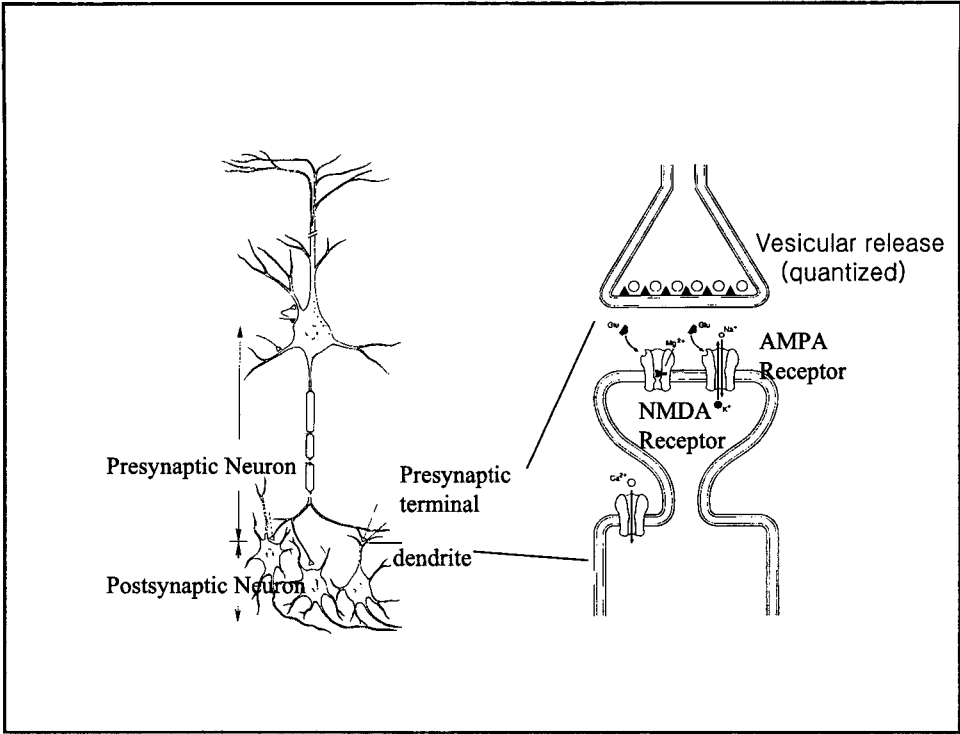
Brain



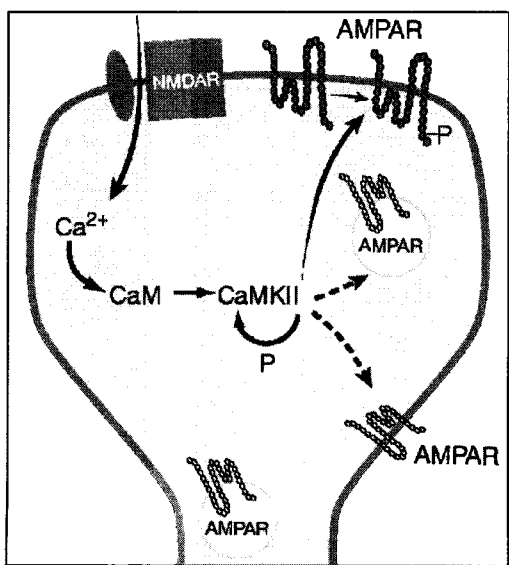
Neural Network



Learned Brain Activity (Emotion)

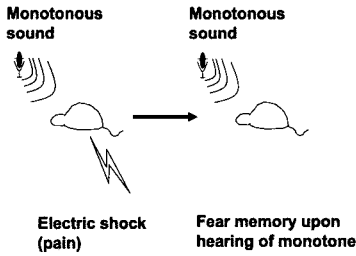


“Post-” model for expression (LTP)

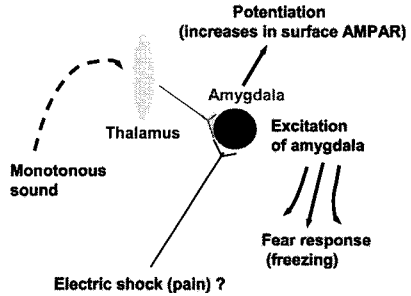


Cellular Mechanism for Fear Conditioning: Potentiation at Thalamus-Amygdala Synapses

