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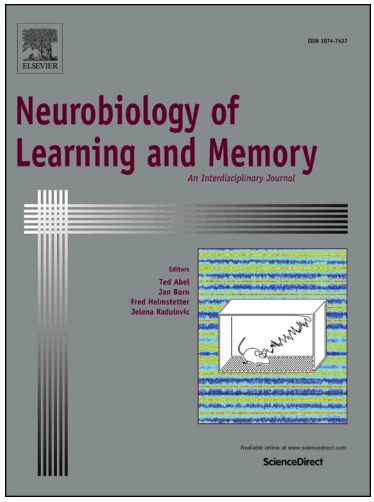

The aging memory: Modulating epigenetic modifications to improve cognitive function

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The aging memory: modulating epigenetic modifications to improve cognitive function

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Abstract

Age-related cognitive decline is a major concern in society. Here, I discuss recent evidence that shows an age-related modulation of gene transcription by epigenetic modifications. Epigenetic modifications, such as histone acetylation, is imbalanced in aging, with an increase in histone deacetylation, that limits the expression of plasticity-related genes. By modifying the balance towards histone acetylation, histone deacetylase inhibitors present a new pharmacological approach to ameliorate age-related cognitive deficits.

With the increase in human life expectancy, age-related neurodegenerative diseases have become one of the major concerns in medical research. During the last 20 years, significant efforts have been made towards a better characterization of several dementia disorders. Alzheimer's disease (AD), one of the most common among elderly patients, has a prevalence from 1-2%, at the age of 65, to 35% or higher after 85 years (Cuadrado-Tejedor et al., 2013; Tayeb et al., 2012). The heavy burden on patients, their family, and society, prompts new target research for possible AD therapeutics that can address the pathophysiology as well as the associated cognitive decline. Since AD is characterized, from the histopathological point of view, by the presence of extracellular plaques of aggregated amyloid-beta (Aβ) peptide and intracellular neurofibrillary tangles of hyper-phosphorylated tau protein, research has focused on understanding means of preventing and removing plaque formation, if formed. Although a very promising avenue, it has failed to deliver consistent results (Tayeb et al., 2012). Soluble amyloid-beta, as well as amyloid aggregates, leads to disturbances in neuronal calcium homoeostasis, resulting in synaptic function deficits and neurotoxicity (Ondrejcak et al., 2010). By focusing on the impact that amyloid-beta accumulation has on neuronal function rather than on its removal, alternative non-amyloid strategies have emerged. Here, I will discuss a recent and promising line of research focusing on the epigenetic modifications of gene transcription associated with aging and AD that may represent a new therapeutic approach to revert cognitive decline associated with aging and AD.

Studies on memory acquisition show that long-term memory undergoes a process of consolidation, dependent on the synthesis of new proteins and gene transcription. Similarly, induction of long-lasting forms of plasticity, such as LTP (long-term potentiation), triggers the transcription of several genes involved in LTP maintenance (McKenzie and Eichenbaum, 2011). One of the most studied pathways that link synaptic plasticity with gene expression depends on the activation of cAMP-response element-binding protein (CREB). The activation of CREB leads to the expression of several genes, generally denominated by immediate-early genes (IEGs), which include *Homer*, *Arc*, *c-fos*, *Zif268* among others (Alberini and Kandel, 2015). In addition to this signaling pathway, other transcription factors, such as the nuclear factor-kappa B (NF-κB), are activated by LTP induction. Interestingly, NF-κB is localized at the synapses, which suggests that it may have a dual role in long-term plasticity, initially as a local signaling molecule