Medical Xpress

Low-dose THC reverses brain aging and enhances cognition in mice, research suggests

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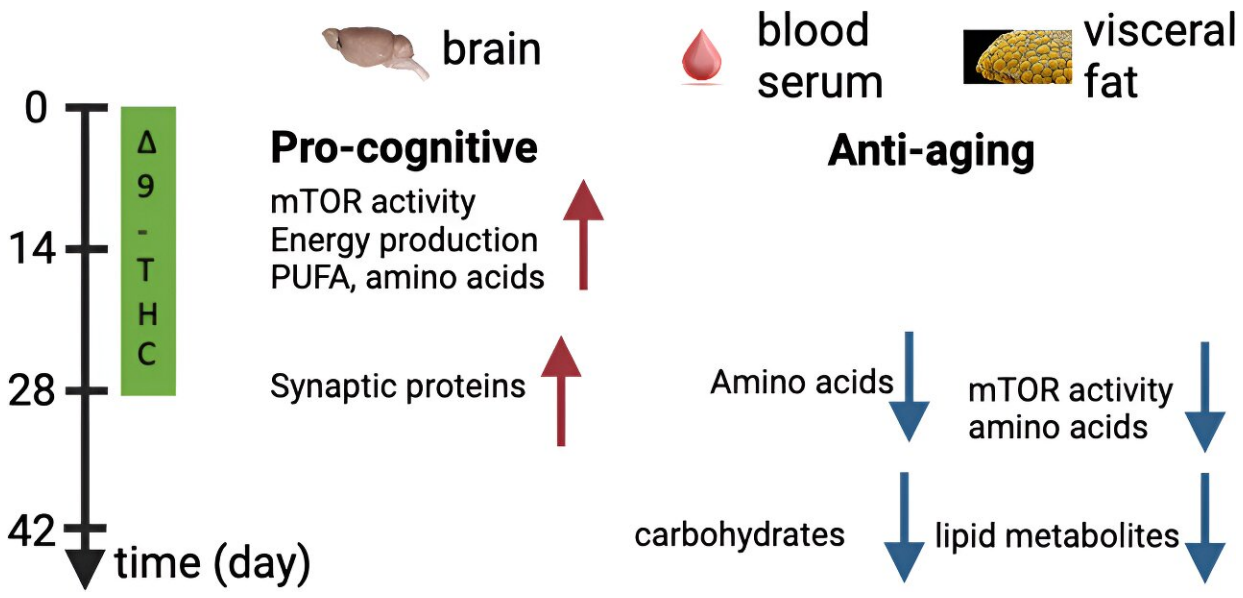

Abstract. Credit: *ACS Pharmacology & Translational Science* (2024). DOI: 10.1021/acsptsci.4c00002, https://pubs.acs.org/doi/10.1021/acsptsci.4c00002

Bonn researchers have clarified the influence of treatment with tetrahydrocannabinol on the metabolic switch mTOR: A low-dose long-term administration of cannabis can not only reverse aging processes in the brain, but also has an anti-aging effect.

Researchers from the University Hospital Bonn (UKB) and the University of Bonn together with a team from Hebrew University

(Israel) have now been able to show this in mice. They found the key to this in the protein switch mTOR, whose signal strength has an influence on cognitive performance and metabolic processes in the entire organism. The results are now presented in the journal *ACS Pharmacology & Translation Science*.

Information about the availability or scarcity of resources is of crucial importance for the regulation of metabolism. The so-called metabolome is a complex reaction network that summarizes all metabolic properties of a cell or tissue. In higher organisms, the protein mTOR [Mechanistic Target of Rapamycin] is the central hub for cell growth and metabolism.

As a sensitive intracellular energy sensor system, its activity has a major influence on aging by regulating cell metabolism. A reduction in mTOR activity through a low-calorie diet, intensive physical activity or pharmacological treatment therefore has a general anti-aging effect.

In addition to an altered metabolism, the aging of the brain is also accompanied by a reduced ability to change neuronal connections, known as synaptic plasticity. Reduced mTOR activity can therefore also have a negative effect on the aging brain by reducing the formation of new synapses on a nerve cell and thus also cognitive abilities.

"Therefore, anti-aging strategies based on the reduction of mTOR activity might not only be ineffective but even counterproductive against brain aging. In our current work, we have now found a strategy to solve this dilemma," says Prof. Dr. Andreas Zimmer, Director of the Institute of Molecular Psychiatry at the UKB and member of the Cluster of Excellence ImmunoSensation2 at the University of Bonn.

Cannabis reverses the aging process in the brain

In a previous study, the Bonn researchers, together with a team from the

Hebrew University of Jerusalem, were able to show that long-term, low-dose administration of tetrahydrocannabinol (THC), the active ingredient in cannabis, has an anti-aging effect on the brain by restoring cognitive abilities and synapse density in old mice. Whether changes in mTOR signaling and the metabolome are linked to the positive effects on the aging brain had remained an open question.

"We have now been able to show that treatment with THC has a tissue-dependent and dual effect on mTOR signaling and the metabolome," says Dr. Andras Bilkei-Gorzo from the Institute of Molecular Psychiatry at the UKB, who is also a researcher at the University of Bonn.

Thus, THC treatment in the brain led to a transient increase in mTOR activity and levels of intermediates involved in energy production and amino acids. The latter enabled an increased synthesis of synaptic proteins and thus the formation of new synapses.

Unexpectedly, on the other hand, the Bonn researchers found a similarly strong reduction in mTOR activity of mice in adipose tissue and in the content of amino acids and carbohydrate metabolites in blood plasma as after a low-calorie diet or after intensive physical activity.

"We concluded that long-term THC treatment initially has a cognition-enhancing effect by increasing energy and synaptic protein production in the brain, followed by an anti-aging effect by decreasing mTOR activity and metabolic processes in the periphery," says Bilkei-Gorzo.

"Our study suggests that a dual effect on mTOR activity and the metabolome could be the basis for an effective anti-aging and cognition-enhancing drug."

More information: Bilkei-Gorzo et al. Bidirectional Effect of Long-Term Δ^9-Tetrahydrocannabinol Treatment on mTOR Activity and

Metabolome, *ACS Pharmacology & Translational Science* (2024). DOI: 10.1021/acsptsci.4c00002. pubs.acs.org/doi/10.1021/acsptsci.4c00002