KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

Module:
Biological Foundations of Mental Health

Week 4:
Biological basis of learning, memory and cognition

Professor
Peter Giese

Topic 1:

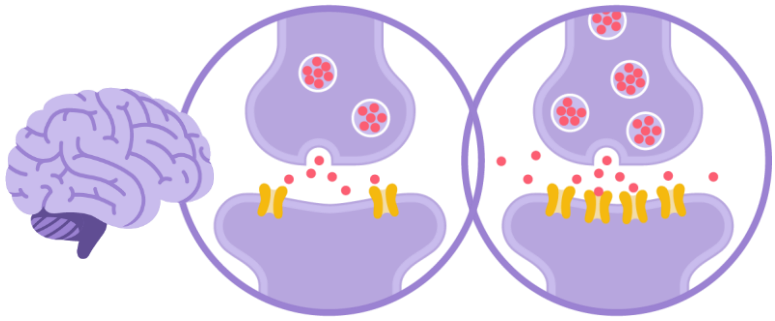
Learning, memory and synaptic plasticity

Part 2 of 4

Part 2

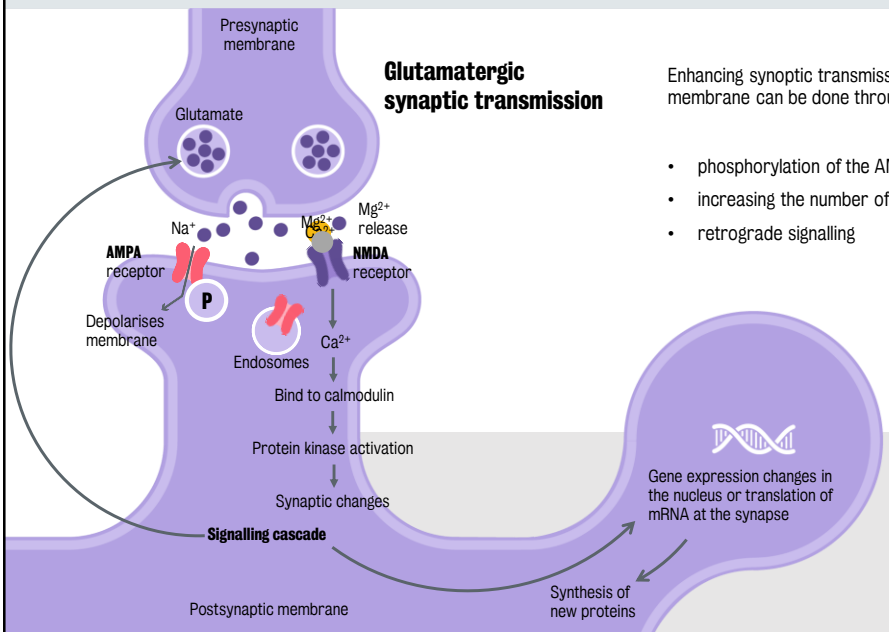
Part 2: Overview

In part two, we will look at long-term potentiation in more detail.



We will also talk about molecular mechanisms that underlie the induction, consolidation and the maintenance of LTP.

Molecular mechanisms of LTP induction



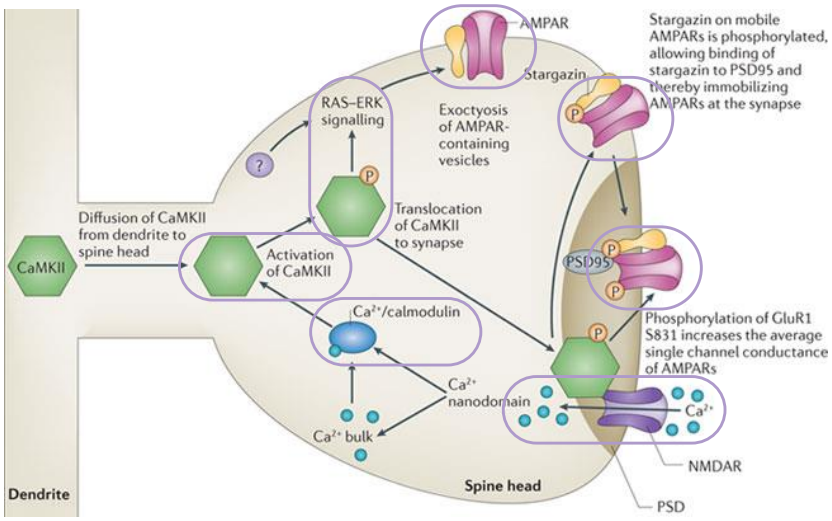
Glutamatergic synaptic transmission

Enhancing synoptic transmission in the postsynaptic membrane can be done through:

- phosphorylation of the AMPA receptors P
- increasing the number of AMPA receptors
- retrograde signalling

Long term potentiation is induced at the postsynaptic site.

The role of CAMKII in LTP production



CaMKII:
calcium calmodulin-dependent kinase II

(P) phosphorylation of the kinase

CaMKII seems to be a critical enzyme for the induction of long-term potentiation.

