

Common nutrient supplementation may hold the answers to combatting Alzheimer's disease

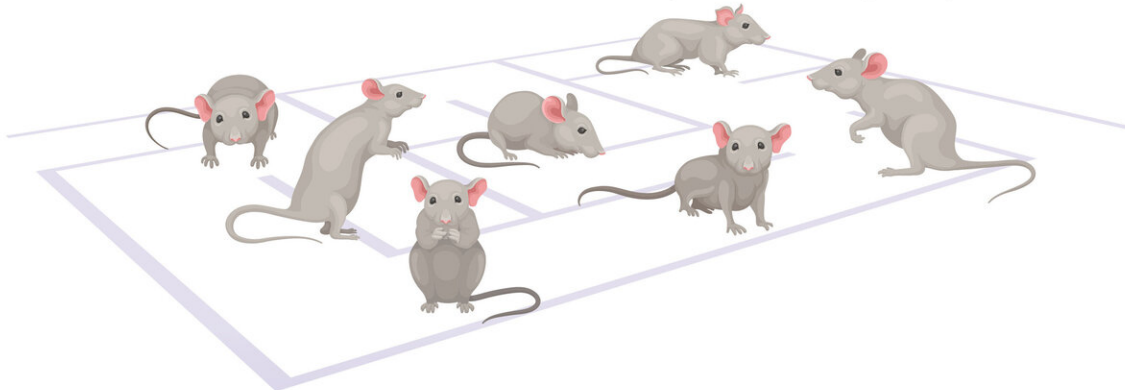
September 27 2019, by Richard Harth

Lifelong **Choline** diet improves Alzheimer's symptoms

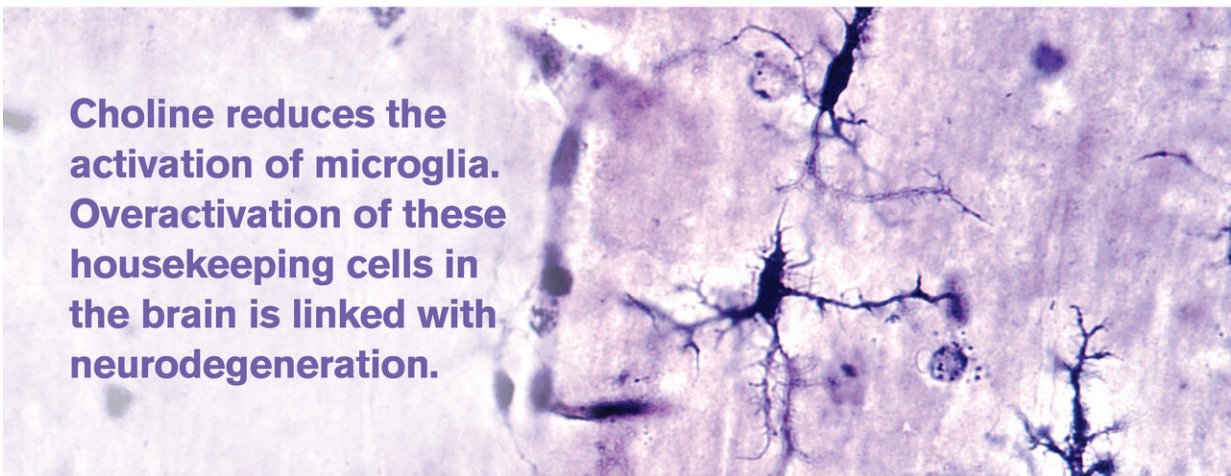
Female mice bred to display Alzheimer's-like symptoms develop progressive cognitive decline.



When mice received additional choline in their diet, they showed marked improvement in cognitive performance.



Choline reduces the activation of microglia. Overactivation of these housekeeping cells in the brain is linked with neurodegeneration.



Results showed that when these mice bred to display symptoms of Alzheimer's disease are given high choline in their diet throughout life, they exhibit improvements in spatial memory, compared with those receiving a normal choline regimen. Credit: Shireen Dooling: Biodesign Institute at Arizona State University

In a new study, Biodesign researchers reveal that a lifelong dietary regimen of choline holds the potential to prevent Alzheimer's disease (AD).

Choline is a safe and easy-to-administer nutrient that is naturally present in some foods and can be used as a dietary supplement. Lead author Ramon Velazquez and his colleagues at the ASU-Banner Neurodegenerative Disease Research Center (NDRC) looked into whether this nutrient could alleviate the effects of Alzheimer's.

Earlier this year, Velazquez and colleagues found transgenerational benefits of AD-like symptoms in mice whose mothers were supplemented with [choline](#). The latest work expands this line of research by exploring the effects of choline administered in adulthood rather than in fetal mice.

The study focuses on female mice bred to develop AD-like symptoms. Given the higher prevalence of AD in human females, the study sought to establish the findings in female mice. Results showed that when these mice are given high choline in their diet throughout life, they exhibit improvements in spatial memory, compared with those receiving a normal choline regimen.

