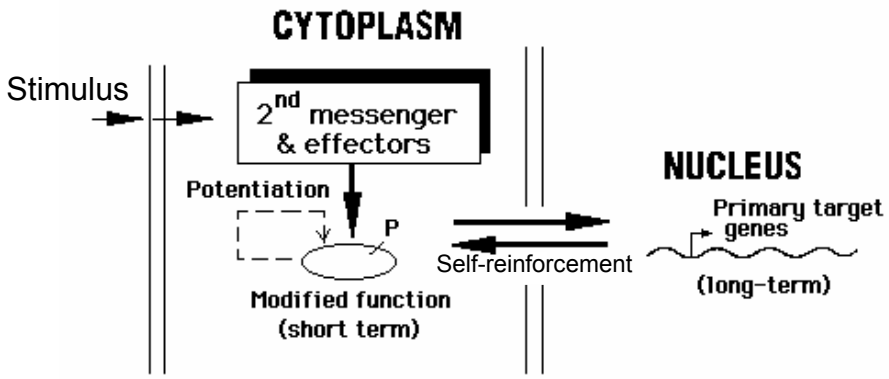
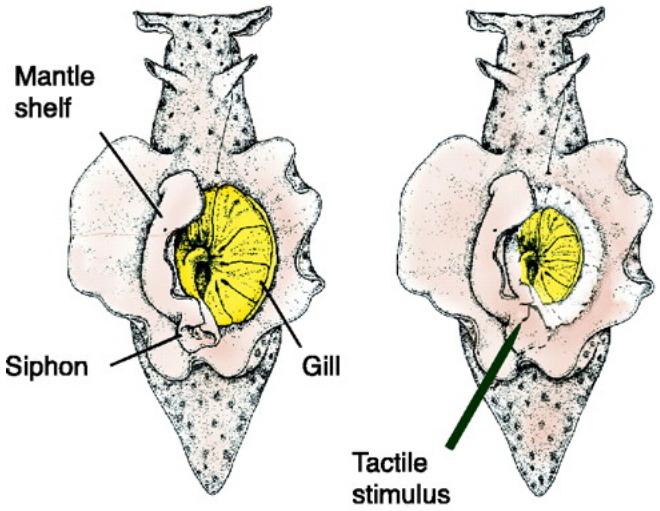
What do neurons do for memory?
A molecular memory of calcium augmentation

- Disclaimer: Memory examples don't fully explains synaptic memory. It demonstrates how molecular memory can be generated from 'common' signaling molecules. It is not intended to literally explain metabolic imprinting.
- Sensitization in Aplysia & long-term potentiation (LTP) in mammals
- A strong initiating stimulus 'sensitizes' the system. Subsequently even weak stimuli elicit a strong response
- Both involve enhanced synaptic transmission via calcium ion flux
- Cognitive kinases: Self-propagating "on" state--a molecular memory. PKA (&PKC in Aplysia) & CaMKII (&PKA) in LTP
- Transition from short-term to long-term memory via gene expression

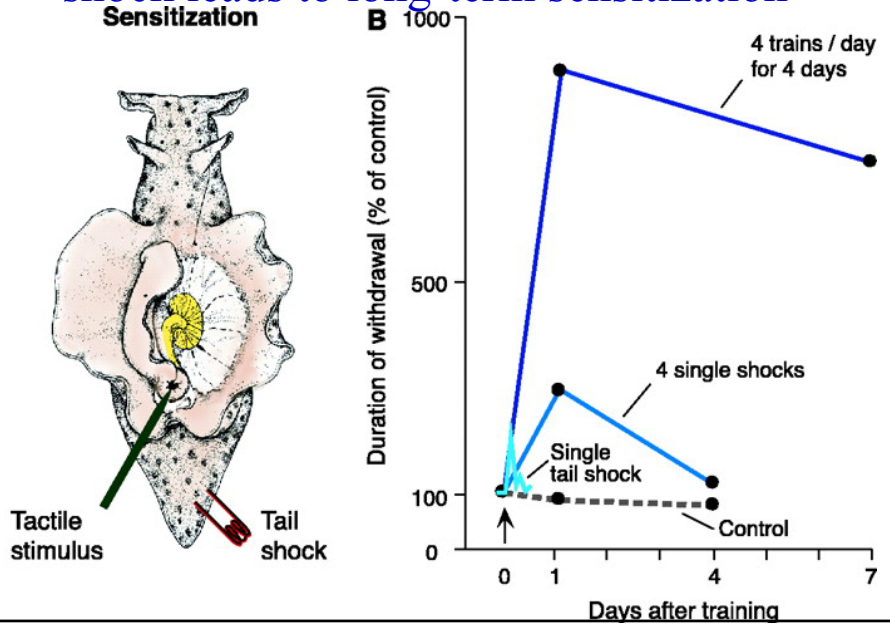
A reversible regulatory system can generate a self-propagating "on" state (molecular memory)



