Loss of memory in Alzheimer's mice models reversed through gene therapy

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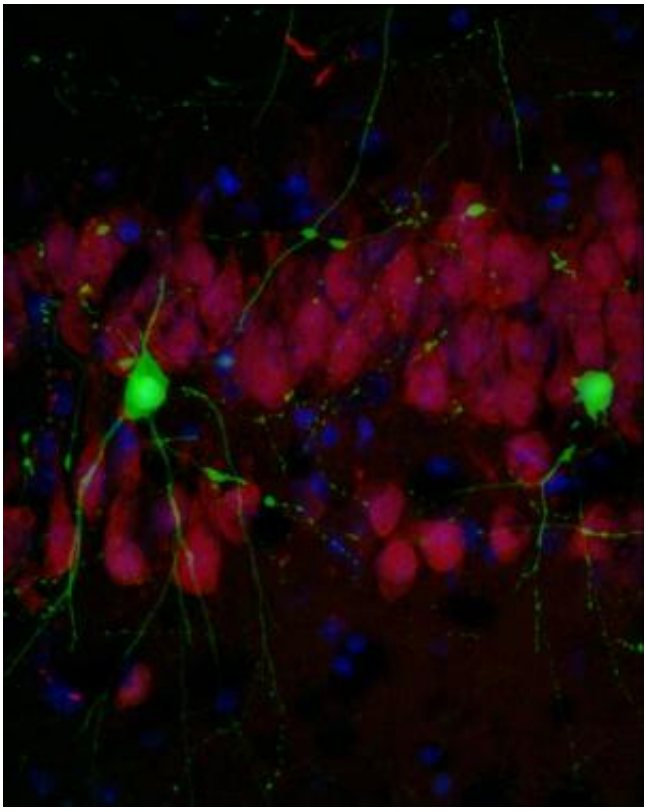

This image shows Crtc1 detection in mice neurons (in green). Credit: Universitat Autonoma de Barcelona

Alzheimer's disease is the leading cause of dementia and affects some 400,000 people in Spain alone. However, no effective cure has yet been found. One of the reasons for this is the lack of knowledge about the cellular mechanisms which cause alterations in nerve transmissions and

the loss of memory in the initial stages of the disease.

Researchers from the Institute of Neuroscience at the Universitat Autònoma de Barcelona have discovered the cellular mechanism involved in memory consolidation and were able to develop a gene therapy which reverses the loss of memory in mice models with initial stages of Alzheimer's disease. The therapy consists of injecting a gene called Crtc1 (CREB regulated transcription coactivator-1) into the hippocampus - a region of the brain essential to memory processing. The protein, restored through gene therapy, gives way to the signals needed to activate the genes involved in long-term memory consolidation.

To identify this protein, researchers compared gene expression in the hippocampus of healthy control mice with that of transgenic mice which had developed the disease. Through DNA microchips, they identified the genes ("transcriptome") and the proteins ("proteome") which expressed themselves in each of the mice in different phases of the disease. Researchers observed that the set of genes involved in memory consolidation coincided with the genes regulating Crtc1, a protein which also controls genes related to the metabolism of glucose and to cancer. The alteration of this group of genes could cause memory loss in the initial stages of Alzheimer's disease.

In persons with the disease, the formation of amyloid plaque aggregates, a process known to cause the onset of Alzheimer's disease, prevents the Crtc1 protein from functioning correctly. "When the Crtc1 protein is altered, the genes responsible for the synapsis or connections between neurons in the hippocampus cannot be activated and the individual cannot perform memory tasks correctly", explains Carlos Saura, researcher of the UAB Institute of Neuroscience and head of the research. According to Saura, "this study opens up new perspectives on therapeutic prevention and treatment of Alzheimer's disease, given that we have demonstrated that a gene therapy which activates the Crtc1

protein is effective in preventing the loss of memory in lab mice."

The research, published today as a featured article in *The Journal of Neuroscience*, the official journal of the US Society of Neuroscience, paves the way for a new therapeutic approach to the disease. One of the main challenges in finding a treatment for the disease in the future is the research and development of pharmacological therapies capable of activating the Crtc1 protein, with the aim of preventing, slowing down or reverting cognitive alterations in patients.

More information: Parra-Damas A., Valero J., Chen M., España J., Martin E., Ferrer I., Rodríguez-Alvarez J. and Saura C.A. "CRTC1 Activates a Transcriptional Program Deregulated at Early Alzheimer's Disease-Related Stages" (2014). *J. Neuroscience*. 34(17)

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