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Commentary

Is CREB the Angry Bird that Releases Memory in Alzheimer's?

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In a now popular video game, pugnacious birds are catapulted at jumbled debris, with the goal of liberating their entrapped comrades. Analogously, potentiation of the cognition-mediating transcriptional factor, cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB), or its downstream effectors, may release memory or cognitive function fettered by Alzheimer's disease pathology.

AD accounts for 50–60% of all cases of dementia, and currently affects 25 million people worldwide. The initial symptoms are cognitive deficits in several domains, including memory, language, and perceptual skills. Gross neuropathological changes such as the formation of extracellular amyloid plaques, composed of β-amyloid (Aβ) aggregates, and intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein are the molecular hallmarks of AD. Currently, there are no therapies to slow or otherwise halt the disruptions in neural communication that drive the progression of AD. Previous studies have linked Aβ to synaptic abnormalities and functional deficits associated with AD (Smith *et al*, 2009). Pathological aggregation of Aβ promotes synaptic dysfunction and disrupts activity-dependent gene transcription essential for learning and long-term memory formation. One such event in AD is the dysregulation of the transcription factor CREB. CREB signaling has a crucial role in orchestrating gene expression necessary for long-term synaptic plasticity and memory (Lopez de Armentia *et al*, 2007) and is highly conserved across species. Though the mechanisms underlying altered activity-dependent gene transcription in AD are largely unknown, selectively targeting CREB and its coactivators in AD patients presents a novel strategy for treating cognitive deficits. Inside this issue, Yiu *et al,* (2011) report the study of mice that express a human β APP_{695} transgene with familial AD mutations, resulting in Aβ pathology in the dorsal hippocampus characteristic of early-onset AD. These mice exhibited pronounced spatial memory impairment.

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The CA1 region of the dorsal hippocampus is among the first to exhibit AD pathology in humans. In particular, the CA1 region, in both human patients and mouse AD models, exhibits deficits in CREB activation, neuronal complexity, and neuronal network activity. The authors postulated that locally and acutely increasing CREB levels in the CA1 region through CREB vector microinjection should restore function in all three domains. Indeed, the rescue was successful, both in terms of facilitating long-term allocentric spatial memory, and reversing the deficits in dendritic arborization and neuronal network activity. This was presumably accomplished by restoring phosphorylated CREB to a level that allowed re-initiation of activity-dependent gene transcription. The results of this rescue closely mirror those of previous studies in which synaptic pathology was reversible by restoring CREB function, through agents such as rolipram (Smith *et al*, 2009). The findings are further validated by the observation that the rescue of spatial memory was anatomically specific to the CA1. The authors highlight the fact that improvements to spatial memory deficits occurred independent of Aβ plaque load. Thus, increasing CREB in the CA1 region does not improve spatial memory through a mechanism of Aβ clearance. This coincides with other studies that suggest the extent of synapse loss is a more robust correlate of cognitive impairment in AD patients than that of either β-amyloid or neurofibrillary tangle pathology (Coleman and Yao, 2003). Perhaps strategies that enhance the CREB signaling cascades can restore learning and memory through compensatory mechanisms that circumvent β-amyloid pathology (Figure 1).

Aβ remains a subject of intense research not only as a potential marker in early diagnosis, but also for its role in dysregulating excitatory activity-dependent receptors and upstream activators of CREB. Amyloid deposition also attenuates CREB activity through its coactivators, CREB-binding protein (Francis *et al*, 2006), and CRTC1 (España *et al*, 2010). Notably, the downregulation of CRTC1-mediated CREB transcription by Aβ disrupts neuronal expression of genes related to synaptic plasticity such as c-fos, Bdnf IV, and Nr4a2 (España *et al*, 2010). Although the selective targeting of CREB may transiently enhance allocentric spatial memory by increasing synaptic plasticity, it remains to be seen whether chronic CREB therapy in later

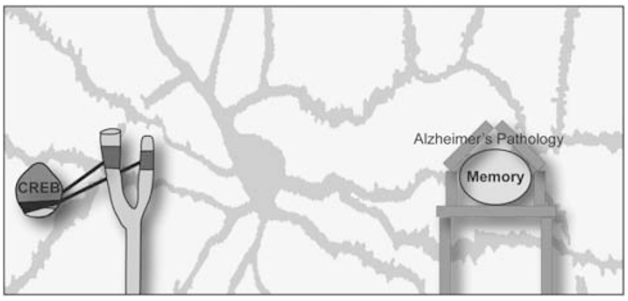

Figure 1 Cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) restores cognition in Alzheimer's disease (AD) model mice.

stages will be beneficial if Aβ deposition remains unchecked. The potential of CREB-mediated pathways, known and unknown, to serve as novel pharmaceutical targets for AD is compelling. However, attaining the same degree of targeting specificity in AD patients through intrahippocampal injections may prove impractical as a long-term and widespread treatment. The authors note that translating these findings will require a greater understanding of CREB-mediated changes in neuronal morphology, as well as any deleterious effects from chronic upregulation of CREB expression. In fact, previous studies have shown that sustained overexpression of CREB in the CA1 region in mice leads to a significant loss of hippocampal neurons and sporadic epileptic seizures (Lopez de Armentia *et al*, 2007).

Throughout the exploration of novel therapeutic strategies, it is important to acknowledge the limitations of familial, early-onset mouse models of AD. Sporadic AD represents the vast majority (90–95%) of cases. Although current AD mouse models approximate the amalgamation of neuropathological insults with great fidelity, perhaps this approach does not encompass the entire scope of age-related cognitive decline. For example, a recent study demonstrated that histone acetylation in adult mice relative to their juvenile counterparts is reduced, thus resulting in deficient learning-induced gene expression (Peleg *et al*, 2010). Furthermore, targeting epigenetic mechanisms may allow recovery of lost long-term memories via synaptogenesis and neural network rewiring (Fischer *et al*, 2007). Further measures linking AD mouse models to human cohorts are necessary to provide mechanistic connections between aging and neurodegenerative disorders. Ultimately, a deeper knowledge of the role of CREB, and how its downstream targets mediate synaptic remodeling, will spur the development of novel therapeutic approaches in the prevention and amelioration of cognitive decline in Alzheimer's patients.

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DISCLOSURE

The authors declare no conflict of interest.

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