

MOLECULAR MECHANISMS OF TRANSCRIPTIONAL REGULATION BY KChIP3/DREAM/CALSENILIN

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KChIPs

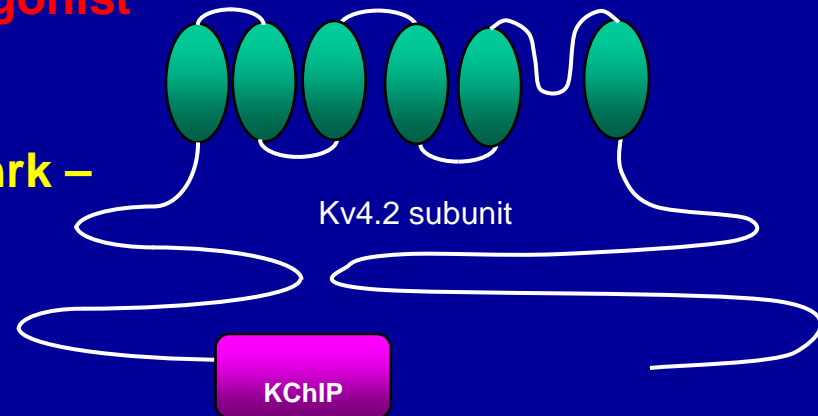
- KChIPs – K⁺ Channel Interacting Proteins – Promote or stabilize Kv4.2/4.3 expression on cell surface, modulate activation, inactivation and rate of recovery from inactivation of Kv4

Reconstitutes some kinetics of A-type current

- Ca²⁺-binding proteins

- KChIP3 is homologous to a protein that is a transcriptional repressor (Downstream Regulatory Element Antagonist Modulator - DREAM) and calsenilin

Modulates expression of prodynorphin, hrk – ICER, N-acetyltransferase



KChIPs increase transient outward (A-type) currents in expression systems, necessary for modulation by kinases

KChIPs are Ca^{2+} -binding proteins – Ca^{2+} -dependent plasticity

KChIPs are transcriptional repressors

KChIP3 is highly expressed in the hippocampus and dentate region

Does KChIP3 play a role in hippocampus-dependent learning and memory???

Fear Conditioning

TRAINING



Dependent on hippocampus and amygdala

- Animal is placed in novel context
- Hears a tone
- Receives foot shock

Dependent on amygdala
More robust

CONTEXTUAL

24 hours later

CUED TEST

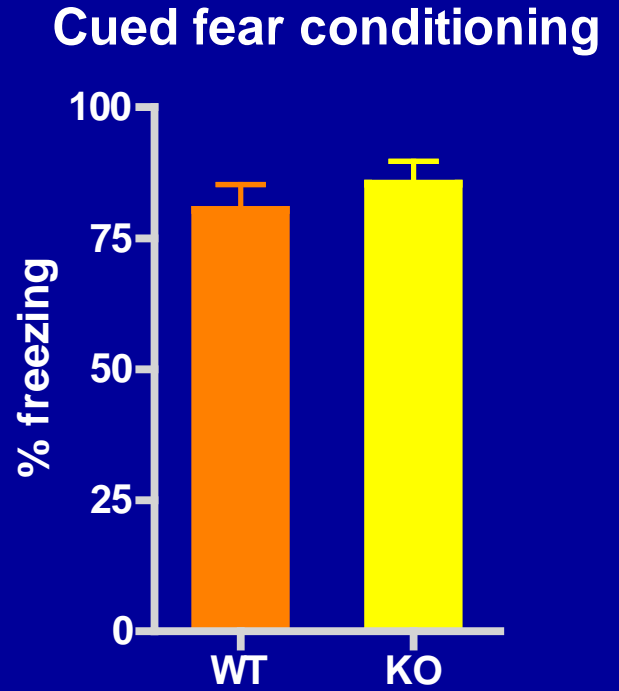
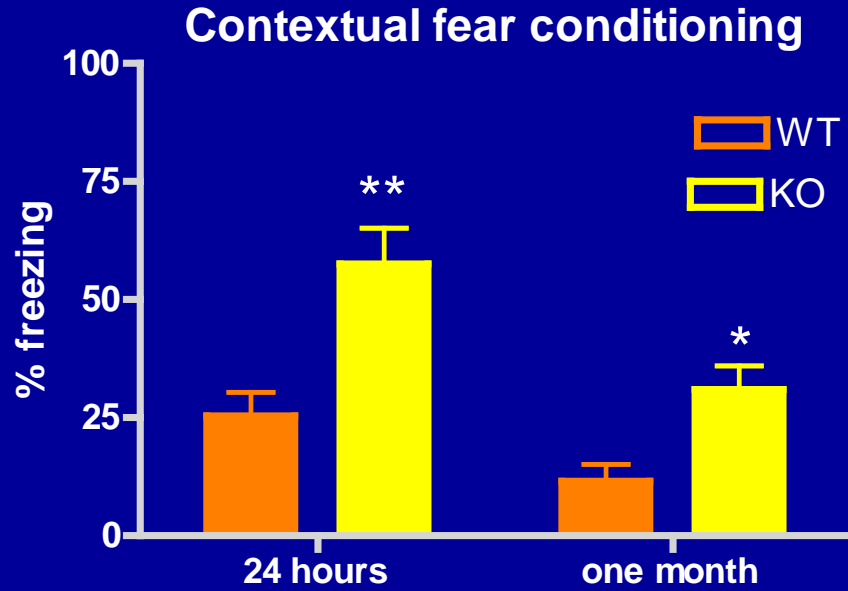