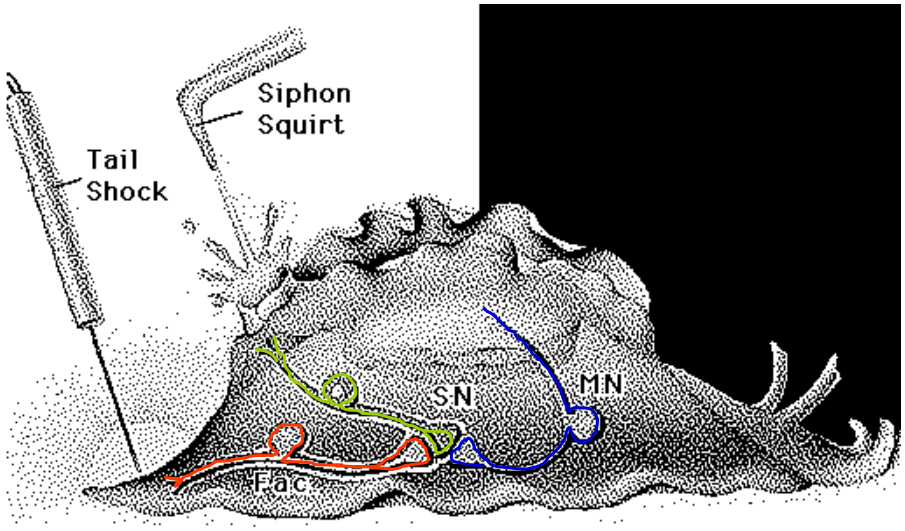
Long-term sensitization of gill-withdrawal reflex in Aplysia (Kandel, Schwartz, Byrne)



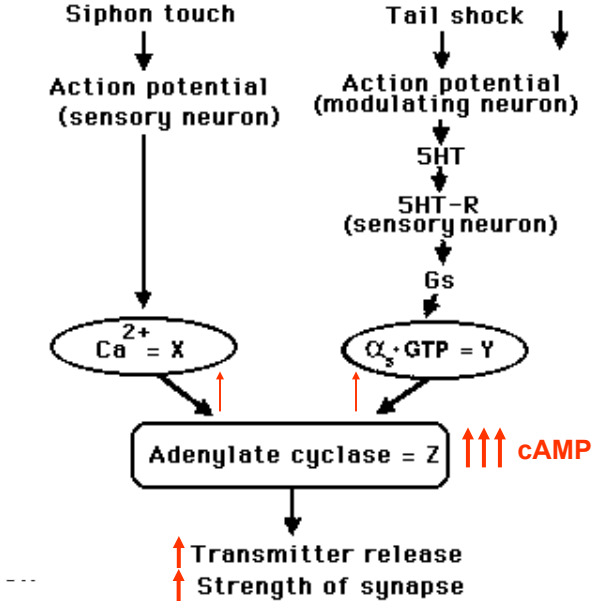
Coincidence of tactile stimulus plus tail shock leads to long-term sensitization



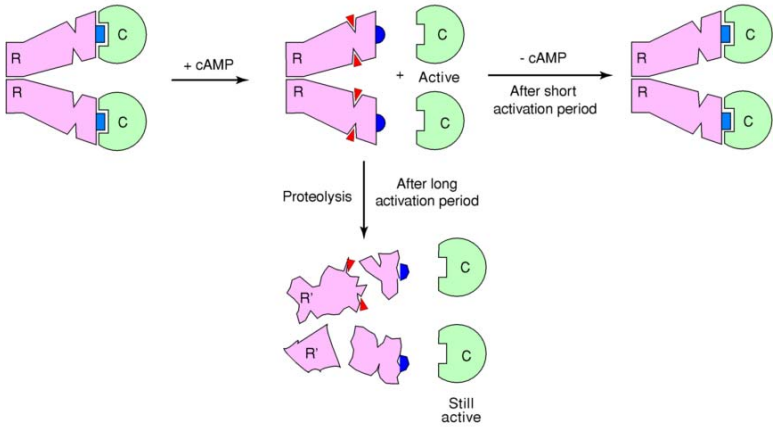
Coincident stimuli sensitize the sensory neuron (SN) to motoneuron (MN) pathway



