How the ketogenic diet improves healthspan and memory in aging mice

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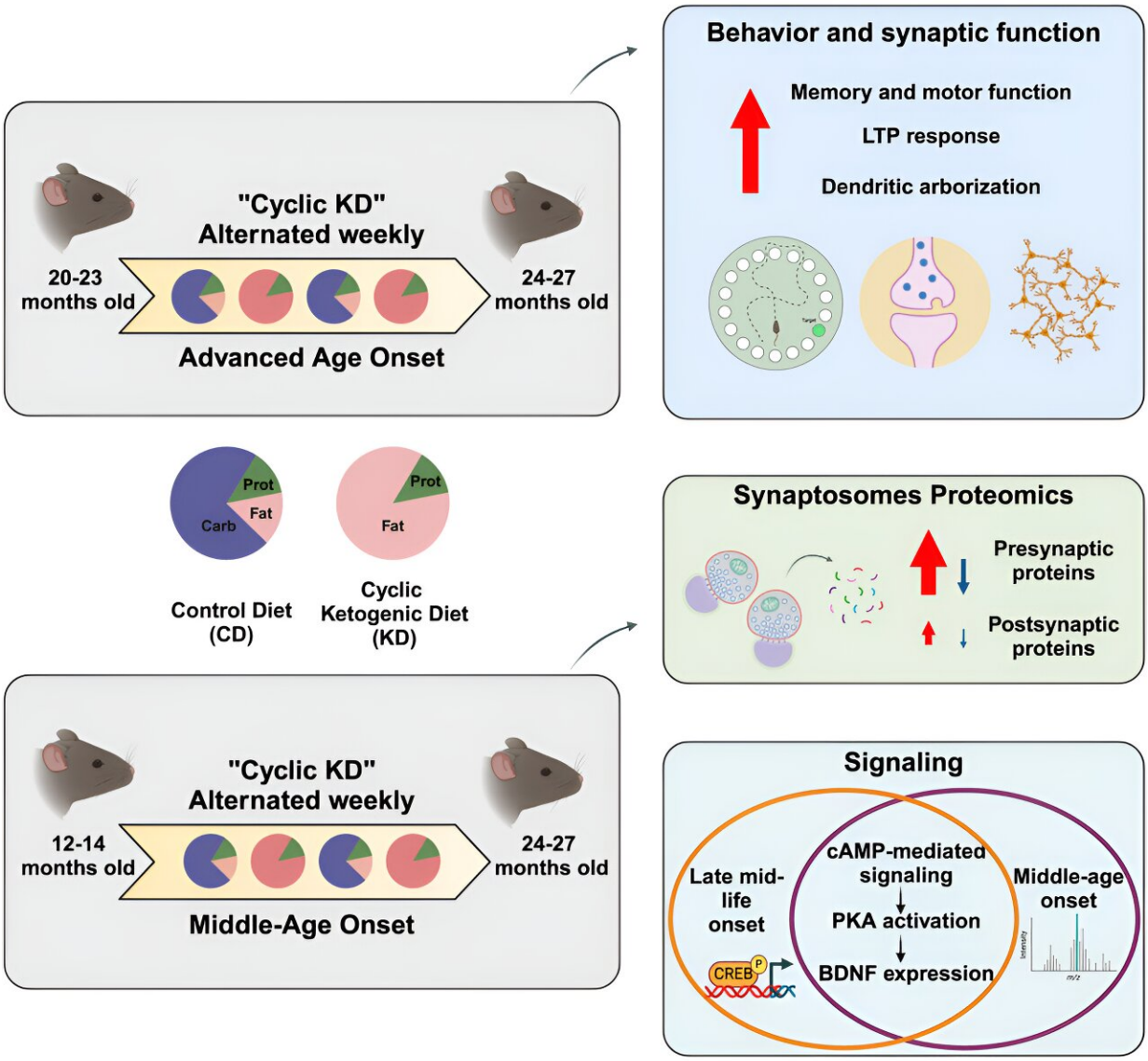

Graphical abstract. Credit: *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101593

The ketogenic diet has its fanatics and detractors among dieters, but either way, the diet has a scientifically documented impact on memory in mice. While uncovering how the high fat, low carbohydrate diet boosts memory in older mice, Buck scientists and a team from the University of Chile identified a new molecular signaling pathway that improves synapse function and helps explain the diet's benefit on brain health and aging.

