CPEB3 as a therapeutic target for Post-traumatic Stress Disorder

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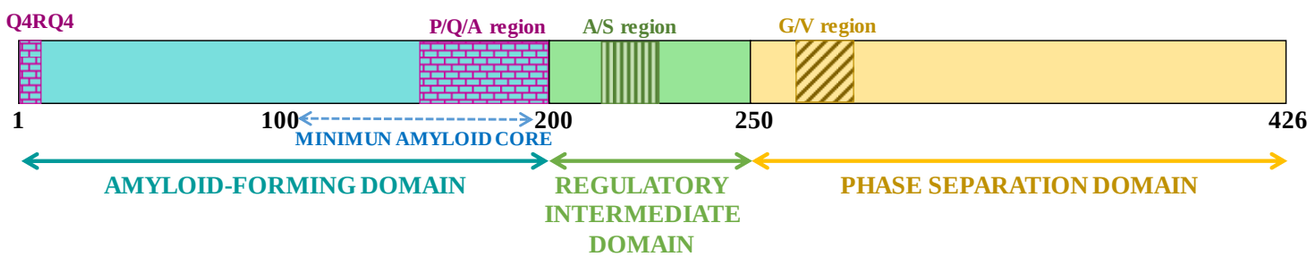
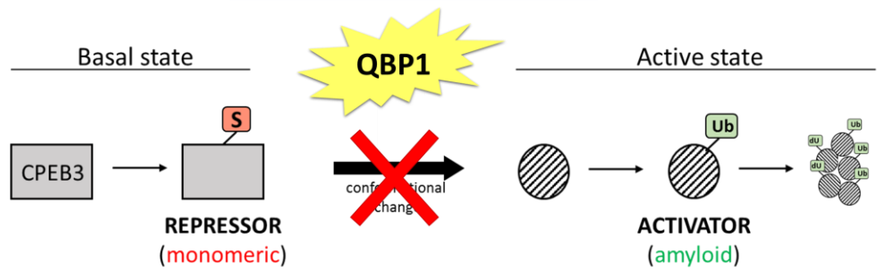
The cytoplasmic polyadenylation element binding protein-3 (**CPEB3) is a functional amyloid** whose importance for long-term memory consolidation in mammals is well established [1]. Its corresponding gene has been recently associated to a **potential risk gene** for Post-traumatic Stress Disorder (PTSD) [2]. This mental health disorder is triggered by the exposure to a traumatic event that manifests with anguish, intrusive memories, and negative mood changes [3]. Currently, there is **no efficient treatment for PTSD** other than symptomatic palliative care. Here, we propose the active amyloid state of CPEB3 [4] as a **promising therapeutic target** to block the consolidation of traumatic memories through by **the anti-amyloidogenic polyglutamine binding peptide 1 (QBP1) [5]**.

We report the preclinical development of this pharmacological treatment for PTSD based on the action of QBP1 peptide. We first characterized both human and murine CPEB3 proteins in vitro, showing how **their amyloid is inhibited by QBP1** without affecting any other functional process (i.e., phase separation). Then, we produced and characterized a novel transgenic mouse that constitutively expresses QBP1 (TgQBP1**)**. TgQBP1 mice have showed that the consolidation of simple **learning is impaired after 24h** for both hippocampal- dependent and aversive memories and that it is **limited to new learned memories and has no effect on short-term memory.** Furthermore, fear-induced **anxiety was reduced in comparison** to WT mice, suggesting that PTSD-like symptoms are also being ameliorated. Intriguingly, we found that aversive memories seem to be more strongly affected in younger mice. Finally, we analyzed the CPEB3 amyloid presence in hippocampal extracted samples showing a **correlative decrease in murine CPEB3 oligomerization** in the TgQBP1 mouse brains. Taking together, these results suggest that QBP1 peptide is a promising lead compound for **prevention and therapy of PTSD and acute stress disorder**.