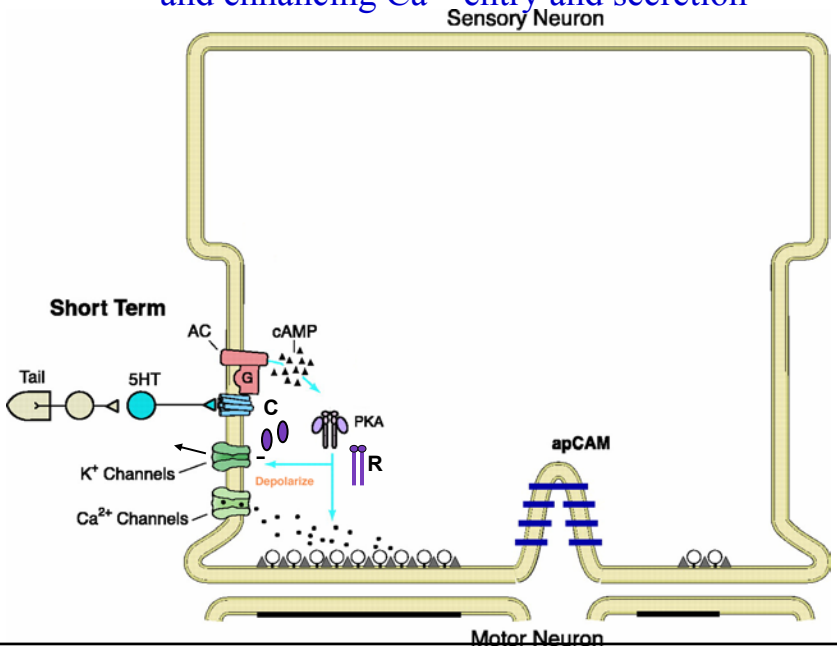
Adenylate cyclase is the coincidence detector that integrates stimuli and amplifies the cAMP response



