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Centre de Neurosciences Psychiatriques

CNP SEMINAR

ANNOUNCEMENT

Friday, October 31, 2014, 14:00

“Histone acetylation: Molecular memory aids on the chromatin”

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Over the past decade, histone acetylation, a core epigenetic modification, has consistently been shown to favor learning and memory across a variety of species and memory tasks. In our own research, we could show that a lack of histone acetylation is causally implicated in cognitive decline associated with neurodegeneration. This effect was mediated, at least in part, by elevated levels of histone deacetylase 2 (HDAC2), but could be counteracted by shRNA-mediated knockdown of HDAC2, which also reinstated synaptic and structural plasticity in the neurodegenerating brain. Thus, elevated levels of HDAC2 seemingly induce an epigenetic blockade of cognitive functions in the neurodegenerating brain, but which is potentially reversible.

Furthermore, we found that a lack of histone acetylation memory aids is one of the causes for the failure of long-term traumatic memories to be updated using cognitive behavioral therapy-like methods in rodents. For long-term fear memories, histone acetylation was reduced in the hippocampus, the site for fear memory formation. This effect was mediated, at least in part, by reduced S-nitrosylation of HDAC2, which resulted in HDAC2 being persistently chromatin-bound. Nevertheless, by the use of HDAC2-targeting HDAC inhibitors, histone acetylation could be reinstated, which primed neuroplasticity-related mechanism, such that even long-term traumatic memories could be permanently relearned.

Together, these results promote HDAC inhibitors as cognitive enhancers not only against cognitive decline associated with neurodegeneration, but also as adjuncts for behavioral therapies aimed at attenuating traumatic memories.

Selected Publications:

1. Gräff J and Tsai LH (2013). Histone acetylation: molecular mnemonics on the chromatin. *Nat. Rev. Neurosci.* 14: 97-111.
2. Gräff J et al. (2012). An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature* 483: 222-226.
3. Gräff J et al. (2014). Epigenetic priming of memory updating during reconsolidation to attenuate remote fear memories. *Cell* 156: 261-276.