Study shows memory loss due to cannabis related to harm to mitochondria

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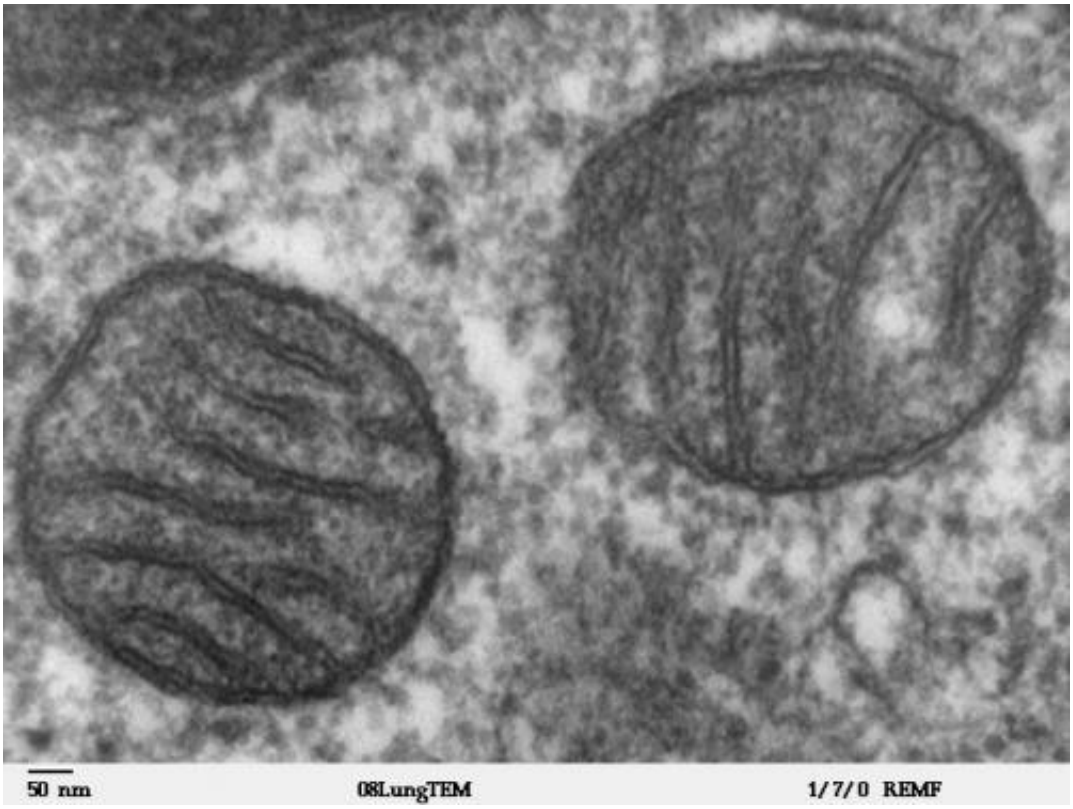

Mitochondria. Credit: Wikipedia commons

(Medical Xpress)—An international team of researchers has found what they believe is the source of memory loss in people who smoke marijuana—disruption to mitochondria. In their paper published in the journal *Nature*, the group describes their study of receptor activation due to exposure to active ingredients in cannabis and its impact on

mitochondria.

A mitochondrion is an organelle located inside of most cells—it is commonly referred to as the part of the cell responsible for energy regulation. In this new effort, the researchers looked into the impact of cannabis on mitochondria in brain cells to find out if it may play a role in immobility, catalepsy (onset of seizures or a trance-like state) or memory loss due to use of the controversial drug.

Prior research has shown that CB_1 receptors are located in the plasma membrane that surrounds typical brain cells. Other research has also shown that chronic use of cannabis can cause memory loss and other problems and that substances in it bind to CB_1 receptors on nerve terminals, which, in turn, can cause a disruption in the transmissions of messages between cells. The net result is memory loss, catatonic states or blackouts. In this new effort, the researchers found that chemicals in cannabis also caused activation of CB_1 receptors in mitochondria in brain cells located in the hippocampus, which is where most memory processing occurs. This, they claim, suggests memory loss due to use of cannabis can be sourced to the impact it has on the organelles.

The team came to this conclusion by removing the CB_1 receptors in mitochondria in mice brain cells and testing the mice to see if they continued to experience memory loss due to the introduction of the cannabis chemicals. The team reports they did not, which suggests that interactions between cannabis chemicals and mitochondria plays a major role in memory loss and likely other negative health effects associated with chronic use of marijuana. They suggest their findings indicate that chronic use of the drug could cause permanent damage to mitochondria, leading to long-term or permanent memory loss and other health problems.

The researchers also suggest their findings indicate that there may be a

way to modify medical cannabis used to treat diseases such as glaucoma so that it does not cause memory loss or other associated health problems , by removing its impact on mitochondria.

More information: Etienne Hebert-Chatelain et al. A cannabinoid link between mitochondria and memory, *Nature* (2016). DOI: 10.1038/nature20127

Abstract
Cellular activity in the brain depends on the high energetic support provided by mitochondria, the cell organelles which use energy sources to generate ATP. Acute cannabinoid intoxication induces amnesia in humans and animals, and the activation of type-1 cannabinoid receptors present at brain mitochondria membranes (mtCB1) can directly alter mitochondrial energetic activity. Although the pathological impact of chronic mitochondrial dysfunctions in the brain is well established, the involvement of acute modulation of mitochondrial activity in high brain functions, including learning and memory, is unknown. Here, we show that acute cannabinoid-induced memory impairment in mice requires activation of hippocampal mtCB1 receptors. Genetic exclusion of CB1 receptors from hippocampal mitochondria prevents cannabinoid-induced reduction of mitochondrial mobility, synaptic transmission and memory formation. mtCB1 receptors signal through intra-mitochondrial Gαi protein activation and consequent inhibition of soluble-adenylyl cyclase (sAC). The resulting inhibition of protein kinase A (PKA)-dependent phosphorylation of specific subunits of the mitochondrial electron transport system eventually leads to decreased cellular respiration. Hippocampal inhibition of sAC activity or manipulation of intra-mitochondrial PKA signalling or phosphorylation of the Complex I subunit NDUFS2 inhibit bioenergetic and amnesic effects of cannabinoids. Thus, the G protein-coupled mtCB1 receptors regulate memory processes via modulation of mitochondrial energy metabolism. By directly linking mitochondrial activity to memory formation, these

data reveal that bioenergetic processes are primary acute regulators of cognitive functions.

Press release