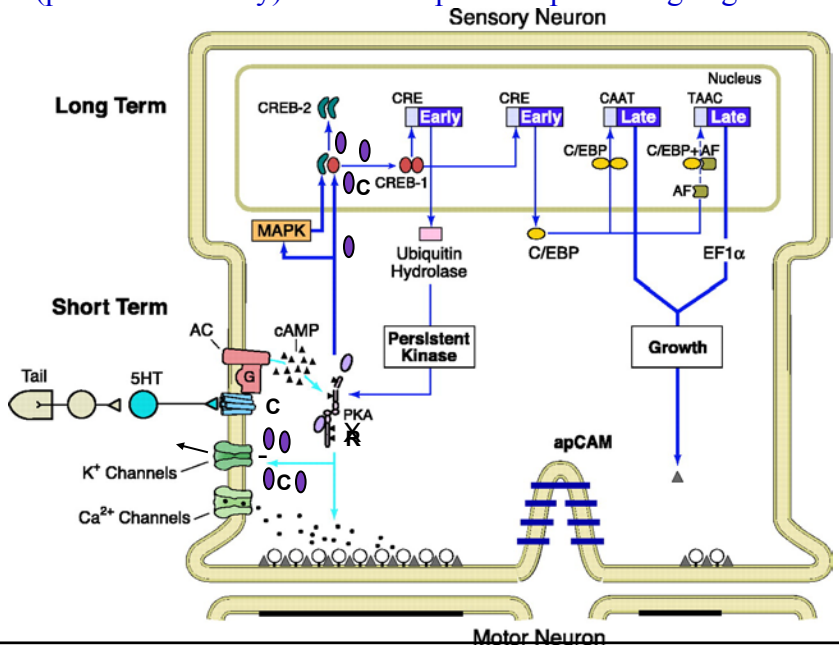
PKA: A cognitive kinase



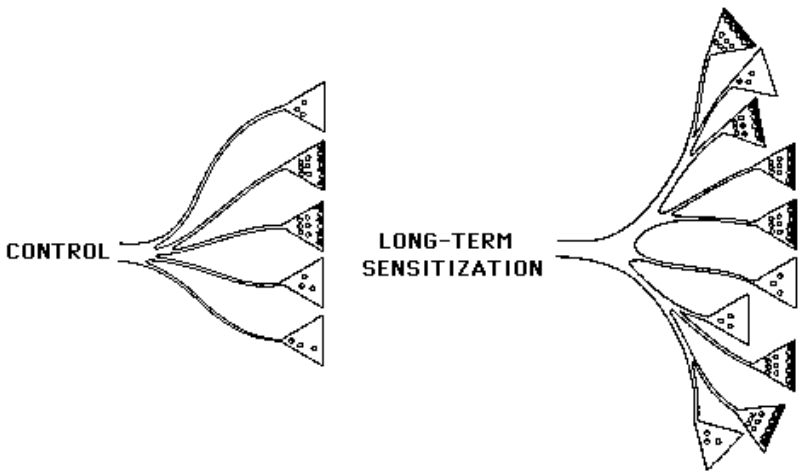
PKA inhibits K^+ channels, promoting depolarization and enhancing Ca^{2+} entry and secretion



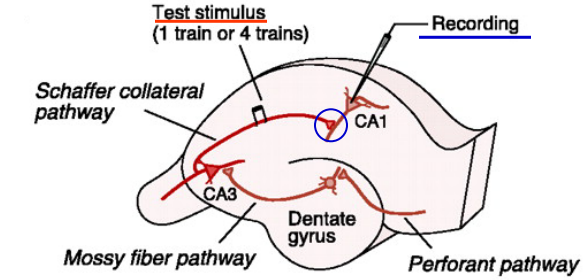
Self-propagation: Strong activation of PKA → degradation of R → Free C (persistent activity) → Gene expression promoting degradation of R

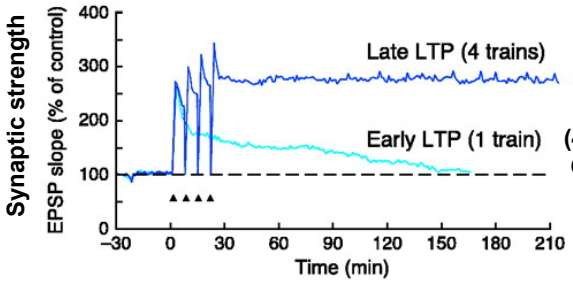


Enhanced PKA signaling leads to elaboration of new synaptic contacts and a long-term sensitization to test stimuli



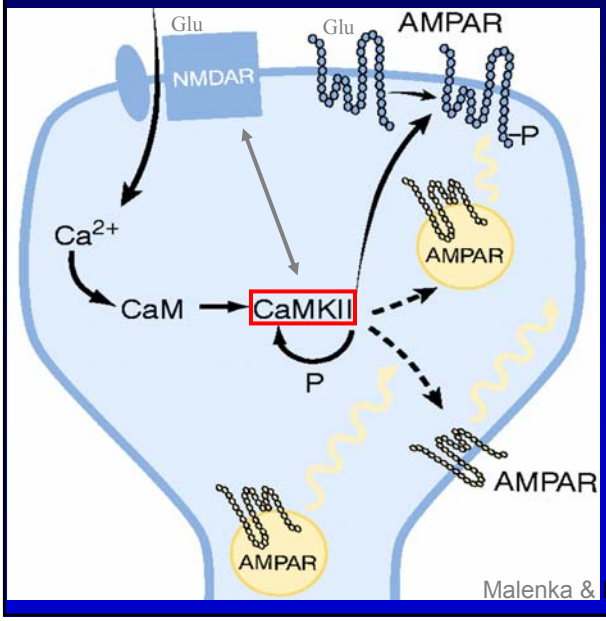
Hippocampal LTP in spatial learning





(4 trains using 286A CaMKII mutant)