- Animal is returned to same context
- Test for freezing behavior

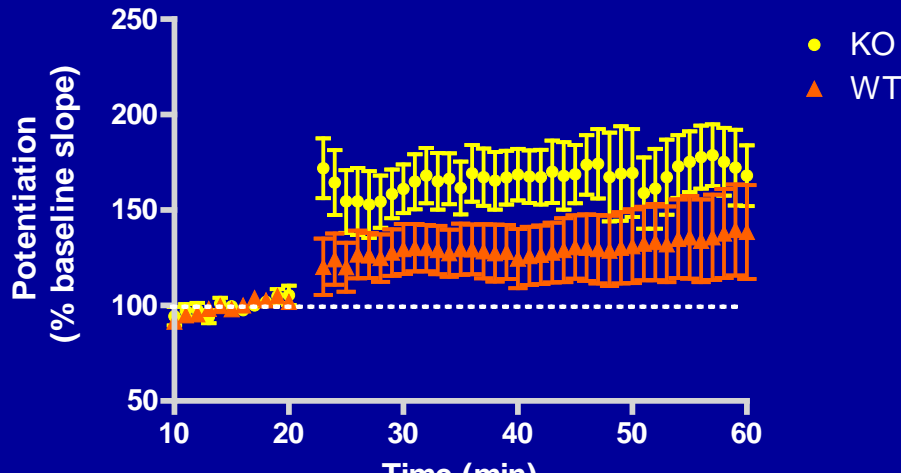


- Animal is placed in novel context
- Hears a tone
- Test for freezing behavior