Fear Conditioning

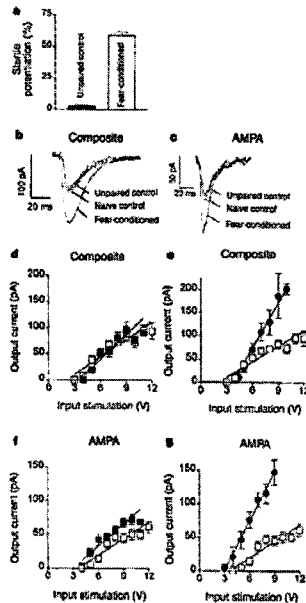


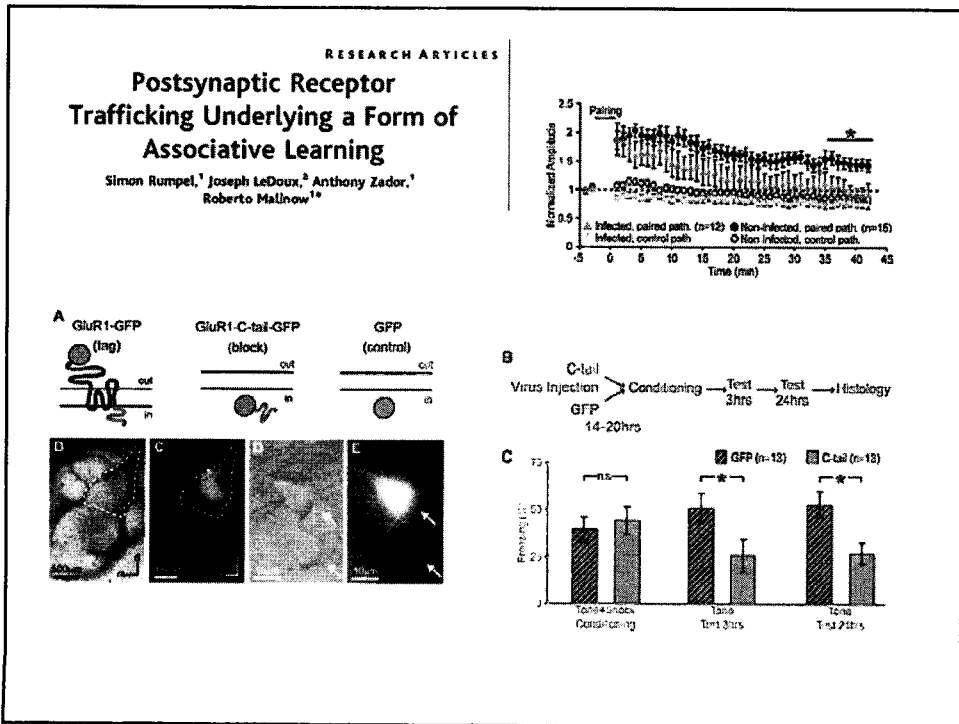
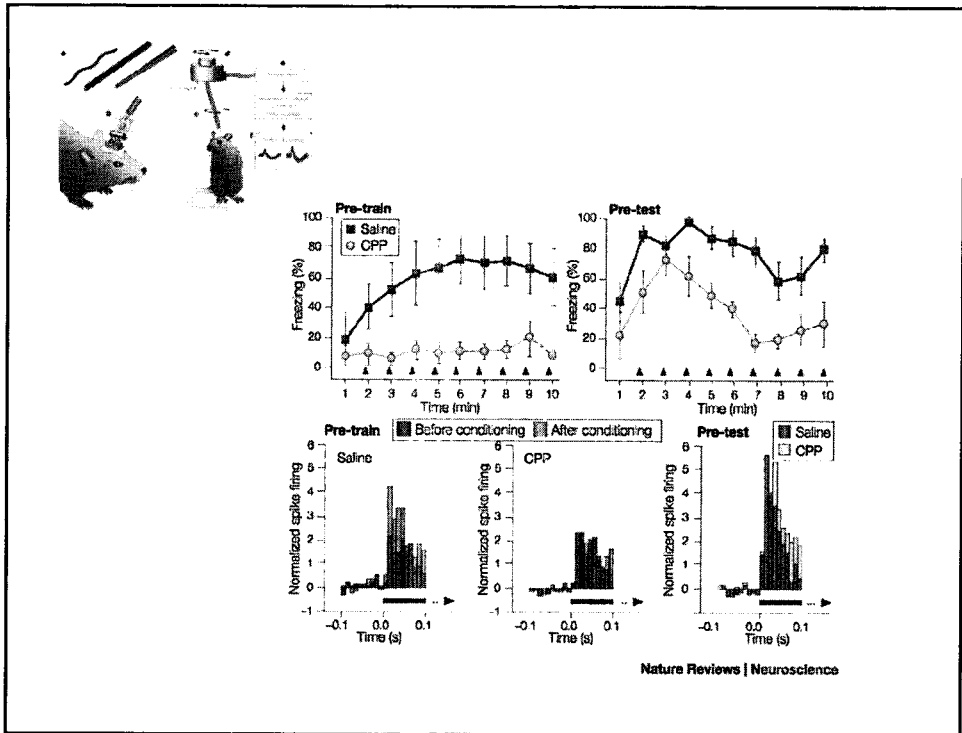
Neural Circuits for Fear Conditioning