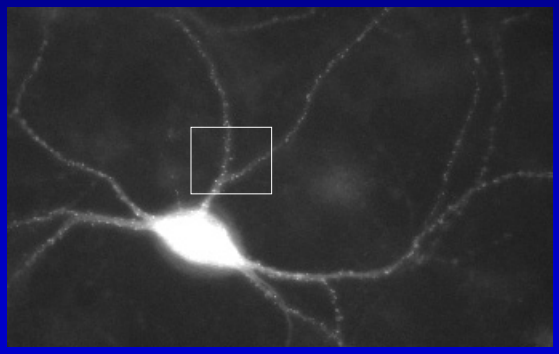
CaMKII in synaptic plasticity: Activation followed by autophosphorylation and/or targeting to NMDA-R

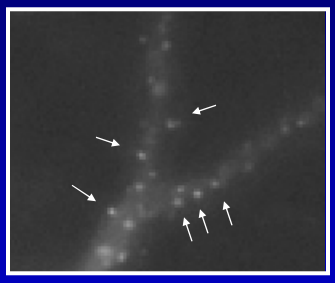


-Coincident stimuli lead to Ca^{2+} entry via NMDA-R
-This potentiates neurotransmission via the AMPA-R
-CaMKII becomes persistently active by two mechanisms: (1) auto-phosporylation that can propagate among ring of subunits; (2) binding to NMDA-R keeps its active site in "on" state.
-CaMKII increases activity of AMPA-R

Malenka & Nicoll (1999)

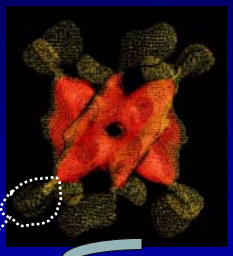
α-CaMKII-GFP in a hippocampal neuron
Translocation to dendritic spines



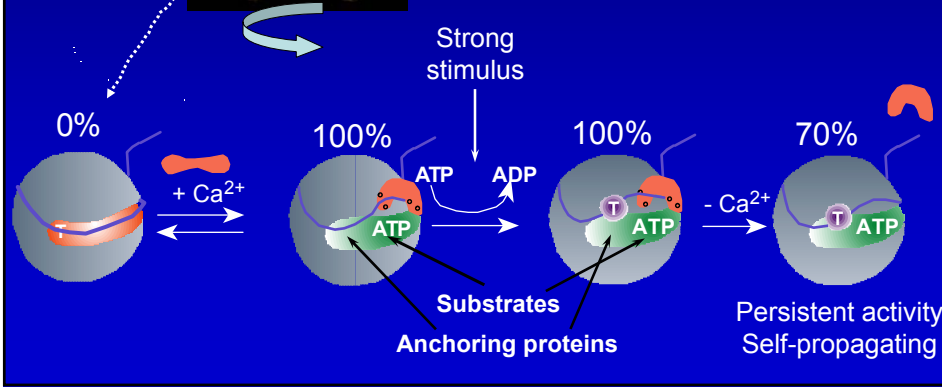


Ca^{2+}
before
stimulation
(2 min)