KChIP3 KO mice exhibit enhanced hippocampus-dependent memory

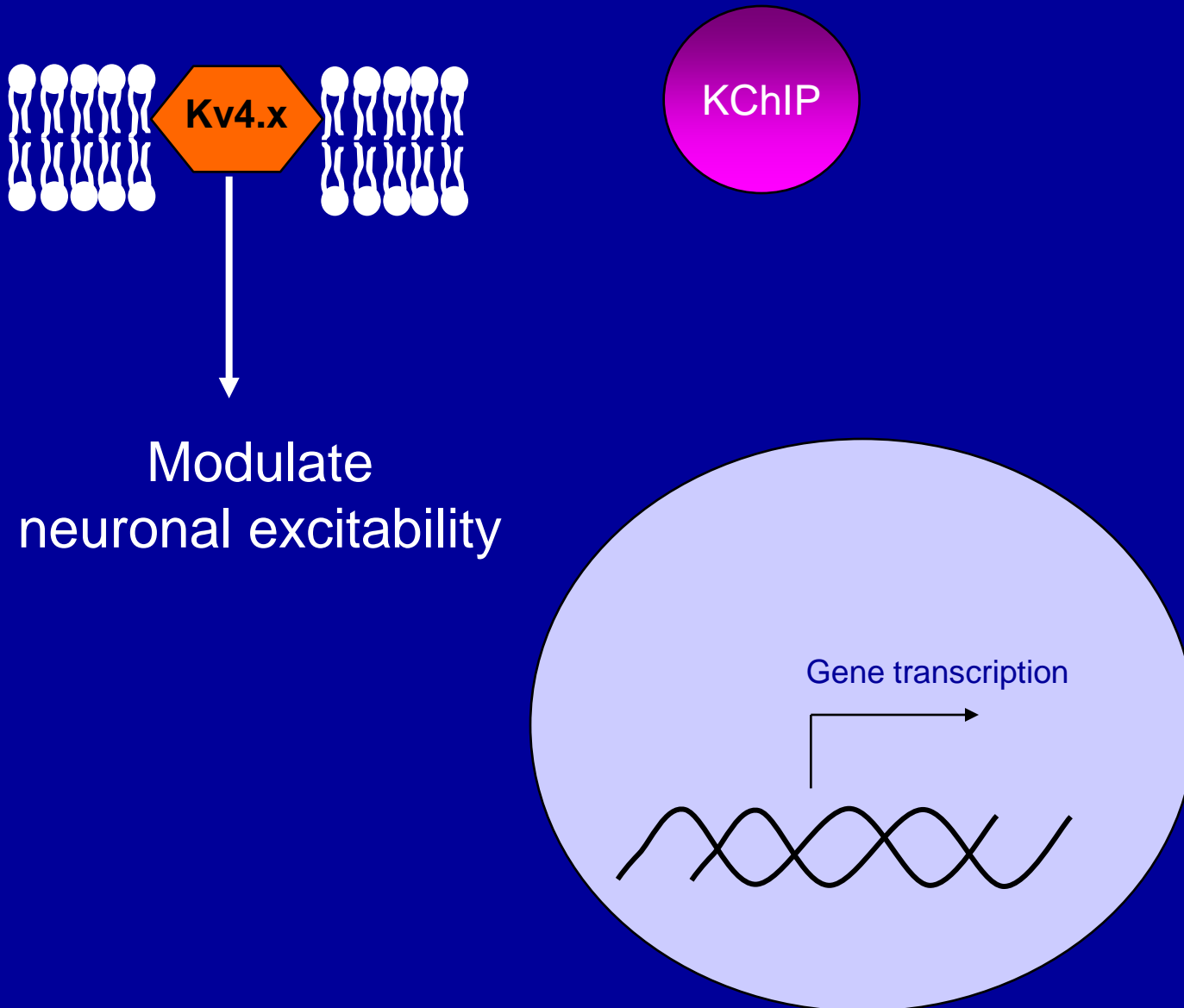


TBS induced LTP

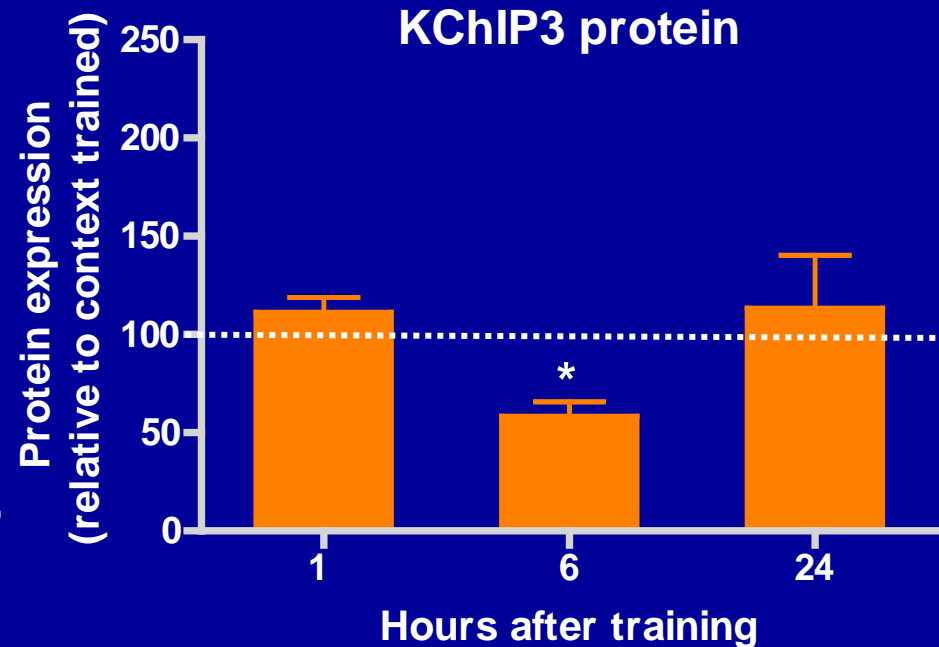
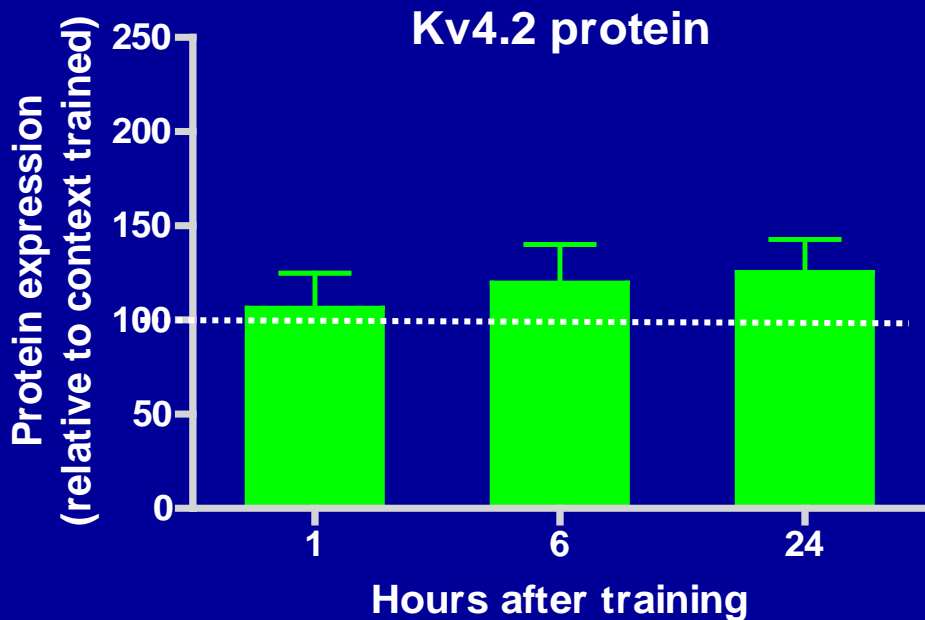
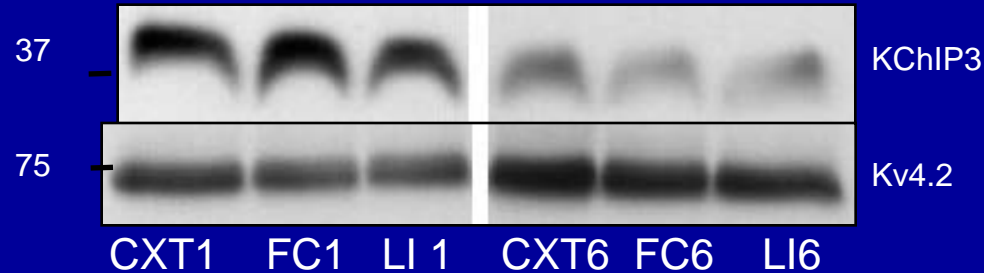