Fear conditioning induces a lasting potentiation of synaptic currents *in vitro*

M. G. McKernan & R. Shinnick-Gallagher





Proposed Molecular Mechanisms for Acquisition and Consolidation of Fear Memory

AMPA phosphorylation Completed within 24 hrs AMPA expression

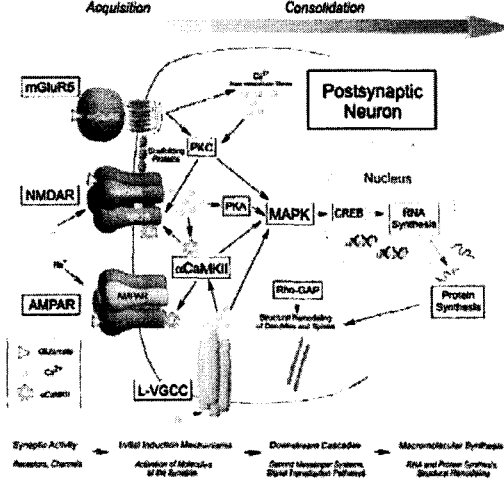
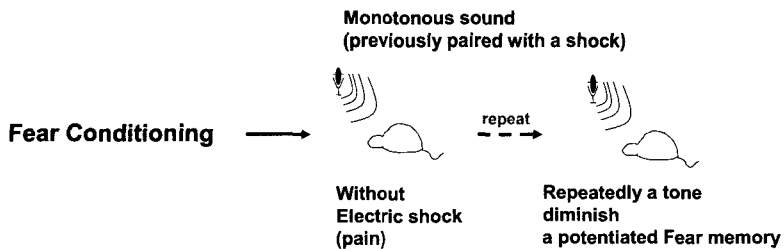
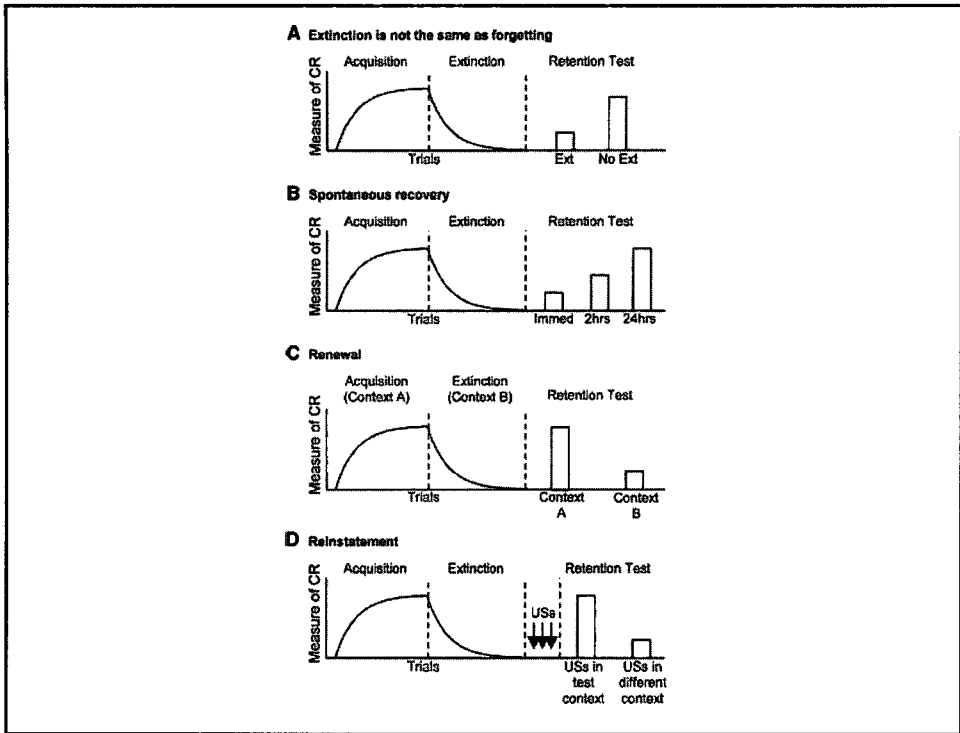