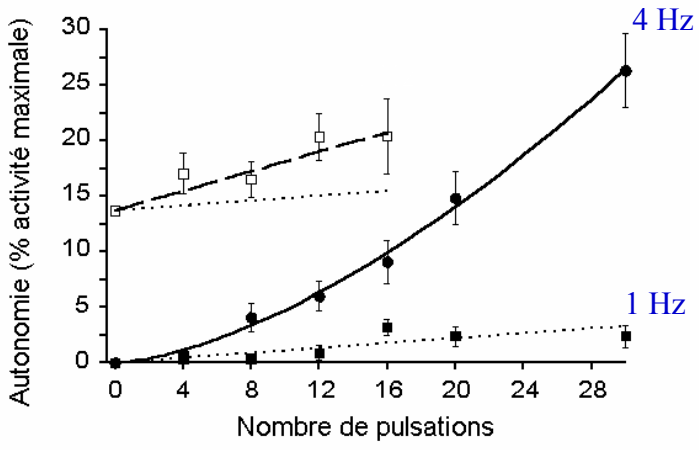
CaMKII: A molecular memory device



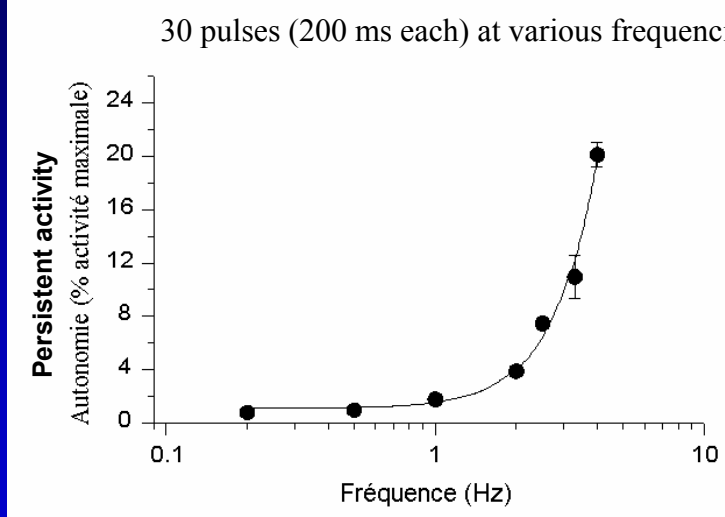
- Persistent activity is generated by:
  - Autophosphorylation
  - Anchoring onto NMDA receptor



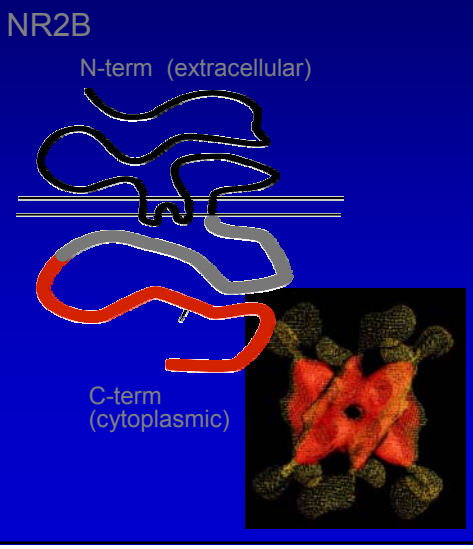
Response to 200 msec pulses of calcium/CaM/ATP

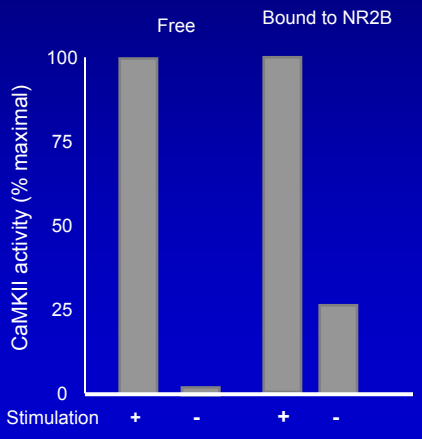


CaMKII activation depends on the frequency of calcium stimuli



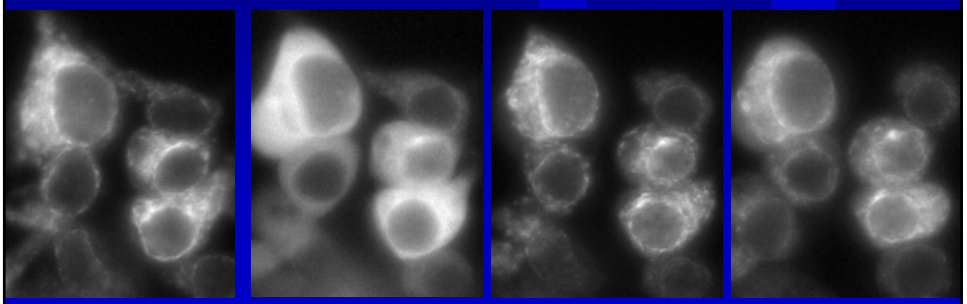
Binding to NMDA-R locks CaMKII in "on" state





Reversible and persistent translocation of CaMKII in HEK cells

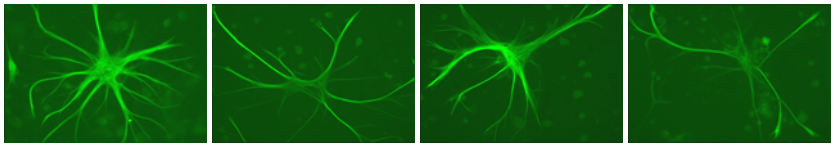
Ca^{2+} stim. 2 min	EGTA 10 min	Ca^{2+} stim. 6 min	EGTA 45 min