Alexander et al 2009

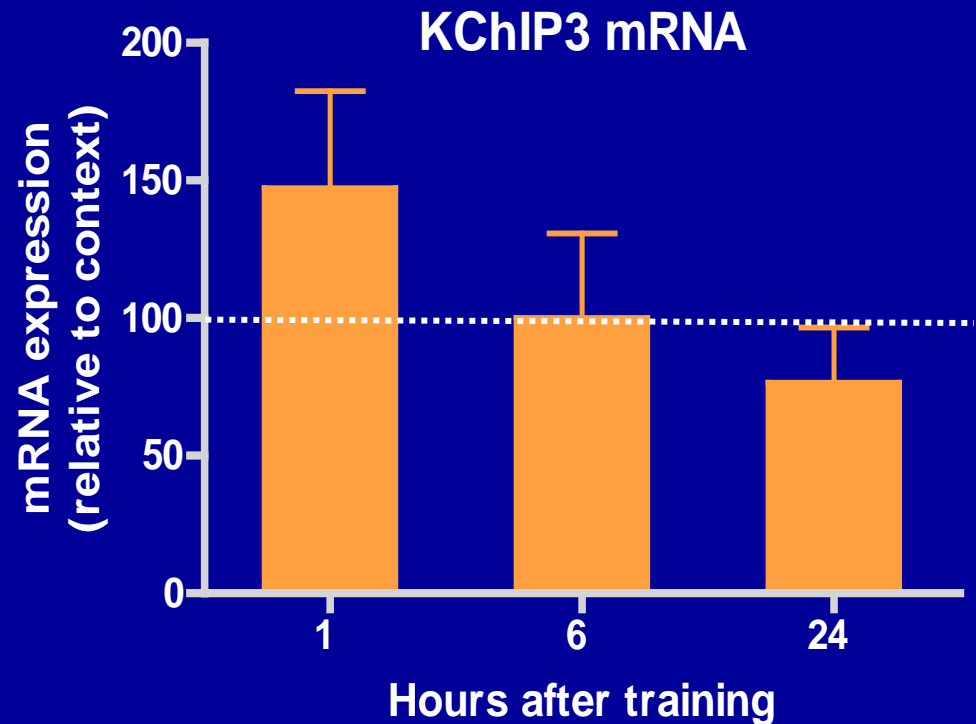
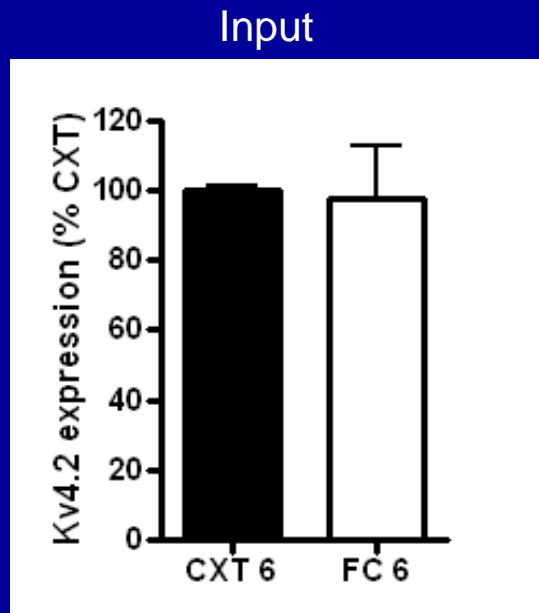
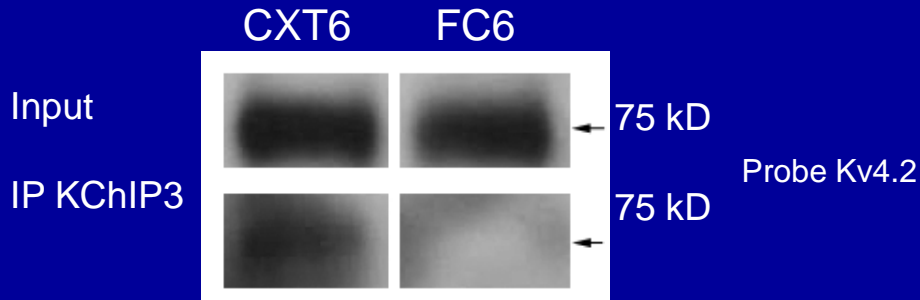
KChIP3 as a regulator of plasticity



