Altered Histone Acetylation Is Associated with Age-Dependent Memory Impairment in Mice

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BIONB 4110 Undergraduate Journal Club
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Fischer Lab at European Neuroscience Institute Göttingen

Lab Focus: Understanding the molecular mechanisms underlying learning and memory under normal and pathological conditions.

Lab Aim: Identify therapeutic strategies to restore neuroplasticity, learning behavior, and long term memory retrieval.

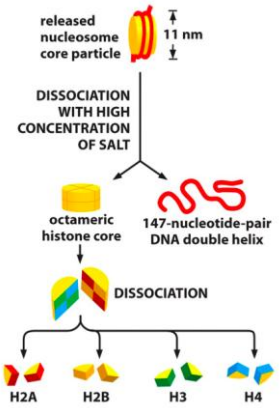
Other Key Authors:
- Sananbenesi- postdoc
- Peleg- PhD student (now graduated)
- Zovoilis- PhD student (now graduated)

André Fischer

Discussion Question

What, in general, is histone acetylation, and

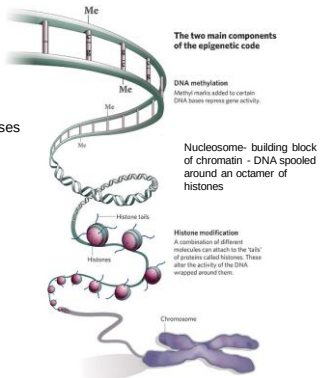
how does it influence the function of a cell?

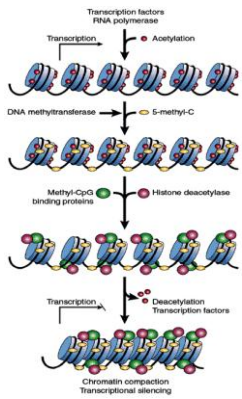


Histone modifications associated with transcription activation or repression

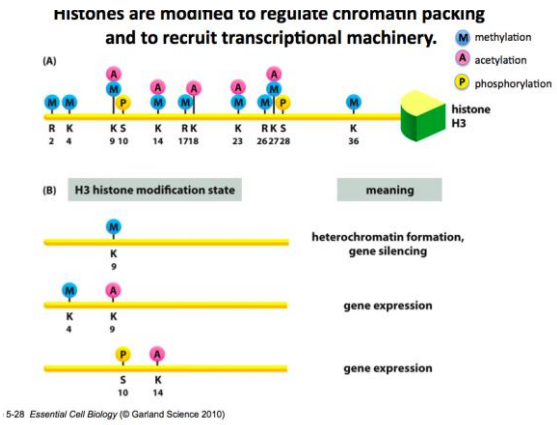
Histone variants;
post-translational modifications of amino acids on histone tails (acetylation, methylation);
covalent modification of DNA bases

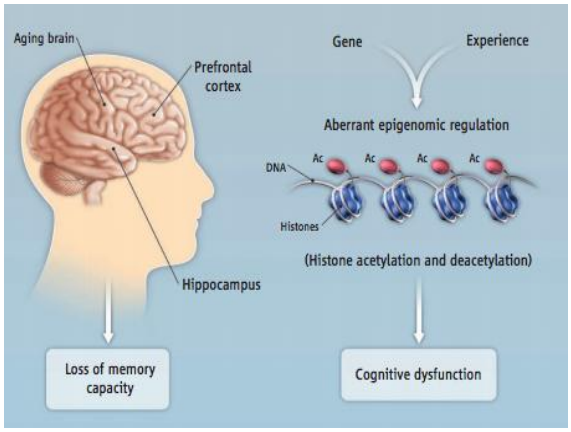
Acetyl Group



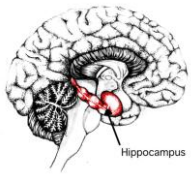


Transcriptionally active chromatin regions tend to be hyperacetylated and hypomethylated





Hippocampus



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METHODS AND RESULTS

Discussion Question

In this study, how was it demonstrated that there was memory impairment in one group of mice compared to another?

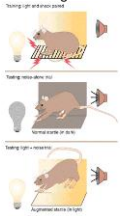
What was the test?

What was measured?

How were the groups compared statistically?