Figure 2. Molecular Mechanisms Underlying the Acquisition and Consolidation of Emotional Learning and Memory in the Lateral Amygdala

From Rodrigues et al., 2004

Fear Extinction: Cellular Mechanism?

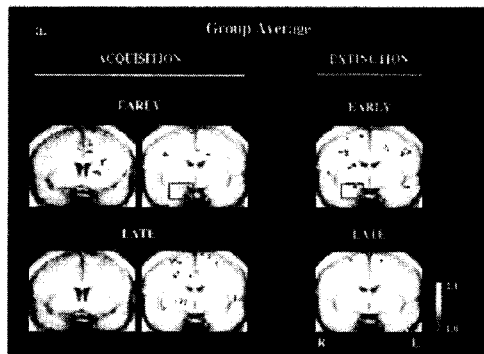


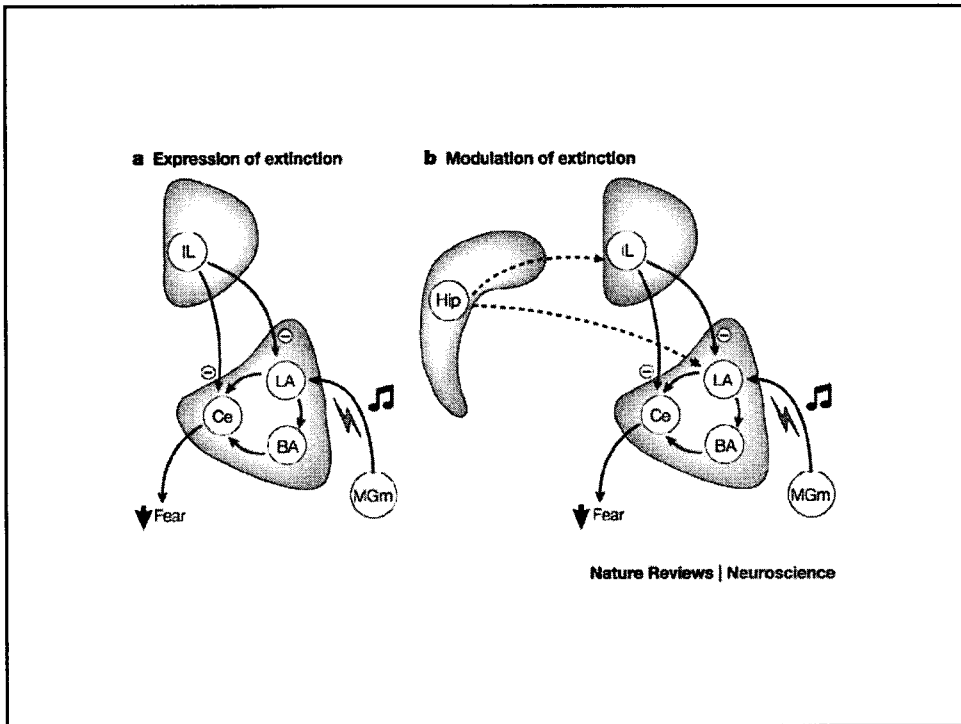
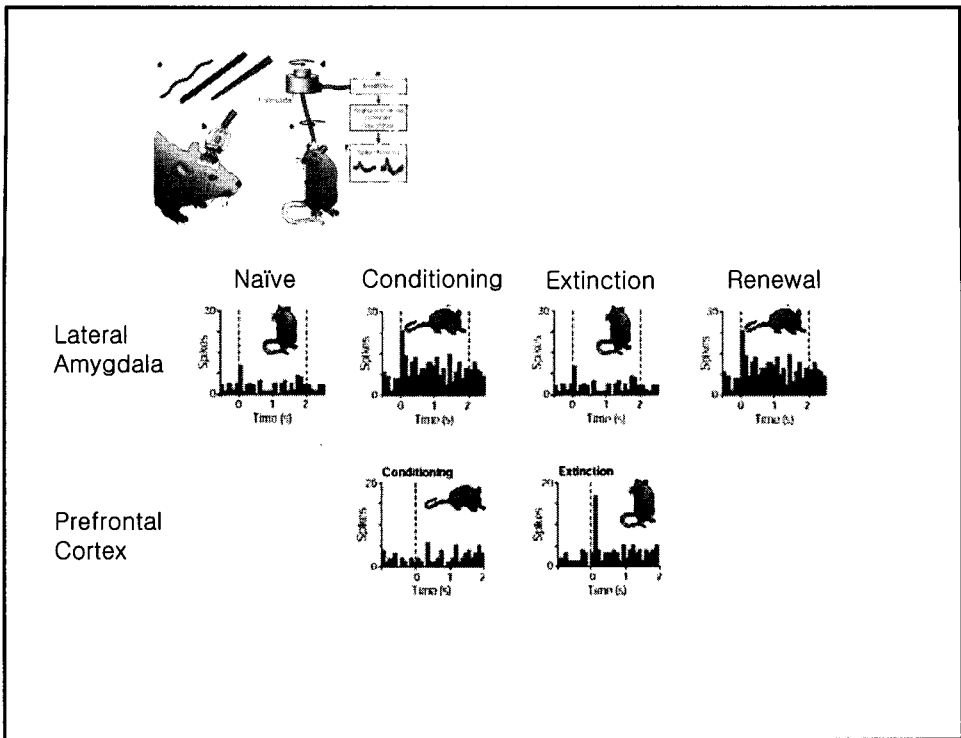