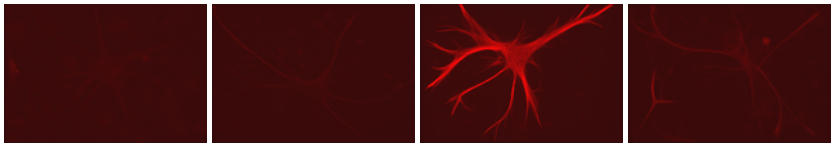
CaMKII - GFP
+NR2B

Phosphorylation of a CaM kinase II substrate *in situ*

anti-vimentin



anti-phospho-vimentin

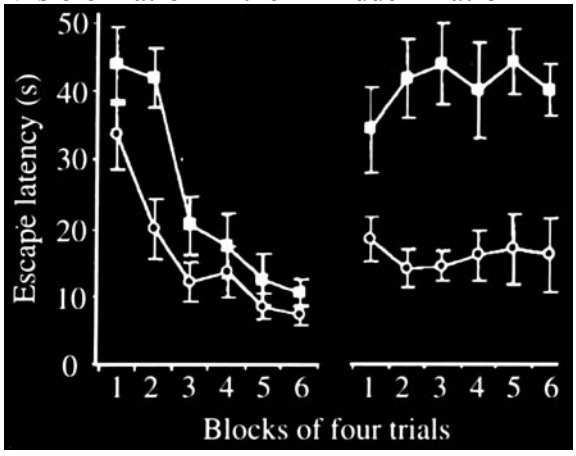


EGTA | Basal Ca^{2+} | Ionomycin | Ionomycin+KN93

Reduced spatial memory in autophosphorylation-deficient mice

Morris water maze test

Visible Platform then Hidden Platform

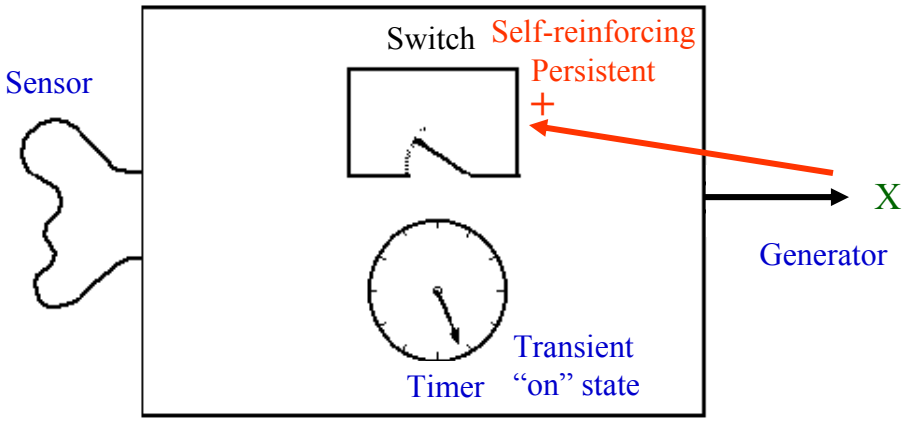


Mutant CaM kinase Thr^{286Ala}

Wild-type

Giese et al., 1998