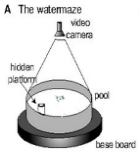
Testing cognitive decline in the aging mouse

Contextual Fear Conditioning

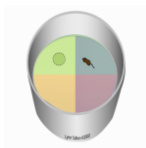


Morris Water Maze: Spatial Memory tests

Escape Latency Test

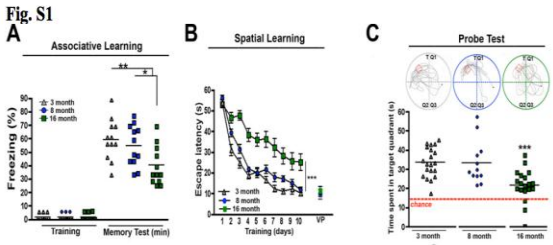


Probe Test



Water Maze Video

Figure S1



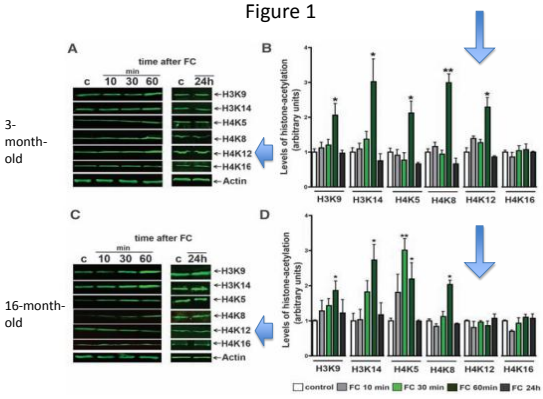
Discussion Question

Before fear conditioning, was there anything unusual about the hippocampal histone acetylation profile of 16-month-old mice compared to that of the 3-moth-old mice?

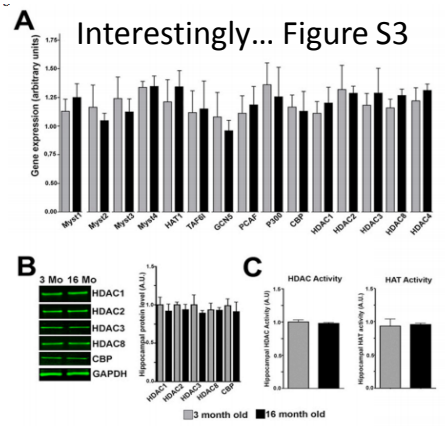
If so, what?

What about after conditioning?

Figure 1



Interestingly… Figure S3



Discussion Question

How did the differences between the transcriptome profiles of the 3-month-old fear conditioned mice and the 3-month-old control mice compare to the differences between the transcriptome profiles of the 16-month-old fear conditioned mice and the 16-month-old control mice?

Figure 2A

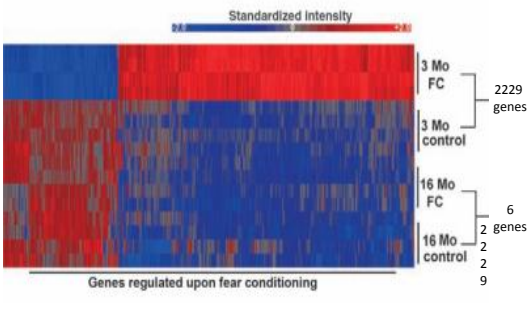
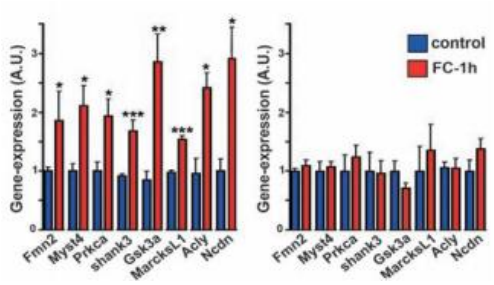


Figure 2B



H4K12 acetylation is associated with increased learning related gene expression!

Do these acetylated histones show on the genes?

