CPEB3: An Essential Prion for Long-term Memory Consolidation and Maintenance

Full Text

Bibliographic review | Bachelor's Degree in Genetics 2020 – 2021 | Eneko Merino Casamayor

Objectives

- To disprove the common misconception of amyloids as pathogenic by nature
- To review the molecular mechanisms by which CPEB3 enables long-term memory consolidation and maintenance
- To analyze the main differences between CPEB3 and pathogenic amyloids

What is CPEB3?

CPEB3 is an RNA-binding protein of the CPEB family (CPEB1, …, CPEB4)

CPEB3 is prionic in nature and regulates the translation of functional postsynaptic components, mediating LTP (long-term potentiation)

The CPEB3 system has been conserved through evolution, its orthologs include CPEB in *Aplysia* and Orb2 in *Drosophila*

Memory consolidation

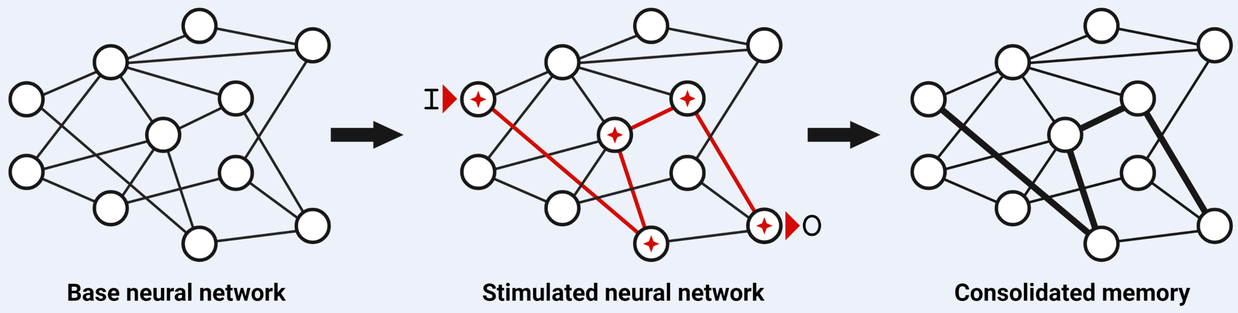


Figure 1. Memory consolidation can be pictured as an increase in synaptic strength (potentiation) as the result of repeated stimulation of a specific neural pathway.

Depending on the duration of the potentiation memory can be divided in two separate types, both operate via independent mechanisms:

- **Short-term memory** → Less than a day in duration, PTMs increase synaptic efficiency
- **Long-term memory** → Duration is indefinite, it is fully dependent on CPEB3 activity

Memory requires amyloid aggregation

Memory consolidation

Translational repressor
In absence of neuronal stimulation CPEB3 is monomeric and it is found in neuronal P bodies, repressing its target mRNAs

Translational activator
Postsynaptic stimulation promotes a change in activity, target mRNAs are polyadenylated and translated

CPEB3 only acts as an activator when forming amyloid fibrils ⚠

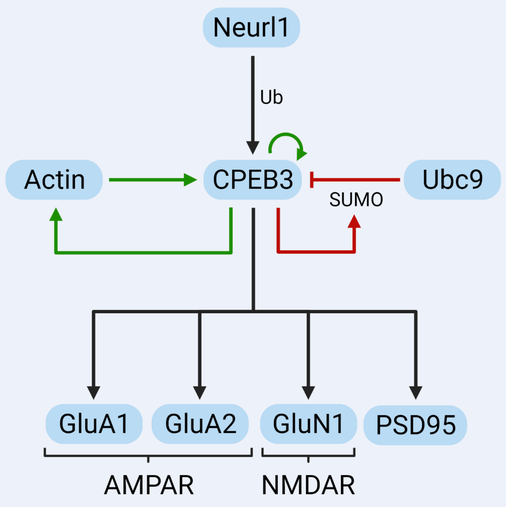


Figure 2. Unlike pathogenic amyloids, CPEB3 aggregation is tightly regulated, imposing several positive and negative feedback loops over itself.