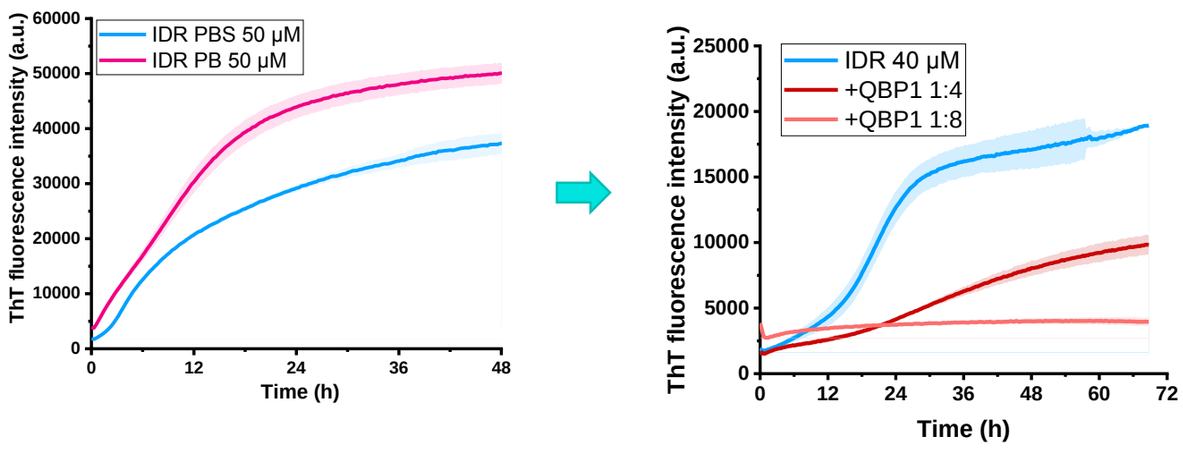
Human CPEB3 organization



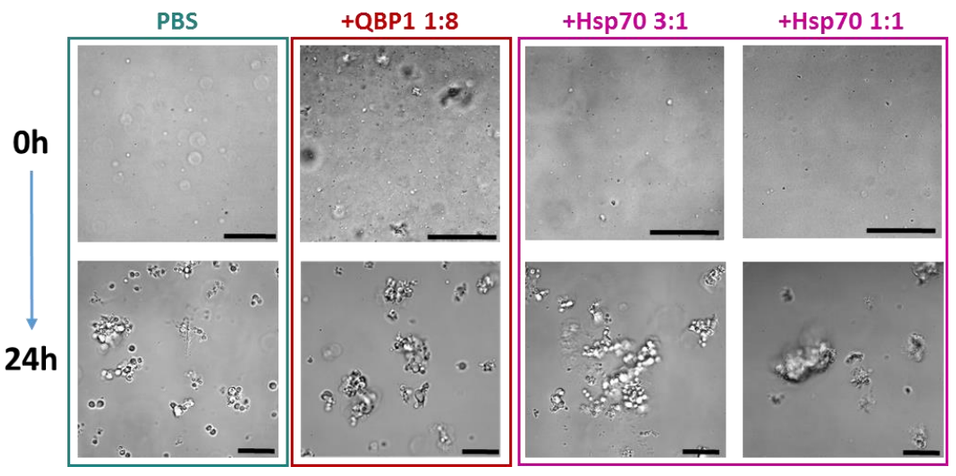
CPEB3 functional switch



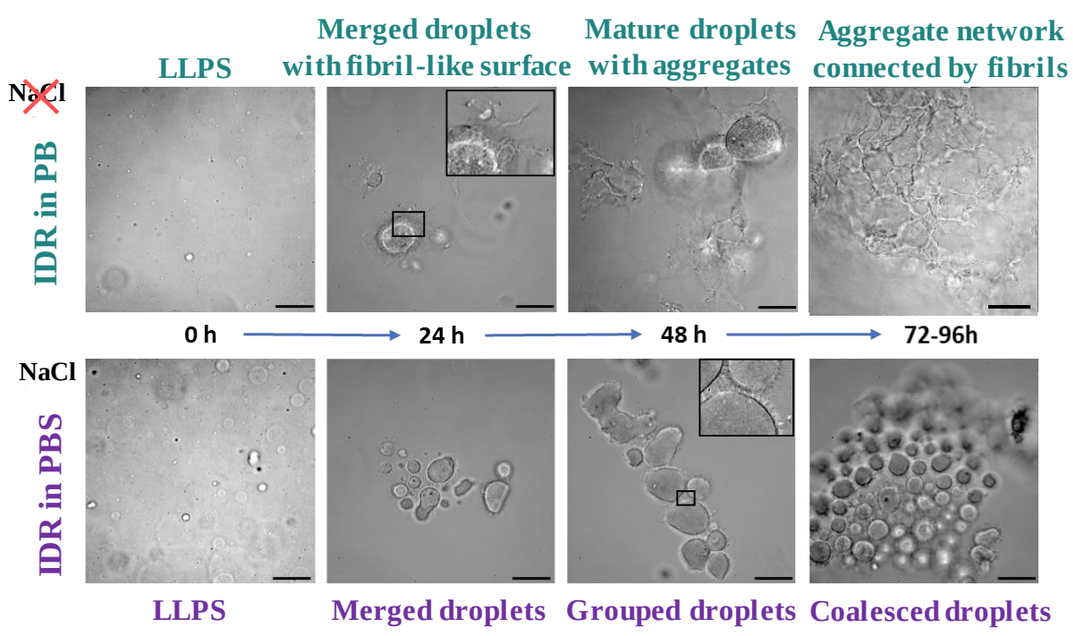
1. Human CPEB3 (hCPEB3) fragments recombinantly produced are inhibited by QBP1 in vitro