Published in the June 5, 2024 issue of *Cell Reports Medicine*, the findings provide new directions for targeting the memory effects on a molecular level, without requiring a ketogenic diet or even the byproducts of it. The paper is titled "Ketogenic diet administration later in life improves memory by modifying the synaptic cortical proteome via the PKA signaling pathway in aging mice."

"Our work indicates that the effects of the ketogenic diet benefit brain function broadly, and we provide a mechanism of action that offers a strategy for the maintenance and improvement of this function during aging," said the study's senior author, Christian González-Billault, Ph.D., who is a professor at the Universidad de Chile and director of their Geroscience Center for Brain Health and Metabolism, and adjunct professor at the Buck Institute.

"Building off our previous work showing that a ketogenic diet improves healthspan and memory in aging mice, this new work indicates that we can start with older animals and still improve the health of the aging brain, and that the changes begin to happen relatively quickly," said John Newman, MD, Ph.D., whose laboratory at Buck collaborated with Dr.

González-Billault on the study.

Newman is both an assistant professor at the Buck Institute, and a geriatrician at University of California, San Francisco. "It is the most detailed study to date of the ketogenic diet and aging brain in mice."

More than a century ago, researchers observed that rats that consumed less food lived longer. "We now know that being able to manipulate lifespan is not about specifically eating less," said Newman, but actually is related to signals inside cells that turn on and off specific pathways in response to available nutrients. Many of those pathways are related to aging, such as controlling protein turnover and metabolism.

Some of those signals are the ketone bodies, which consist of acetoacetate (AcAc), β-hydroxybutyrate (BHB) and to a much lesser extent, acetone. These molecules are routinely produced in the liver. They ramp up when glucose is in short supply, whether due to caloric restriction, intense exercise or low carbohydrate intake, such as with a ketogenic diet.

Seven years ago, Newman led a team that published the first proof of the concept that if a ketogenic diet exposes mice to increased levels of ketone bodies over much of their adult life, it helps them to live longer and age in a more healthy way. "The most striking effect on their health as they aged was that their memory was preserved; it was possibly even better than when they were younger," he said.

The current study, designed to answer what part of the ketogenic diet was having the effect and how it was affecting the brain on a molecular level to improve memory, was led by González-Billault in a collaboration with scientists at the Buck. Mice on a ketogenic diet are fed a ratio of 90% calories from fat and 10% from protein, while mice on a control diet received the same amount of protein but only 13% fat.

The test mice, of "advanced age" of more than two years old, received one week of the ketogenic diet, cycled with one week of the control diet, to keep the mice from overeating and becoming obese.

The benefits of the ketogenic diet, said, González-Billault, were demonstrated through neurophysiological and behavioral experiments with the mice that test how well the mechanisms involved in memory generation, storage, and retrieval function in aged animals.

When these showed that the ketogenic diet appeared to benefit how well the synapses responsible for memory worked, they took a deep dive into the protein composition at these synapses in the hippocampus, in a collaboration with Buck professor Birgit Schilling, Ph.D., who directs the Proteomics and Mass Spectrometry Center.

"Surprisingly, we saw that the ketogenic diet caused dramatic changes in the proteins of the synapse," said Schilling. Even more surprising, she said, was that the changes started after a relatively brief exposure to the diet (tested after only one week on the diet) and only became more pronounced over time (tested again after six weeks and a year).

Further testing indicated that in synapses, a particular signaling pathway (protein kinase A, which is critical to synapse activity) was activated by the ketogenic diet. In isolated cells, the team then showed that it appears that BHB, the main ketone body produced in a ketogenic diet, is activating this pathway.

This leads to the idea, said González-Billault, that ketone bodies (specifically BHB) play a crucial role not only as an energy source, but also as a signaling molecule.

"BHB is almost certainly not the only molecule in play, but we think this is an important part of understanding how the ketogenic diet and ketone

bodies work," said Newman "This is the first study to really connect deep molecular mechanisms of ketone bodies all the way through to improving the aging brain."

Looking forward, he said, the next step would be to see if the same memory protection could be achieved by using BHB alone, or possibly going even more targeted than that by manipulating the protein kinase A signaling pathway directly.

"If we could recreate some of the big-picture effects on synapse function and memory just by manipulating that signaling pathway in the right cells," he said, "we wouldn't even need to eat a ketogenic diet in the end."

More information: Diego Acuña-Catalán et al, Ketogenic diet administration later in life improves memory by modifying the synaptic cortical proteome via the PKA signaling pathway in aging mice, *Cell Reports Medicine* (2024). DOI: 10.1016/j.xcrm.2024.101593

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