A molecular switch for memory and addiction

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Learning and memory formation are based on the creation of new connections between neurons in the brain. Also, behaviors such as nicotine addiction manifest themselves in long-term changes of neuronal connectivity and can – at least in this respect – be viewed as a form of learning. A team around Pierluigi Nicotera, scientific director of the German Center for Neurodegenerative Diseases (DZNE) and collaborating laboratories at the MRC, UK and University of Modena, Italy have now discovered a molecular switch that plays a crucial role in establishing addictive behavior and memory processes. These results may contribute to new strategies for preventing memory loss or treating addictive behavior. The study is published online in *EMBO Journal* on November 26th.

Neuronal signals are passed from one nerve cell to the next in form of chemical compounds called neurotransmitters. This signal transmission is a first step and prerequisite for any learning process in the brain. It induces a sequence of events in the downstream cell that eventually lead to changes in neuronal connectivity and thus to memory consolidation. Also nicotine or cocaine can trigger the rearrangement of brain connections in an equivalent manner.

A first step in the induction of neuronal plasticity – the formation of new connections in the brain – involves calcium. As a response to neurotransmitters, nicotine or cocaine, calcium increases at the site of neuronal connection, the synapse. In a second step, this calcium increase will induce gene expression – the synthesis of proteins that will lead to

new or reinforced synaptic connectivity. It has been generally accepted that the increase of calcium is only part of the first step in this process and does not depend on gene expression. Pierluigi Nicotera and his colleagues now challenge this idea. Their study shows that the expression of genes involved in calcium signaling is required to induce plasticity in nerve cells after repeated stimulation with nicotine or cocaine.

The scientists found that nicotine administration to mice induces the expression of a gene called type 2 ryanodine receptor (RyR2). RyR2 protein is involved in releasing calcium from a cell internal calcium store, the endoplasmic reticulum, thus leading to a long-lasting reinforcement of calcium signaling in a self-sustained manner. This sustained calcium-increase then leads to neuronal plasticity. Specifically, RyR2 is expressed in a number of brain areas associated with cognition and addiction as the cortex and ventral midbrain, suggesting that RyR2 induction plays a pivotal role in these processes. This idea was confirmed in an additional experiment, in which the authors of the study demonstrate that a reduction of RyR2-activation in living animals abolishes behavior associated with learning, memory and addiction. This shows that RyR2 is absolutely required to develop long-term changes in the brain that lead to addiction.

These results are a major step forwards in understanding the molecular processes underlying memory and addiction. On the long run, the scientists hope that these insights will contribute to the development of therapies for the treatment of addictive disorders or strategies to counteract memory loss in neurodegenerative diseases like Alzheimer's disease.

More information: Elena Ziviani, Giordano Lippi, Daniele Bano, Eliana Munarriz, Stefania Guiducci, Michele Zoli, Kenneth W Young and Pierluigi Nicotera. Ryanodine receptor-2 upregulation and nicotine-mediated plasticity. *EMBO Journal*, published online on 26th November

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