Signaling Machines



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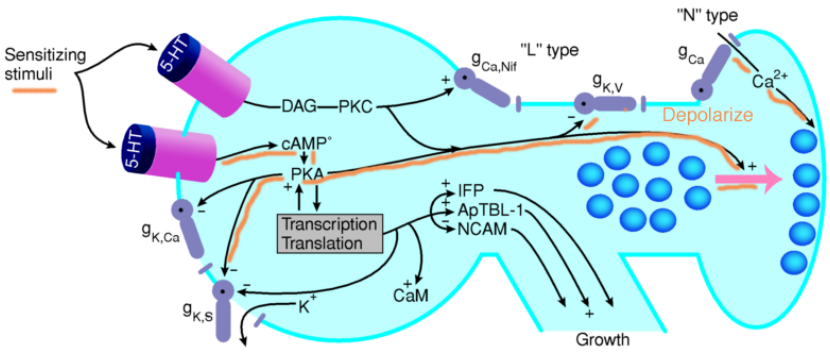
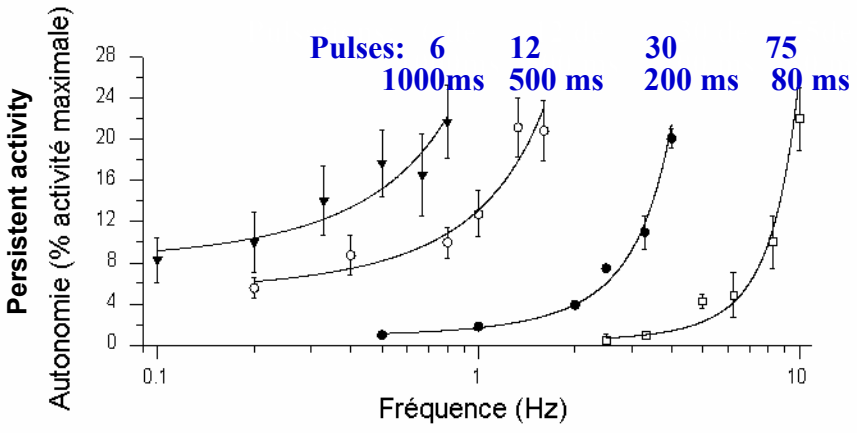
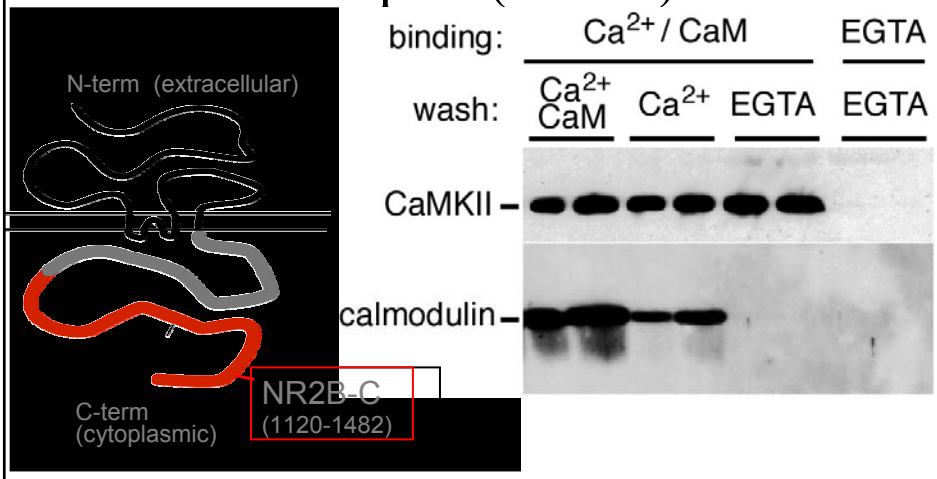


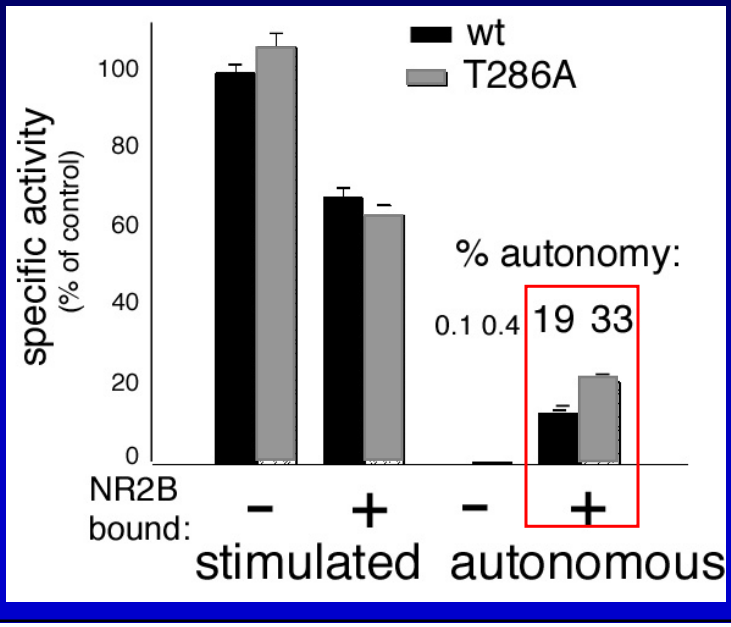
Frequency response changes with pulse duration



Activated kinase binds to NMDA receptor (NR2B)



Binding to NR2B-C makes the kinase autonomous of Ca^{2+}/CaM without autophosphorylation at T286



Increased activation with each successive Ca^{2+} spike