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LEARNING AND MEMORY

HDAC2 is the one

Inhibitors of histone deacetylase (HDAC) enzymes have been shown to improve learning and memory; however, multiple forms of HDAC exist, and the development of more effective HDAC inhibitors would benefit from knowing the specific HDAC(s) that are involved in the regulation of synaptic plasticity. Tsai and colleagues now show that in neurons HDAC2 is responsible.

The authors generated mice that overexpressed either HDAC1 or HDAC2 specifically in neurons. In Pavlovian fear conditioning tests mice that overexpressed HDAC2 showed impaired associative learning compared with wild-type (WT) mice, whereas HDAC1-overexpressing mice did not differ from WT mice. HDAC2-overexpressing mice also performed worse than WT and HDAC1-overexpressing mice in tests of spatial learning and spatial working memory. Conversely, HDAC2-deficient mice showed the opposite behavioural phenotype.

As synaptic plasticity is assumed to underlie learning and memory, the authors next investigated whether HDAC2 regulates this process. They found that HDAC2-overexpressing, but not HDAC1-overexpressing, mice had lower dendritic spine density and fewer synapses in the hippocampus than WT mice. HDAC2-deficient mice showed the opposite pattern. Moreover, levels of synaptophysin, a marker for presynaptic terminals, in the CA1 and the amygdala were lower than normal in HDAC2 overexpressors and higher than normal in HDAC2-deficient mice. In addition, high frequency stimulation-induced long-term potentiation in CA1 neurons was impaired in HDAC2 overexpressors and increased in HDAC2-deficient mice. This suggests that HDAC2 negatively regulates synapse formation and synaptic plasticity.

Chromatin immunoprecipitation assays showed that HDAC2 associated (to a greater extent than HDAC1) with the promoters of genes involved in synaptic plasticity, including the gene that encodes brain-derived neurotrophic factor. In the brains of HDAC2-overexpressing mice, the levels of the protein products of these genes were decreased, whereas they were increased in the brains of HDAC2-deficient mice. In addition, in nuclear extracts HDAC2 but not HDAC1 immunoprecipitated with the corepressor COREST (also known as RCOR2), whereas both HDAC1 and HDAC2 co-immunoprecipitated with SIN3A and MTA2. COREST suppresses neuronal gene expression, which may explain why HDAC2 preferentially associates with the promoters of genes involved in synaptic plasticity.

Having shown that HDAC2 negatively regulates synaptic plasticity, spine formation, gene expression and learning and memory, the authors tested whether HDAC2 is a main target of HDAC inhibitors, which can improve memory. They injected the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) into HDAC2-overexpressing and -deficient mice. The treatment normalized contextual fear conditioning and dendritic spine and synapse numbers in HDAC2-overexpressing mice, but had no effect in HDAC2-deficient mice.

These findings show that HDAC2, but not HDAC1, modulates synaptic plasticity and suggest that it is a major target for the HDAC inhibitor SAHA. The study opens the door to the development of HDAC2-specific inhibitors that might improve memory in patients with neurodegenerative disorders.

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ORIGINAL RESEARCH PAPER Guan, J.-S. *et al.* HDAC2 negatively regulates memory formation and synaptic plasticity. *Nature* **459**, 55–60 (2009)