Human Amygdala Activation during Conditioned Fear Acquisition and Extinction: a Mixed-Trial fMRI Study

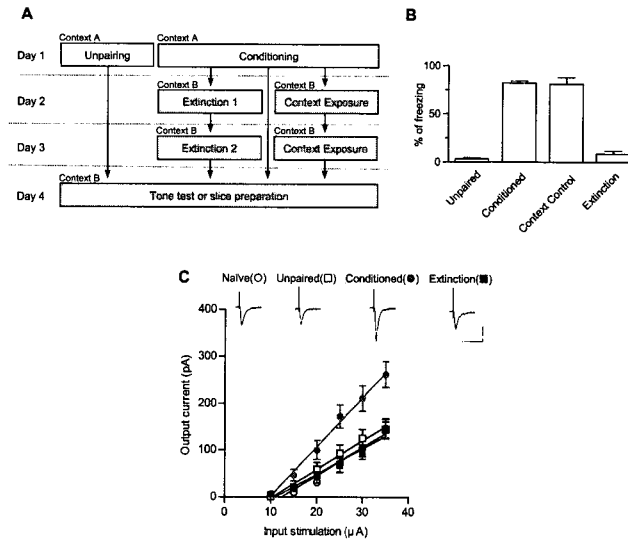
Kevin S. LaBar,¹ J. Christopher Gatenby,¹
John C. Gore,¹ Joseph E. LeDoux,¹
and Elizabeth A. Phelps^{2,3}

to investigate amygdala function
have produced inconsistent
Whereas neuropsychologic