Notably, findings published in July 2019 from a group in China found benefits of lifelong choline supplementation in male mice with AD-like symptoms. "Our results nicely replicate findings by this group in females," Velazquez says.

Intriguingly, the beneficial effects of lifelong choline supplementation reduce the activation of microglia. Microglia are specialized cells that rid the brain of deleterious debris. Although they naturally occur to keep the brain healthy, if they are overactivated, brain inflammation and neuronal death, common symptoms of AD, will occur.

The observed reductions in disease-associated microglia, which are present in various neurodegenerative diseases, offer exciting new avenues of research and suggest ways of treating a broad range of disorders, including traumatic brain injuries, multiple sclerosis and Parkinson's disease.

The findings appear in the current issue of the journal *Aging Cell*.

Supplementing the brain with additional choline

Choline acts to protect the brain from Alzheimer's disease in at least two ways, both of which are explored in the new study. First, choline blocks the production of amyloid-beta plaques. Amyloid-beta plaques are the hallmark pathology observed in Alzheimer's disease.

Secondly, choline supplementation reduces the activation of microglia. Over-activation of microglia causes brain inflammation and can eventually lead to neuronal death, thereby compromising cognitive function. Choline supplementation reduces the activation of microglia, offering further protection from the ravages of AD.

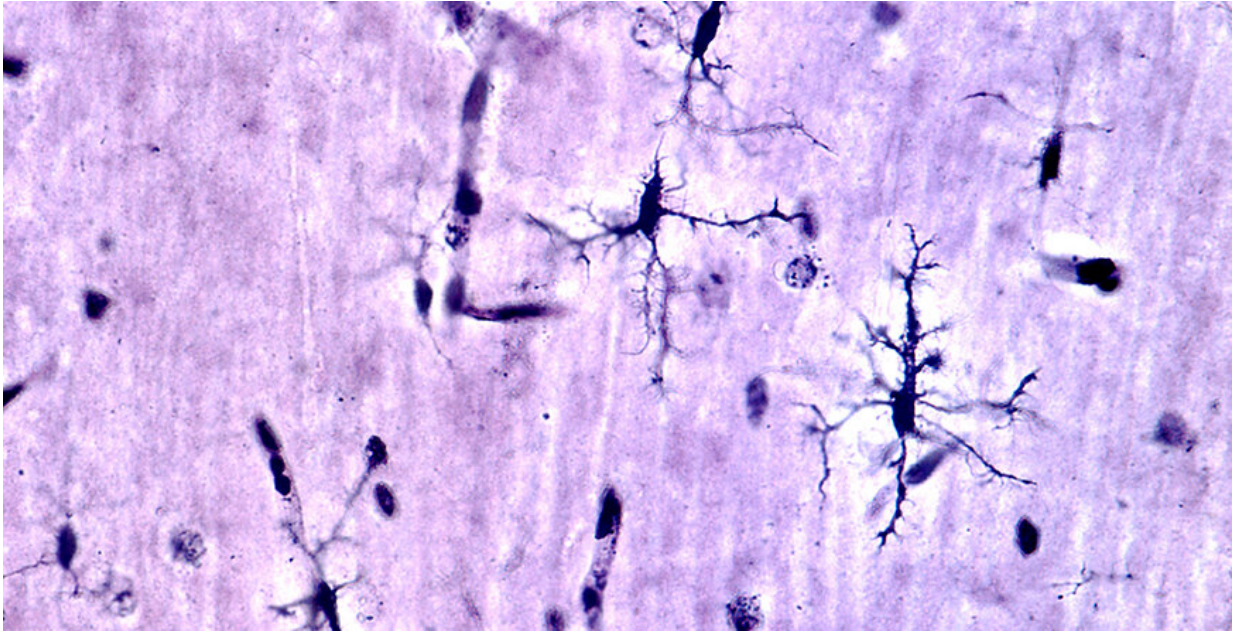
Mechanistically, the reductions in microglia activation are driven by

alteration of two key receptors, the alpha7 nicotinic acetylcholine and Sigma-1 receptor. A new report this year found that choline can act as an agonist for Sigma-1 receptors. These results confirm that lifelong choline supplementation can alter the expression of the Sigma-1 receptor, which thereby attenuates microglia activation. (An agonist is a substance that activates a given receptor.)

The devastating decline

In the scientific community, it is well understood that Alzheimer's disease causes harm to the brain long before clinical symptoms are made evident. And once these symptoms are identified, it is too late—the disease has become irreversible. In addition to causing disorientation and memory loss, the disease causes loss of motor control in those who are afflicted.

Approximately 6 million individuals are living with AD in the U.S. currently, and the disease is projected to afflict 14 million Americans in the next four decades. Economically, the costs associated with managing Alzheimer's are expected to exceed \$20 trillion in the same time span.