Membrane KChIP3 is decreased 6 hours after training for fear conditioning

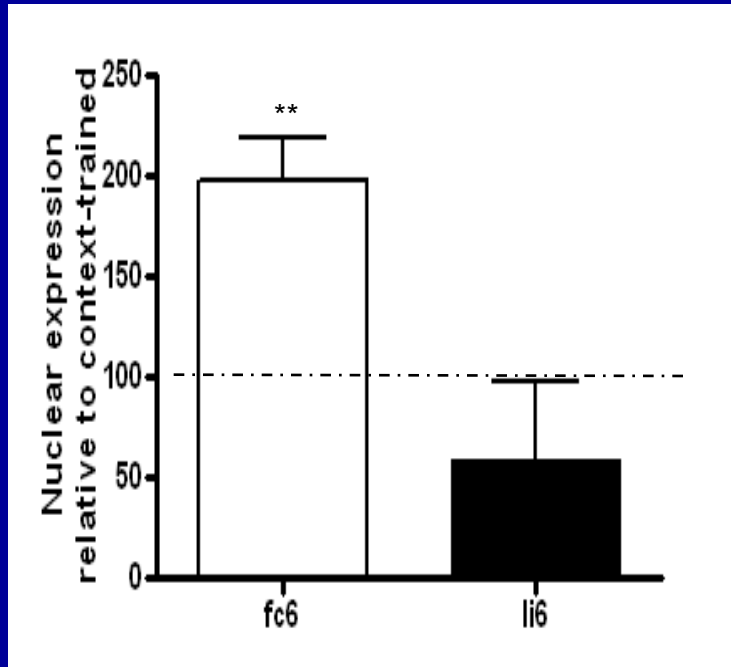
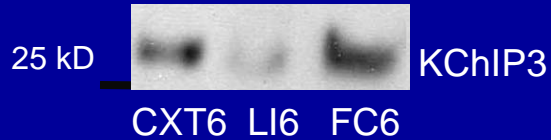