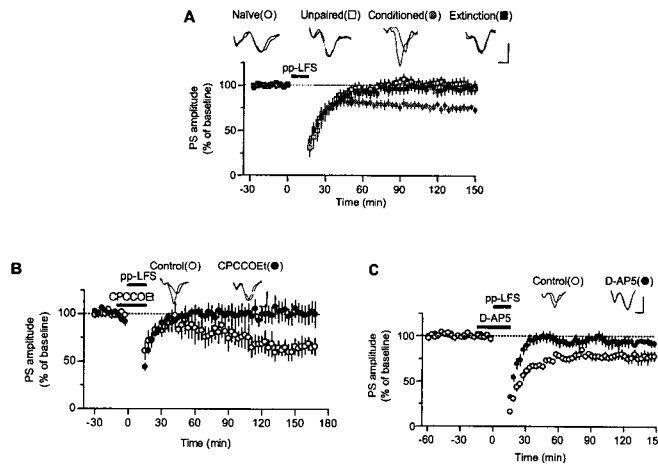




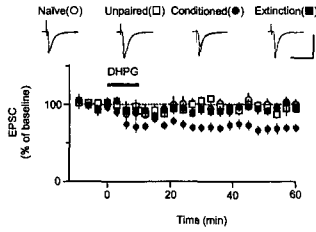
Extinction results in reversal of conditioning-induced potentiation Use of Consolidated memory traces



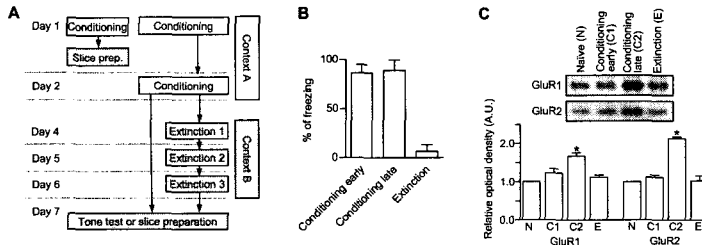
pp-LFS Produces *Ex Vivo* Depotentiation at Thalamo-Amygdala Synapses



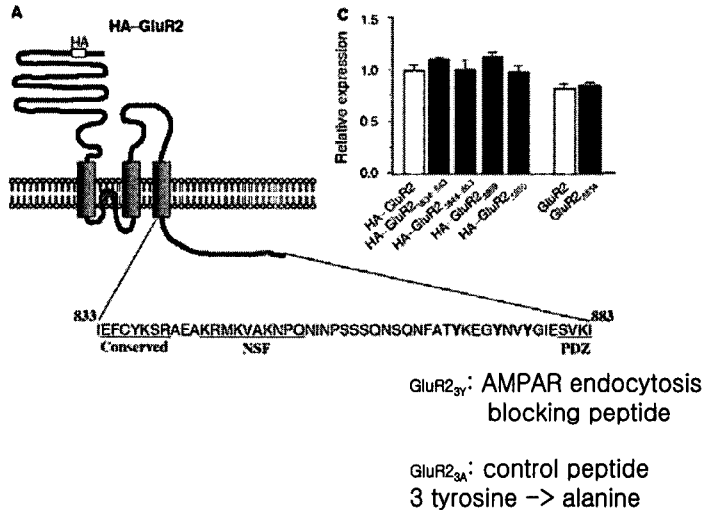
Group I Metabotropic Glutamate Receptor Agonist, DHPG, Produces *Ex Vivo* Depotentiation at Thalamo-Amygdala Synapses



Expression of Surface AMPAR at Amygdala Synaptosomal Preparation

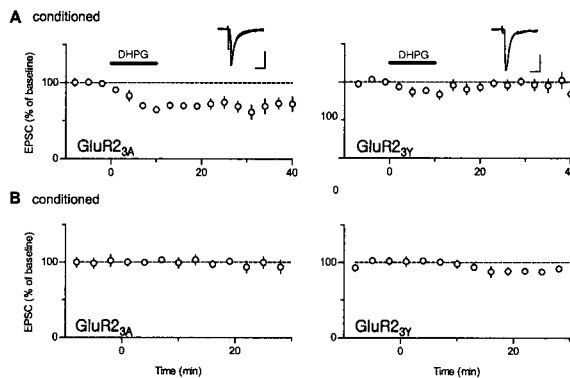


Removal of AMPA receptors with Extinction?