Microglia are specialized cells that work to clear away debris in the brain and perform other essential duties. These cells typically become dysregulated in Alzheimer's disease (AD), leading to inflammation and neuronal death. Intriguingly, the beneficial effects of lifelong choline supplementation reduce the activation of microglia in mice bred to develop AD-like symptoms. The choline-rich diet is shown to improve cognitive function. Credit: Arizona State University

To develop more effective treatments, we first need to understand the disease itself, which is one of the tallest orders facing modern medicine today.

Women are at a particular increased risk of developing Alzheimer's disease. This study shows that the simple addition of choline in the diet throughout life may reduce AD pathology in those most affected by the disease. Additionally, these results have implications for other neurodegenerative afflictions where activated microglia are rampant says Velazquez.

Guidelines for dietary choline

Prior research concerning Alzheimer's has indicated that there is no one factor at play. Rather, a multitude of factors that are believed to contribute to the development of the disease, including genetics, age and lifestyle. Additionally, studies suggest that diet can have a significant effect in increasing or lowering the risk of cognitive decline.

A recent report suggested that plant-based diets may be determinantal due to the lack of important nutrients, including choline. Another recent report found that the increase in cases of dementia in the United Kingdom may be associated with a lack of recommendations for choline in the diet throughout life. In fact, as of August 2019, AD and other forms of dementia are now the leading cause of death in England and Wales.

The current established adequate intake level of choline for adult women (>19yrs of age) is 425mg/day, and 550mg/day for adult men. A converging line of evidence indicates that even the current recommended daily intake (RDI) may not be optimal for a proper aging process, especially in women. This is relevant, given the higher incidence of AD seen in women. This suggests that additional choline in diet may be beneficial in preventing neuropathological changes associated with the aging brain.

The tolerable upper limit (TUL) of choline unlikely to cause side effects for adult females and males (>19yrs of age) is 3500mg/day, which is 8.24 times higher than the 425mg/day recommendation for females and 6.36 times higher than the 550mg/day recommendation for males. "Our choline supplemented diet regimen was only 4.5 times the RDI, which is well below the TUL and makes this a safe strategy", Velazquez says.

Choline can be found in various foods. According to the United States

Department of Agriculture (USDA), high levels of choline are found in chicken liver (3oz; 247mg), eggs (1 large egg with yolk; 147mg), beef grass-fed steak (3oz; 55mg), wheat germ (1oz toast; 51mg), milk (8oz; 38mg), and Brussel sprouts (1/2 cup; 32mg). Additionally, vitamin supplements containing choline, for example choline bitartrate and choline chloride, are widely available at affordable costs. The vitamin supplements containing choline are particularly relevant for those who are on plant-based diets.

Effects of choline

All plant and animal cells require choline to maintain their structural integrity. It has long been recognized that choline is particularly important for brain function.

The human body uses choline to produce acetylcholine, a neurotransmitter responsible for functioning memory, muscle control and mood. Choline also is used to build cell membranes and plays a vital role in regulating gene expression. Additionally, a new report in Jan 2019 found that choline acts as an agonist for Sigma-1 receptors, which are implicated in AD pathogenesis.

In this study, researchers used a water maze to determine whether the mice with AD-like symptoms that received lifelong supplemental choline exhibited improvements in spatial memory. It was found that this was indeed the case, and subsequent examination of mouse tissue extracted from the hippocampus, a brain region known to play a central role in memory formation, confirmed changes in toxic amyloid-beta and reductions in microglia activation, which reduces brain inflammation.

Due to alterations of key microglia receptors induced by choline, the improvements in behavior may be attributed to reduced microglia activation. "We found that lifelong choline supplementation altered the

alpha7 nicotinic acetylcholine and Sigma-1 receptor, which may have resulted in the reduction of diseased associated activated microglia," Velazquez said. These receptors regulate CNS immune response and their dysregulation contributes to AD pathogenesis.

The study's significance establishes beneficial effects of nutrient supplementation in females throughout life. "Our work nicely complements recent work showing benefits in male AD-mice on a lifelong choline supplementation regimen." "No one has shown lifelong benefits of choline supplementation in female AD-mice." "That's what is novel about our work."

Choline is an attractive candidate for prevention of AD as it is considered a very safe alternative, compared with many pharmaceuticals. "At 4.5 times the RDI (recommended daily intake), we are well under the tolerable upper limit, making this a safe preventive therapeutic strategy."

Although the results improve the understanding of the disease, the authors suggest that clinical trials will be necessary to confirm whether choline can be used as a viable treatment in the future.

More information: Ramon Velazquez et al, Lifelong choline supplementation ameliorates Alzheimer's disease pathology and associated cognitive deficits by attenuating microglia activation, *Aging Cell* (2019). [DOI: 10.1111/ace1.13037](https://doi.org/10.1111/ace1.13037)

Provided by Arizona State University

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