Kv4.2/KChIP3 Interaction is decreased KChIP3 mRNA is not changed

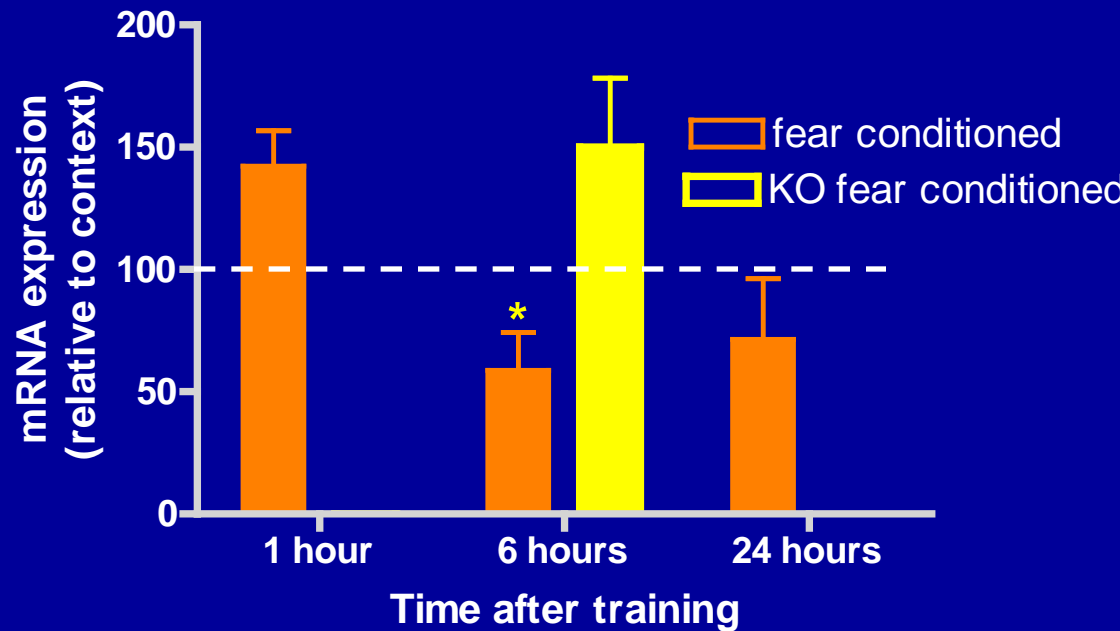


Regulation of transcription

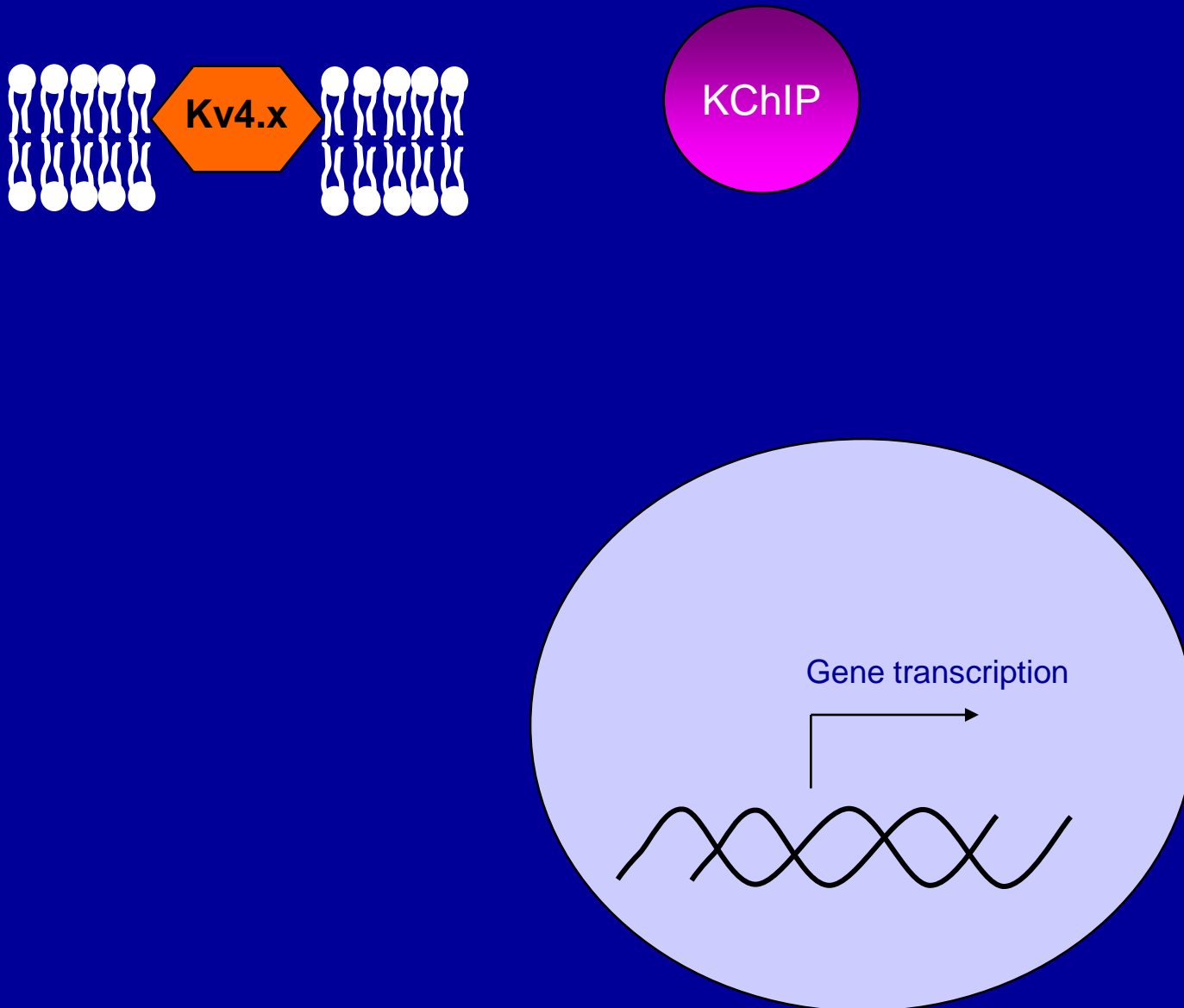