The Peptides Blocking AMPAR Internalization Attenuate Both Depotentiation and Extinction

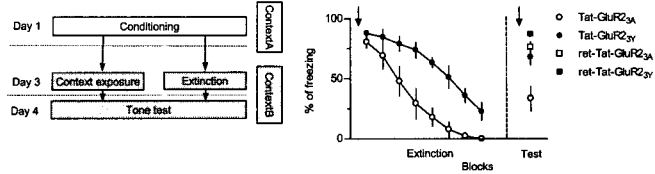
Peptides injected into recorded neurons



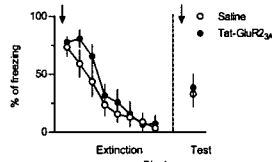
Peptides injected into LA in vivo
(TAAT sequence)



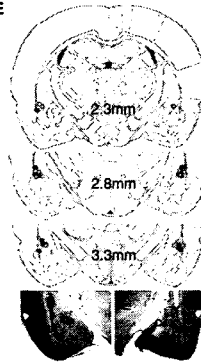
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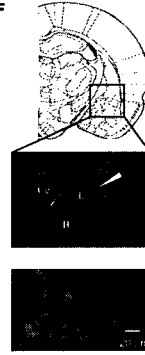
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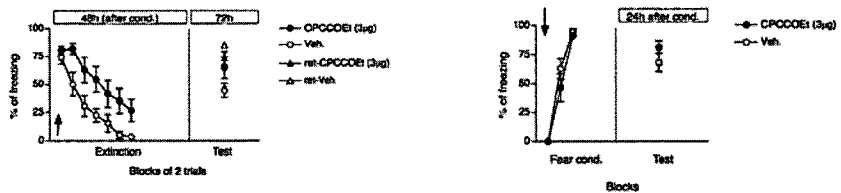


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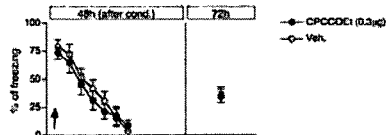


Blockade of Amygdala mGluR1 Impairs Fear Extinction, but not Conditioning

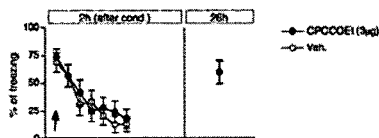
A.



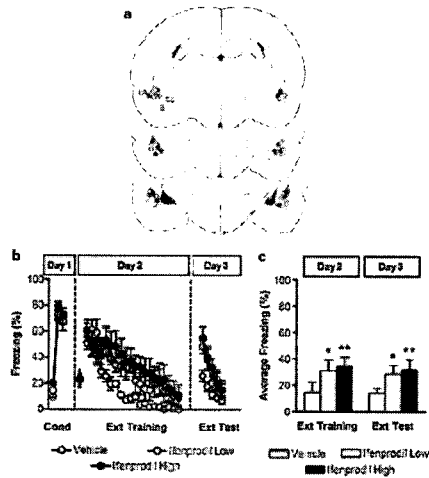
B.



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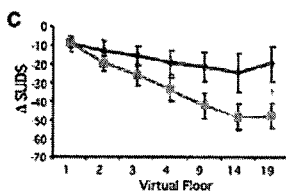
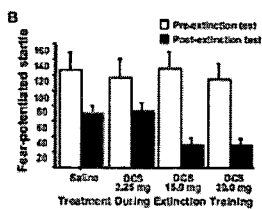


Blockade of Amygdala NMDAR Impairs Fear Extinction



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¹Center for Neural Science, New York University, New York, NY, USA
Neuropsychopharmacology (2007) 32, 1929–1940

Activation of Amygdala NMDAR facilitates Fear Extinction



Michael Davis, Kerry Ressler, Barbara O. Rothbaum, and Rick Richardson

BIOL PSYCHIATRY 2005;58:569–575