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Commentary

Forgot your HAT? CBP Might be to Blame

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The complexity of long-term memory (LTM) formation is astounding. A simplified version could be described as requiring ordered communication between different brain regions to process multiple modes of external input, activation at discrete synapses on specific cell types, and a tightly regulated program of gene transcription and protein translation, followed by trafficking of certain plasticity-related proteins back to the synaptic site of activation. In light of these many, ordered steps, the relatively rare occurrence of memory failure is a testament to how carefully the brain regulates cognition. Fascination with what might orchestrate the highly complex transcriptional program that supports memory, as well as the hope of identifying new therapeutic targets, has led a number of investigators to epigenetics.

The term epigenetics, first coined by Conrad Waddington in the 1940s, refers to changes that occur above ('epi-') the genome. Epigenetics has traditionally been studied in terms of development, differentiation, and disease states that involve unchecked transcription, such as cancer. The observed stability of epigenetic marks led to the traditional definition of epigenetics as the study of heritable changes in phenotype or gene expression that do not involve changes to the DNA sequence itself. However, recent epigenetic investigations in the adult brain have revealed that these mechanisms can modify neuronal gene transcription in very important ways that do not necessarily alter heritability.

Epigenetic mechanisms consist of a set of posttranslational modifications of DNA and nuclear proteins that produce lasting alterations in chromatin structure as a direct consequence, and lasting changes in gene expression patterns as an indirect consequence. DNA is tightly packed into a DNA–histone complex known as chromatin. In its native, compact state, chromatin serves as a physical barrier to transcription that can be relaxed by modifying the N-terminus of histones. Acetylation of lysine residues is one such modification, catalyzed by histone acetyltransferases (HATs). HATs, such as CREB-binding protein (CBP), serve to neutralize the positive charge of histones and disrupt the histone–DNA interaction. Histone acetylation facilitates binding of transcription factors, such as CREB, and RNA polymerase II to DNA, resulting in the increased initiation of transcription. Chromatin can be returned to its native state through removal of acetyl groups by histone deacetylases (HDACs).

An impressive body of data indicates that histone acetylation is critical to mammalian synaptic plasticity (eg, long-term potentiation (LTP)) and memory. Initial evidence came from the discovery that Rubinstein–Taybi syndrome (RTS), marked by mental retardation, can be attributed to point mutations in CBP (Petrij *et al*, 1995). Further, a *Cbp* mutant mouse model of RTS demonstrated LTM deficits (Oike *et al*, 1999). Additional evidence for histone acetylation's critical role in memory continued to accumulate, including further proof that memory is disrupted in several different *Cbp* mutants. Interestingly, both CBP and another HAT, p300, interact with transcription factors that participate in LTM (eg, CREB). Subsequent studies have revealed similar memory disruptions following loss of p300 (Oliveira *et al*, 2011). This collective evidence on HATs highlights the importance of better understanding their individual roles in memory.

Although multiple lines of *Cbp* mutant mice have been generated and confirmed to have LTM deficits, technical limitations have prevented CBP from being studied within a setting of regional specificity. Furthermore, issues of embryonic lethality have prevented the effects of complete CBP loss from being tested in a memory model. Given the high degree of homology between the various HATs and similar ability to acetylate specific lysine residues, there is an outstanding question of just how well we understand CBP's contribution to memory. Can the memory and plasticity effects reported to date be attributed to compensatory mechanisms? To directly test this question, Barrett *et al* took the elegant approach of viral-mediated knockdown of CBP specifically within the CA1 subregion of the hippocampus in adult mice. Injecting AAV-Cre into the hippocampus of $Cbp^{flox/flox}$ mice 2 weeks before behavioral testing removed the complications of developmental compensation due to prenatal or early life loss of this critical HAT. Further, it allowed only a very limited window for potential p300 compensation to occur. Importantly,

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Barrett *et al* demonstrate that there were no changes in hippocampal p300 or CREB phosphorylation levels following AAV-Cre knockdown of CBP. The specific loss of CBP did, however, result in diminished acetylation at lysine residues known to be targeted by CBP, a failure of LTP to stabilize, and a reduction in LTM for two hippocampus-dependent tasks, contextual fear conditioning and object location (Barrett *et al*, 2011).

This same group has previously reported that HDAC inhibition, which indirectly elevates acetylation levels, is uniquely capable of supporting a LTM after subthreshold training in the object location task (Stefanko *et al*, 2009). In the current study, HDAC inhibition failed to accomplish this LTM support in the absence of hippocampal CBP. The result of this clever experiment indicates that p300 is unable to compensate for the loss of its sister HAT—a clear demonstration of CBP's requirement for LTM in the adult hippocampus. No longer can CBP be lumped into a p300/CBP reference in the adult hippocampus, as Barrett *et al* have clearly identified CBP as an independently operating HAT with therapeutic potential for the treatment of memory disorders.

DISCLOSURE

The author declares that, except for income received from my primary employer, no financial support or compensation has been received by any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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