Nuclear Fraction



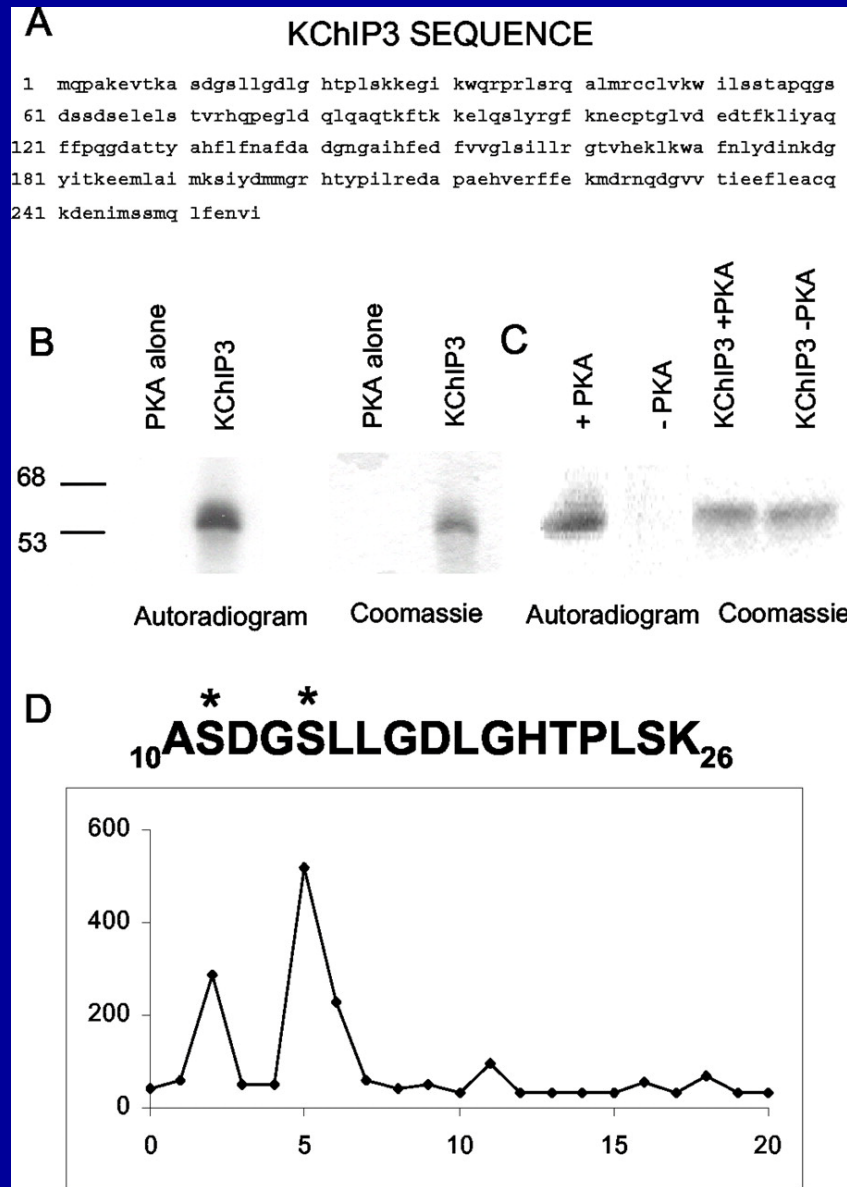
Prodynorphin mRNA



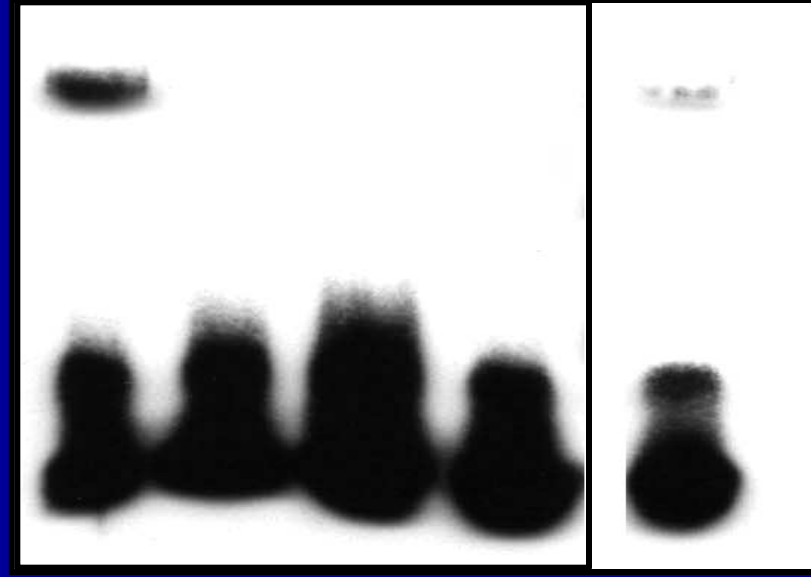
KChIP3 as a regulator of learning and memory



