

Epigenetic mechanisms control neuronal plasticity and memory in the aging brain

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Epigenetics and Memory

Long-term memory formation is a process that requires the expression of specific genes. Activating these genes enables neurons to enhance their communication (synaptic plasticity), which is thought to underlie aspects of long-term memory formation. In the aging brain, studies have demonstrated that gene expression is impaired, correlating with deficits in memory formation. In the Wood lab, we are testing the hypothesis that epigenetic mechanisms are dysregulated in the aging brain, leading to abnormal suppression of gene expression, and impaired synaptic plasticity and memory formation. We are testing this hypothesis using genetically modified mice in which we can remove a gene expression inhibitor called histone deacetylase 3 (HDAC3). We predict that removal of HDAC3 will increase gene expression in the aging brain and restore synaptic plasticity and long-term memory formation.

1 Removing HDAC3 in a mouse

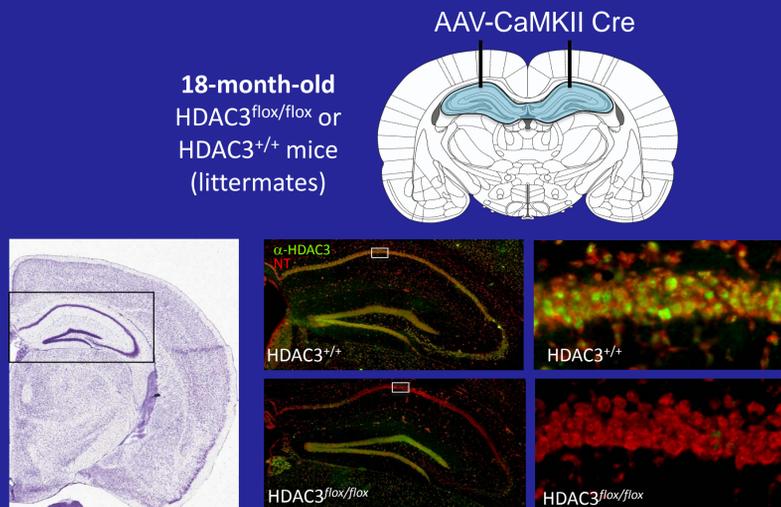


Figure 1 summarizes the approach used to remove HDAC3 from the hippocampus of genetically modified mice. The images show the expression of HDAC3 in the hippocampus in normal mice ($HDAC3^{+/+}$) and the absence of HDAC3 in mutant mice ($HDAC3^{flox/flox}$) after treatment with the virus expressing Cre recombinase only in neurons (AAV-CaMKII-Cre) and thus restricting the elimination of HDAC3 to neurons only. We remove HDAC3 from the hippocampus because this brain region is critical for key forms of synaptic plasticity and memory formation.

2

Rescue of age-related memory impairment by removal of HDAC3

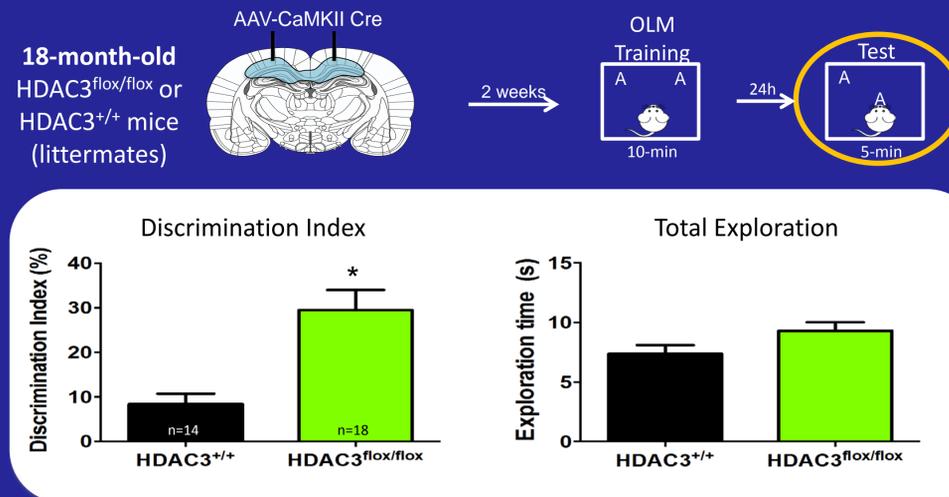


Figure 2 shows data from a long-term memory experiment using aging normal mice ($HDAC3^{+/+}$) and aging mutant mice ($HDAC3^{flox/flox}$) in which HDAC3 has been removed from the hippocampus. The bottom left panel shows that aging normal mice ($HDAC3^{+/+}$; black bar) fail to show significant long-term memory for object location – a key form of memory that is hippocampus-dependent. In contrast, aging mutant mice ($HDAC3^{flox/flox}$) form excellent long-term memory. These results demonstrate that removing HDAC3 in the aging hippocampus rescues age-dependent deficits in long-term memory.

Conclusions

The results shown here provide support for the hypothesis that epigenetic mechanisms abnormally suppress gene expression that is required for normal long-lasting forms of synaptic plasticity and long-term memory. HDAC3 is a key negative regulator of synaptic plasticity and memory in the young adult mouse brain. Removal of HDAC3 in the aging mouse brain rescues age-related synaptic plasticity impairments and long-term memory deficits. The Wood lab is currently working with two industry partners to develop small molecule inhibitors of HDAC3 for clinical therapeutics.

3

Rescue of age-related synaptic plasticity impairments by removal of HDAC3

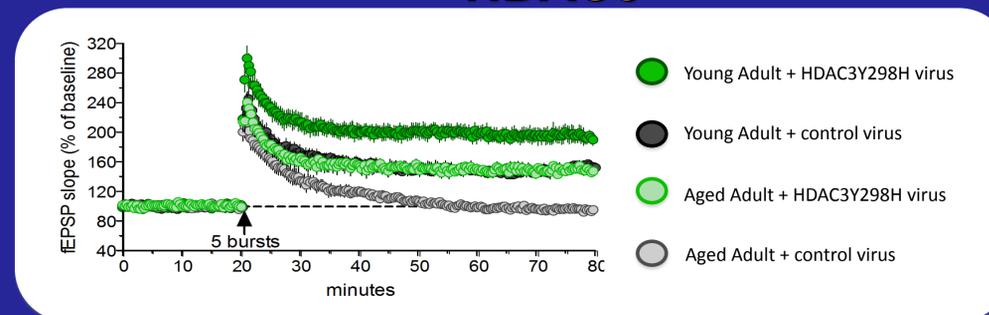


Figure 3 shows that age-related synaptic plasticity impairments can be rescued by removal of HDAC3. In this experiment, a virus is used to deliver a mutant form of HDAC3 (Y298H) that blocks its activity (meaning HDAC3 can no longer suppress gene expression as it normally does). Young Adult mice (dark green data points) have enhanced synaptic plasticity as a result of blocking HDAC3, as compared to Young Adult mice receiving a control virus (dark grey data points). Notice that Aged Adult mice exhibit significantly impaired synaptic plasticity normally (light grey data points). In contrast, Aged Adult mice with the virus that blocks HDAC3 (light green data points) show synaptic plasticity at similar levels as a Young Adult. These results demonstrate that removing HDAC3 activity can significantly improve synaptic plasticity in the hippocampus of the aged brain.

The following current and former lab members contributed to this work: Janine Kwapis, PhD; Eniko Kramar, PhD; and Dina Matheos, PhD.

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