MedicalXpress

How obesity makes memory go bad

January 29 2016, by Jeff Hansen

University of Alabama at Birmingham researchers are probing how obesity makes memory goes bad, and the underlying molecular mechanism that drives this decline.

They have found that epigenetic changes dysregulate memory-associated genes, and a particular enzyme in brain neurons of the hippocampus appears to be a link between chronic obesity and cognitive decline. Their work is published in the Jan. 27 issue of *Journal of Neuroscience*.

Obesity plagues developed nations, and among the numerous negative health outcomes associated with obesity is a memory impairment that is seen in middle-aged and older obese people. The cause of this decline? Experiments with obese rodents have given a clue: altered gene expression in the hippocampus area of the brain. Until now, the reasons gene expression was changed, as well as the mechanism by which obesity leads to pathogenic memory impairment, have not been known.

There was one suspect: epigenetic dysregulation in neurons of the hippocampus. Foundational experiments over the past decade have linked the creation of long-term memories to changes in DNA methylation and hydroxymethylation—changes caused by epigenetic mechanisms that sit above the level of the genes.

Such lasting molecular changes to DNA appear to play an important role in promoting or suppressing memory formation through their ability to increase or reduce the expression of genes that help brain neurons create new synaptic connections.

UAB researchers have now shown that epigenetic changes are indeed associated with changes in the expression of memory-associated genes within the hippocampus of obese mice, and these epigenetic changes correlate with diminished object location spatial memory in the obese mice. The UAB researchers have also implicated reduced amounts of one particular memory-associated gene product—SIRT1—as the principal pathogenic cause of obesity-induced memory impairment. The hippocampus subregion of the brain is important for consolidation of long-term memory.

Corresponding author J. David Sweatt, Ph.D., first author Frankie D. Heyward, Ph.D., and colleagues in the UAB Department of Neurobiology, Evelyn F. McKnight Brain Institute, write that these data "provide the first evidence that high-fat-diet-induced obesity leads to the time-dependent development of aberrant epigenetic modifications within the hippocampus, as well as corresponding reduction in the expression of various memory-related genes."

Sweatt noted, "We feel this is a very exciting finding that identifies a new linkage between diet, epigenetics and cognitive function, especially in light of the burgeoning obesity epidemic in the U.S. and elsewhere."

This work, they write, "offers a novel working model that may serve as a conceptual basis for the development of therapeutic interventions for obesity-induced memory impairment."

In details about the cause of altered gene expression, the UAB researchers found that:

Mice with diet-induced obesity at 20 weeks had impaired performance in object location memory tests, and their hippocampus had impaired synaptic plasticity, as measured by long-term potentiation.

Four memory-associated genes—Ppargc1a, Ppp1cb, Reln and Sirt1—showed significantly decreased gene expression at 23 weeks of diet-induced obesity, as has been seen before, and the latter three had significantly increased DNA methylation in their gene promoter regions. Increased methylation is known to decrease gene expression. Furthermore, the Sirt1 promoter region also had significantly decreased DNA hydroxymethylation. Gene expression increases or decreases as DNA hydroxymethylation increases or decreases.

Obesity-induced memory impairment develops over time. At just 13 weeks of diet-induced obesity, seven weeks earlier than the experiments above, mice did not have significant object location memory impairment, and at 16 weeks of diet-induced obesity, also seven weeks earlier than above, none of the genes showed significant increases in DNA methylation. Only one gene at 16 weeks—Ppargc1a—showed significant decreases in gene expression and DNA hydroxymethylation.

To probe the mechanism by which obesity leads to pathogenic memory impairment, the UAB researchers focused on the gene Sirt1, which makes an enzyme that is active in the neuron during energy expenditure and fat mobilization. This enzyme appears to be depleted and dysfunctional in obesity, and the deletion of the Sirt1 gene in the brain shortly after birth is known to impair memory and the ability to form new neural synapses. These roles for the SIRT1 gene product—in both high-fat-diet-induced molecular pathology and in memory impairment—suggest that it might be a link between chronic obesity and cognitive decline.

Heyward, Sweatt and colleagues found that the hippocampus of obese mice had significantly diminished protein expression of SIRT1, and a substrate of the enzyme, acetylated-p53, was significantly increased, suggesting reduced enzymatic activity. Also, a targeted deletion of Sirt1 in the forebrain region that includes the hippocampus at age 8-12 weeks

showed decreased Sirt1 mRNA and protein in the hippocampus, and these mice showed impaired object-location memory when tested two weeks later.

Furthermore, chemical activation of SIRT1 in diet-induced obese mice by feeding them resveratrol showed decreased levels of acetylated-p53, suggesting increased SIRT1 enzymatic activity, and the resveratrol-fed obese mice had a normal object-location memory, as compared with the control obese mice. The resveratrol-fed obese mice did not show an enhanced memory compared with normal mice. This suggests that resveratrol preserved their hippocampus-dependent spatial memory and SIRT1 function in the hippocampus.

About 10 years ago, Sweatt's lab made the seminal discovery that everyday experiences tap into epigenetic mechanisms in subregions of the brain, and the resulting epigenetic changes in DNA are critically important for long-term memory formation and the stable storage of long-term memory. The 2007 Neuron paper "Covalent modification of DNA regulates memory formation," by Courtney Miller, Ph.D., and Sweatt, was the first to show that active regulation of the chemical structure of DNA is involved in learning and experience-driven changes in the brain.

Obesity and cognitive decline

Evidence that suggests a link between the two includes:

- People aged 40-45 who were obese had a 74 percent increased risk of dementia 21 years later; and those who were overweight had a 35 percent greater risk. This study cohort had 10,276 men and women. Whitmer, RA, et al., BMJ 2005.
- A study of 2,223 healthy workers found that a higher body-mass index was associated with lower cognitive scores, after

adjustment for age, sex, educational level, blood pressure, diabetes and other co-variables. Also, a higher BMI at baseline was associated with higher cognitive decline at a follow-up five years later. Cournot, M., et al., Neurology 2006.

- Metabolic syndrome in 73 people with an average age of 60 was associated with significant reductions in recall and overall intellectual functioning, compared with age- and education-matched controls. Hassenstab, J.J., et al., Dementia and Geriatric Cognitive Disorders 2010.
- A study of 8,534 twin individuals who were 65 or older showed that being overweight or obese at mid-life, with an average age of 43, was related to later dementia at the older age. Xu, W.L., et al., Neurology 2011.

More information: Obesity Weighs down Memory through a Mechanism Involving the Neuroepigenetic Dysregulation of Sirt1. *Journal of Neuroscience*, 27 January 2016, 36(4): 1324-1335; DOI: 10.1523/JNEUROSCI.1934-15.2016

Provided by University of Alabama at Birmingham