ChIP

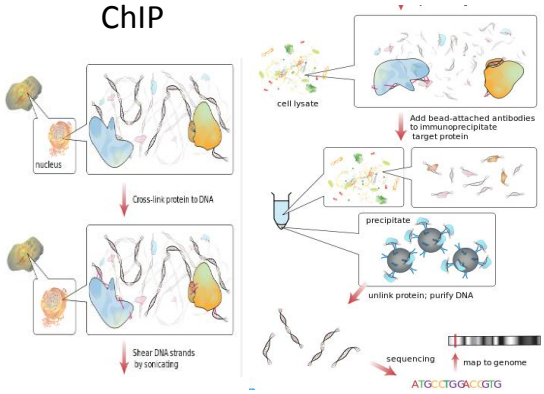


Figure 2C

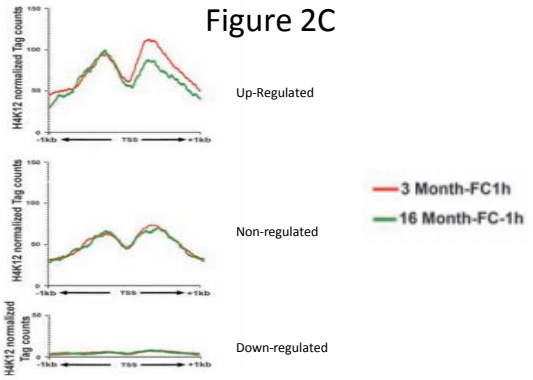
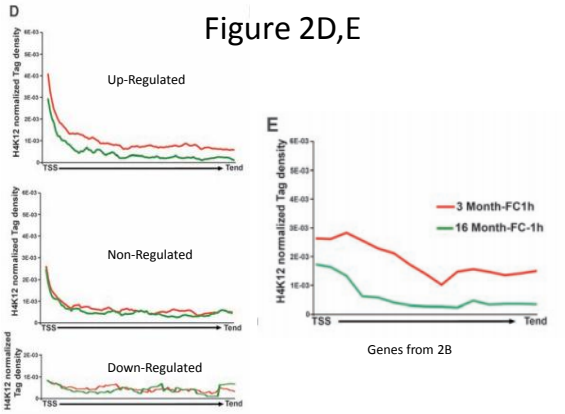


Figure 2D,E



Discussion Question

What hypothesis was tested by injecting 16-month-old mice with SAHA?

Figure 3A,B

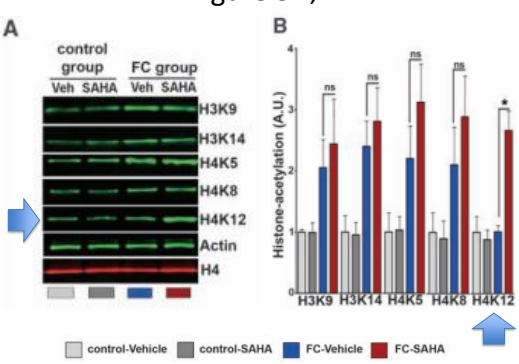


Figure 3C,D

TSS to Tend

Promoter Region

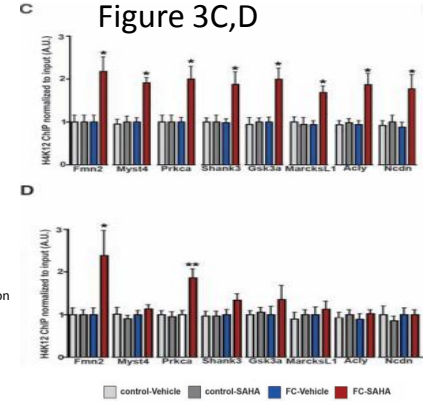


Figure 3E, S17C

SAHA Inhibition

MS-275 Inhibition

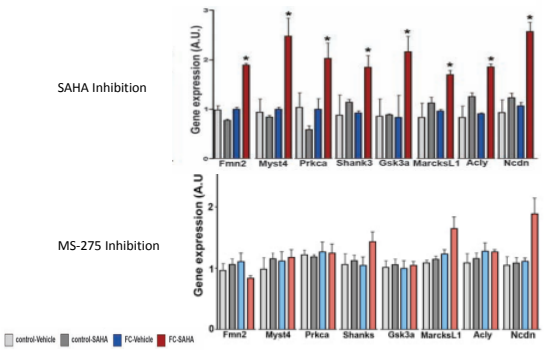
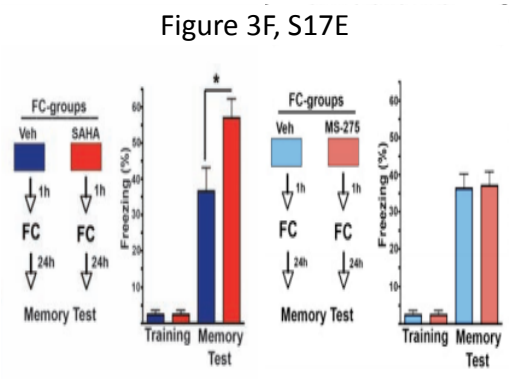


Figure 3F, S17E



SAHA MS-275

Conclusions

- Changes in histone acetylation on specific gene regions are associated with changes in gene expression.
- Loss of ability to regulate H4K12 acetylation is associated with a decline in associative memory.
- Blocking deacetylation of H4K12 restores associative memory in aging mice.