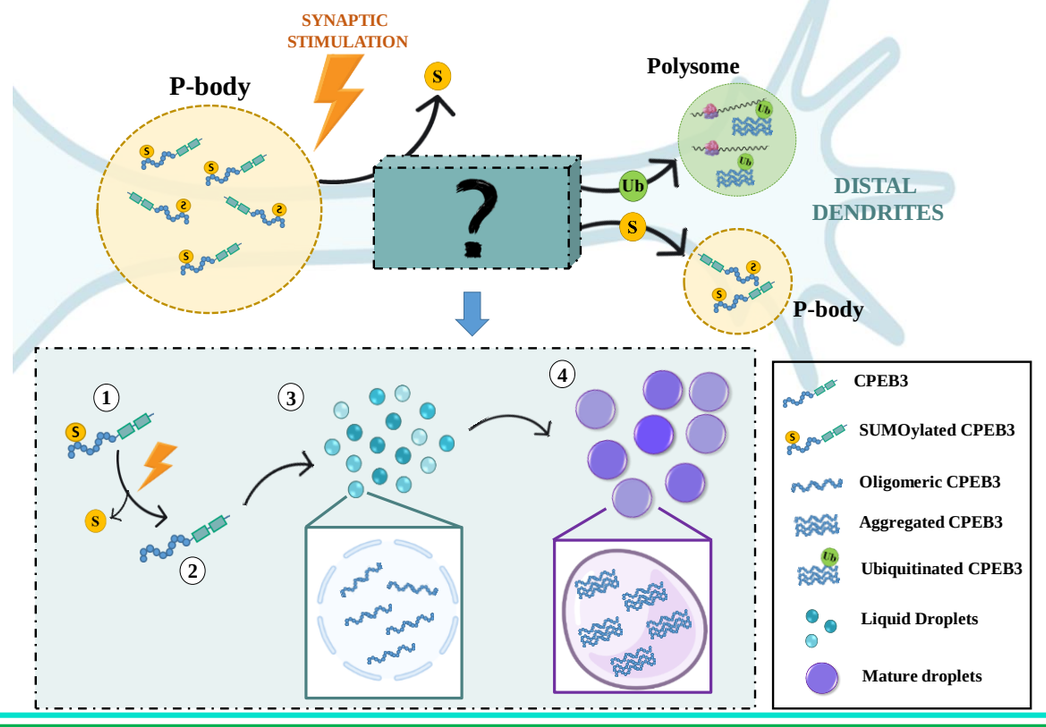
3. QBP1 and Hsp70 does not alter the functional formation of liquid droplets



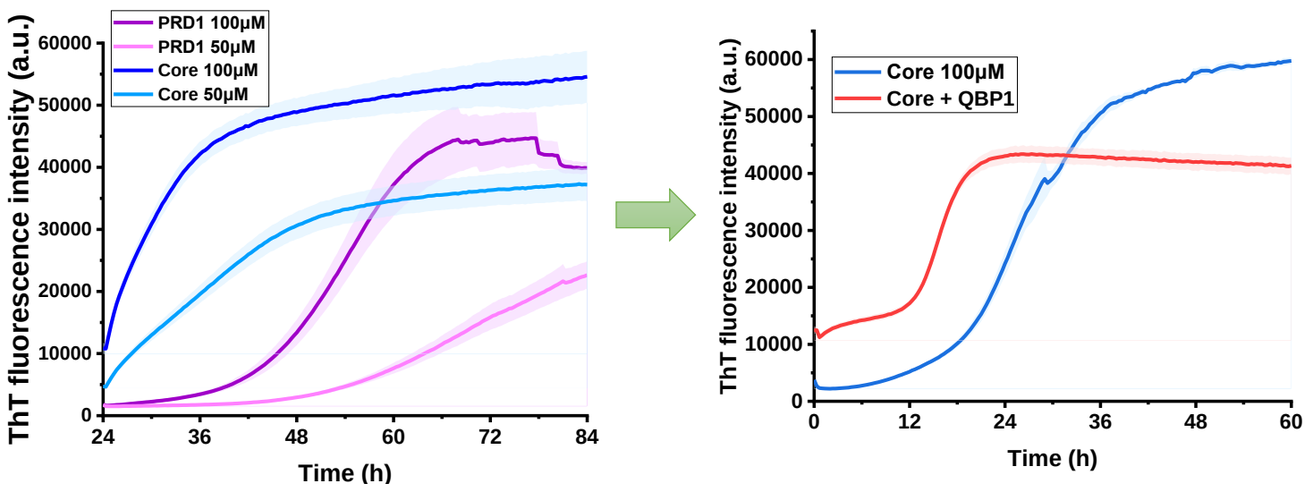
2. hCPEB3 modulates its amyloid assembly by confining it within liquid droplets