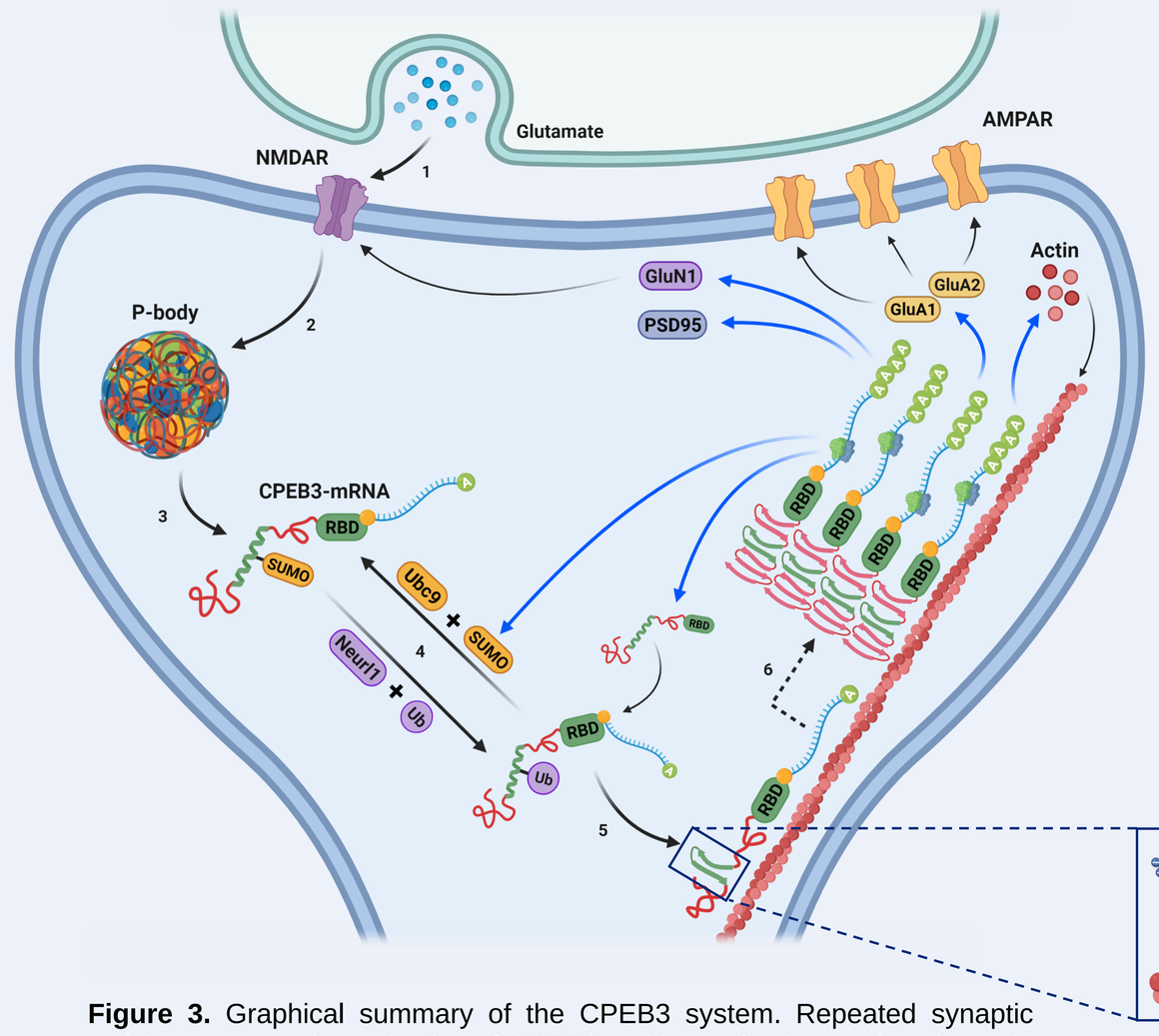


Figure 3. Graphical summary of the CPEB3 system. Repeated synaptic activity promotes the activation of CPEB3 and its nucleation against the actin cytoskeleton. CPEB3 fibrils recruit the translational machinery of the cell, increasing the expression of NMDA receptor subunit GluN1, AMPA receptor subunits GluA1 and GluA2, PSD95 (post-synaptic density 95) and actin, as well as its own (CPEB3).

Memory maintenance

Self-sustain
Active CPEB3 transmits the active conformation to newly synthetized CPEB3, overcoming protein turnover

Spatial constriction
CPEB3 amyloid fibrils are anchored to the actin cytoskeleton, preventing the active form from diffusing to adjacent spines

Memory reconsolidation

It is hypothesized that memory reconsolidation is much more efficient than learning because of residual CPEB3 oligomers in dendritic spines

CPEB3 oligomers would act as seeds, accelerating the aggregation process

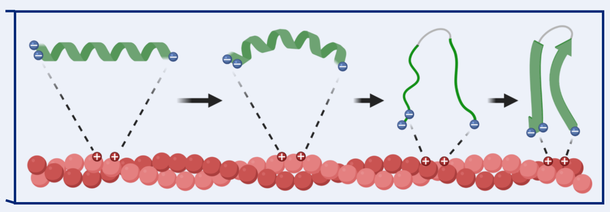


Figure 4. The CPEB3 *zipper* motif initiates nucleation and anchors the fibril to the actin cytoskeleton.