Lisman et al. (2012)

The late phase of LTP

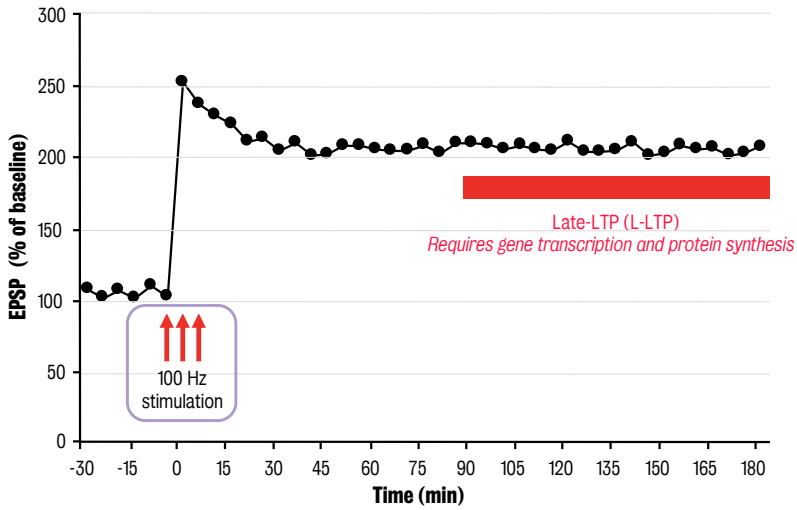
Long-term potentiation varies in terms of its duration.

Late LTP or **L-LTP:**
Terms introduced by **Eric Kandel**.
Nobel Laureate

Long lasting forms of LTP require protein synthesis and gene transcription.

The proteins required for the induction of LTP also contribute to its long lasting nature.

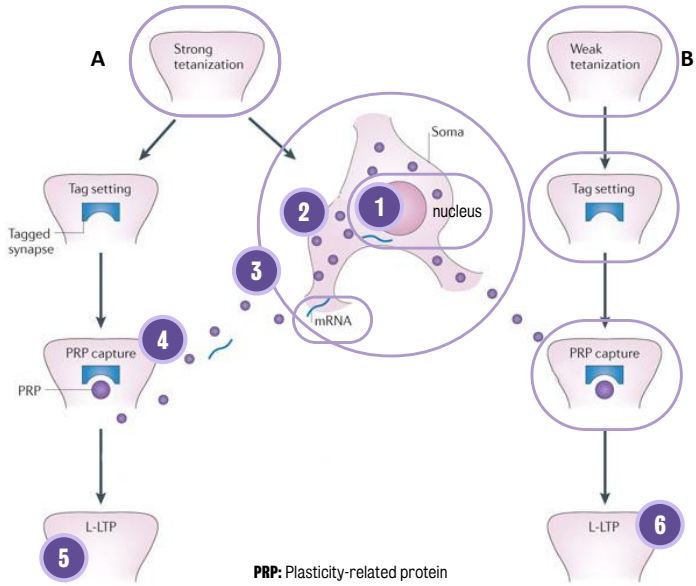
LTP needs to undergo a protein synthesis-dependent process to be lost-lasting



Synaptic tagging (synaptic capture)

How can these new synthesised proteins be delivered specifically to the synapses undergoing long term potentiation?

1. Once the signal reaches the nucleus, it results in gene expression, followed by mRNA translation and protein synthesis
2. Importins are thought to be important molecules for gene expression
3. These newly synthesised proteins can only be taken up by tetanised synapses
4. The strong tetanisation induces a molecular change, a so called tag setting, that captures PRP
5. Late phase LTP
6. Early phase LTP transforms into late phase LTP due to it coinciding in time with a strong tetanisation



PRP: Plasticity-related protein

Redondo and Morris (2011)

LTP maintenance

LTP induction
Requires NMDA receptors and CaMKII

LTP consolidation
Requires protein synthesis that is taken up by activated synapses only

This mechanism only lasts for as long as PKMζ is around (a few hours to a day at most)

How is long term potentiation kept over a lifetime?

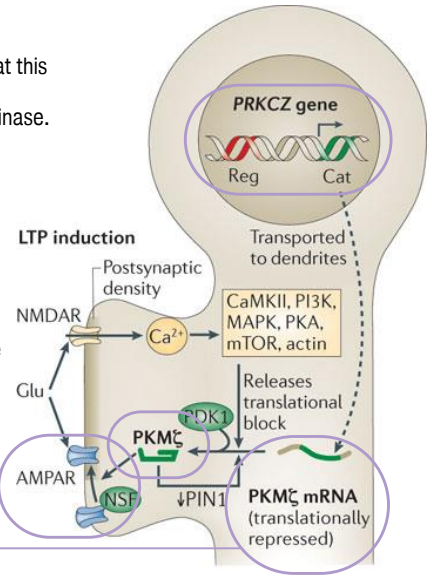
Once PKMζ is turned over, it is replaced by newly synthesised PKMζ.

An active form of PKMζ should always be present in the synapses that maintain LTP.

LTP maintenance
It has been suggested that this is mediated by the local translation of the PKMζ kinase.

PKMζ:
Lacks a regulatory domain. Therefore its catalytic domain is active all the time once it has been produced.

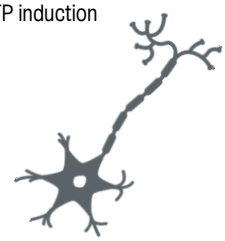
When late phase LTP is induced, the repression is relieved and PKMζ mRNA can be translated



Sacktor (2011)

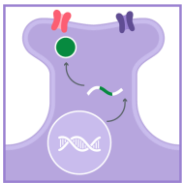
Part 2: Summary

Molecular principles of LTP induction



Consolidation of early LTP into late phase LTP via synthesis of new proteins

Research is undergoing on the importance of these proteins in late phase LTP



The importance of PKMζ in the maintenance of LTP

End of part 2