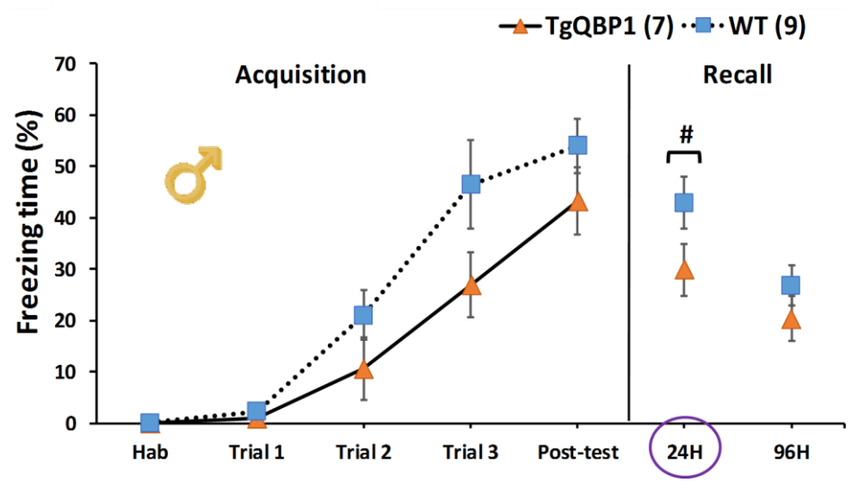
4. Proposed modulation of phase separation over amyloid assembly on hCPEB3



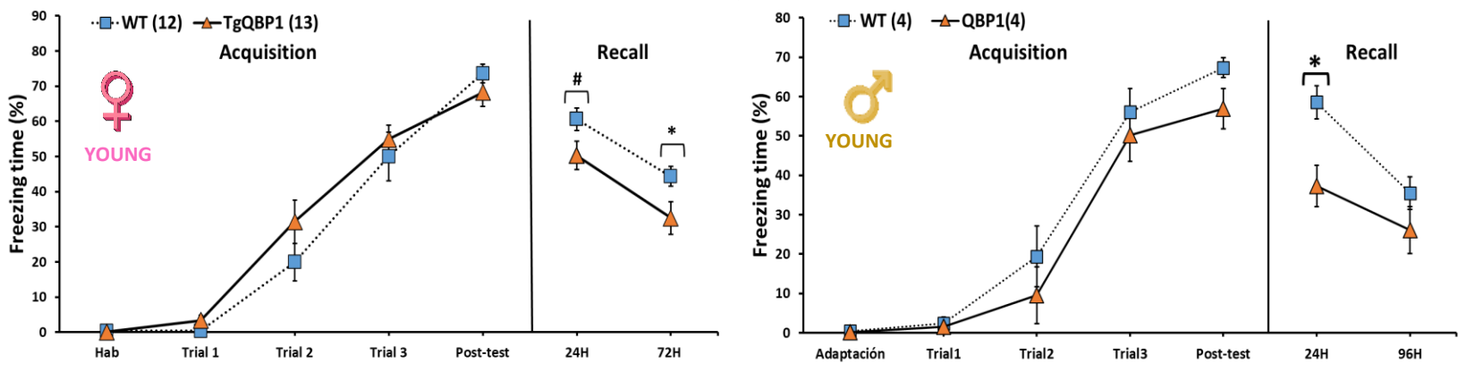
1. Murine CPEB3 amyloid assembly is also inhibited by QBP1 in vitro



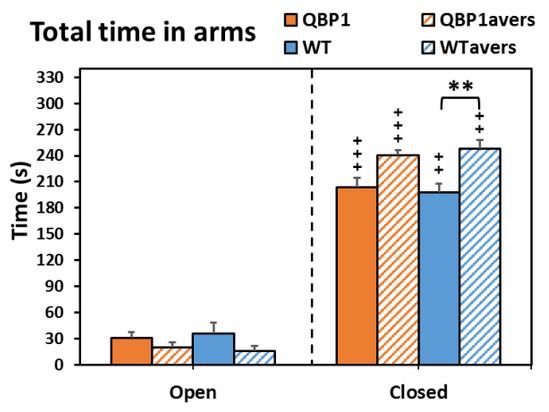
2. QBP1 significantly reduces long-term consolidation of aversive memories



3. QBP1 memory impairment is more pronounced in younger mice



4. QBP1 significantly reduces fear-induced anxiety levels in mice



4. Decreased CPEB3 oligomerization and altered posttranslational modifications after learning

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QBP1 peptide is a lead compound for PTSD therapy: harmless, focused on the cause of the disease and with an specific effect only in long-term memory consolidation