Perspectives for the future

Future research

- The 3D structures of monomeric and fibrillar CPEB3 have not been defined
- We are still far from understanding all CPEB3 targets and interactions
- The role of the remaining CPEB proteins in synaptic plasticity is unclear

Personal contribution

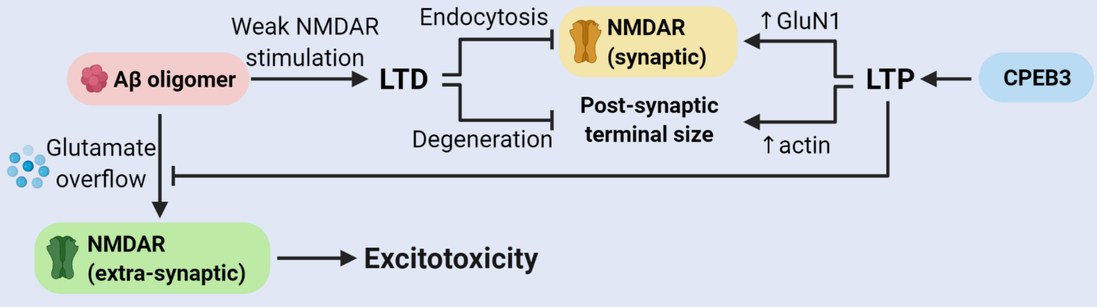
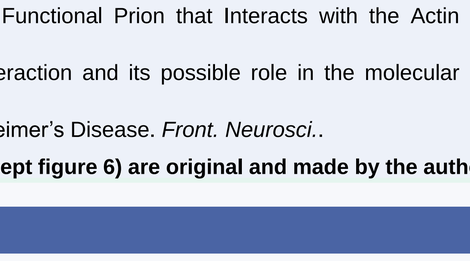


Figure 5. The pharmacological modulation of CPEB3 activity might be an option to ameliorate the synaptic loss and neurotoxicity of Aβ (amyloid β) oligomers in Alzheimer's disease. Aβ and CPEB3 have opposed effects, Aβ induces LTD (long-term depression) whereas CPEB3 induces LTP (long-term potentiation).

Conclusions

1. Amyloids are not pathogenic by nature
2. The aggregation of functional prions is tightly regulated to prevent toxic effects
3. Long-term memory consolidation, maintenance and reconsolidation rely on CPEB3 fibrilation
4. The CPEB3-like mechanism is shared between distant taxa
5. Loss of CPEB3 activity impairs normal cognitive functions



Hervas, R., Rau, M. (2020). Cryo-EM structure of a neuronal functional amyloid implicated in memory persistence in Drosophila. (Figure 4A). *Science*.

Figure 6. Cryo-EM Orb2 fibrils in *Drosophila* brain.

References

[1] Fioriti, L., Myers, C. (2015). The Persistence of Hippocampal-Based Memory Requires Protein Synthesis Mediated by the Prion-like Protein CPEB3. *Neuron.*

[2] Lisman, J. (2017). Glutamatergic synapses are structurally and biochemically complex because of multiple plasticity processes: Long-term potentiation, long-term depression, short-term potentiation and scaling. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.*

[3] Ford, L., Ling, E. (2019). CPEB3 inhibits translation of mRNA targets by localizing them to P bodies. *Proc. Natl. Acad. Sci. U.S.A.*

[4] Stephan, J. S., Fioriti, L. (2015). The CPEB3 Protein Is a Functional Prion that Interacts with the Actin Cytoskeleton. *Cell Rep.*

[5] Gu, X., Schafer, N. (2020). Exploring the F-actin/CPEB3 interaction and its possible role in the molecular mechanism of long-term memory. *Proc. Natl. Acad. Sci. U.S.A.*

[6] Liu, J., Chang, L. (2019). The Role of NMDA Receptors in Alzheimer's Disease. *Front. Neurosci.*.

*** All figures (except figure 6) are original and made by the author**