KChIP3 is phosphorylated by PKA



KChIP3/DNA binding *in vitro* requires phosphorylation of KChIP3



P KChIP3

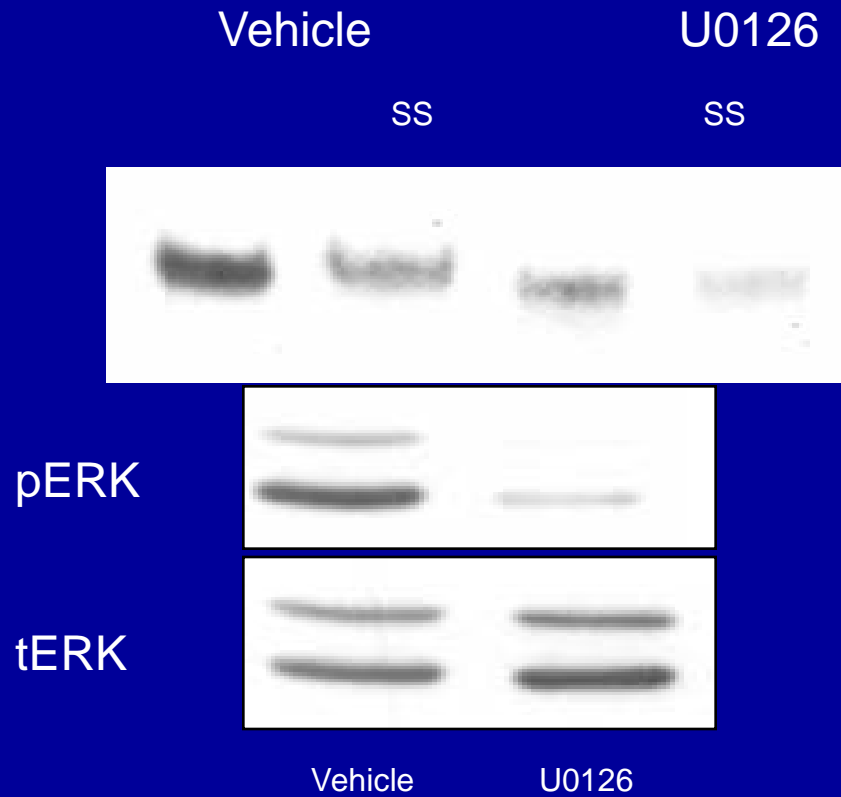
P mut KChIP3

KChIP3

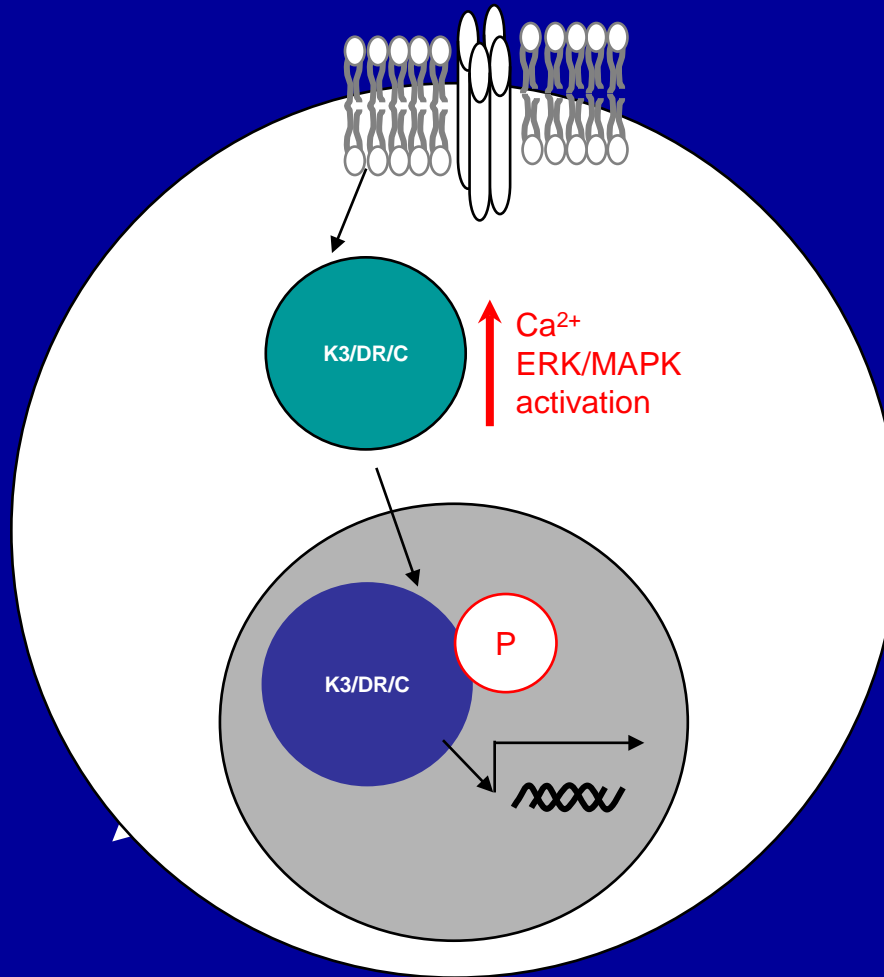
Mut KChIP3

+unbio

KChIP3/DNA binding is decreased by inhibition of ERK/MAPK



SUMMARY





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