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Choline and Its Role in Our Brain Functioning Various Lifetime Phases

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Introduction

The hypothesis that choline supplementation may improve learning ability and memory in healthy adult individuals was first tested by Poly and colleagues [1] who found a relation between dietary choline intake, cognitive function, and brain morphology in a large, non-demented community-based cohort from the Framingham Offspring population. Specifically, participants completed a food-frequency questionnaire administered from 1991 to 1995 (exam 5; remote intake) and from 1998 to 2001 (exam 7; concurrent intake) and underwent neuropsychological evaluation and brain MRI at exam 7. Four neuropsychological factors were considered: verbal memory (VM), visual memory (VsM), verbal learning, and executive function. MRI measures included White Matter Hyperintensity volume (WMHV). They observed that performance on the VM and VsM factors was better with higher concurrent choline intake in multivariable-adjusted models for VM and VsM and that remote choline intake was inversely related to log-transformed WMHV. Furthermore, an inverse association was detected between remote higher choline intake and presence of large WMHV.

In this context, it is essential to consider what memory and learning truly represent. Traditional views often treat memory as a passive storage system, where information is retained through repetition and recall strategies. However, from a new way of studying and implementing knowledge capabilities (the so-called Phenomenic Learning perspective), memory is not merely about storing data but rather about how deeply one experiences the subject matter. The brain does not retain isolated facts but creates meaningful cognitive structures, integrating new knowledge into existing frameworks.

Thus, the beneficial effects of choline on memory and learning may not be limited to improving simple recall but could also enhance cognitive flexibility, association-building, and the ability to contextualize information in a broader framework of understanding. This suggests that higher choline intake (as indicated in the previously cited studies of around 486 mg, the recom-

mended daily intake indicated by the Ministry of Health) may facilitate not just retention, but the entire process of experiencing, connecting, and internalizing knowledge in a way that makes it effortlessly accessible.

In this review, we examine the pathophysiologic mechanisms of neurodegeneration, the role of choline to improve cognitive and memory functions and its potential therapeutic applications.

Pathophysiologic Mechanisms of Neurodegeneration

Advances in the field of epigenetics are revealing complex interactions between genes and environment and how these interactions impact health [2]. In this regard, nutrition is considered an important environmental factor that has been shown to influence mental health. Nutrients interact with epigenome and could negatively or positively impact the expression of many genes in the brain, thus altering brain structure and function throughout life. It is quite remarkable that the influence of these factors during early life could leave long-lasting imprints or marks on the genome, alter when and how much of genes will be expressed resulting in positive or negative outcomes later in life at all system levels including the brain. Several investigations have shown that supplementation or depletion of specific nutrients during critical period of brain development, such as early life and possibly during adulthood when the brain is mature, could impact brain structure and function later on life and affect positively or negatively its cognitive functions. DNA methylation is considered one of the best understood types of epigenetic mechanisms; it is a physiological process that regulates gene expression and function in health and diseased states [3], playing an essential role in brain plasticity, neuronal survival, and learning and memory functions throughout the lifespan. DNA methylation has been linked to many essential neurological functions such as memory formation [4, 5], neuronal excitability and synaptic transmission and connectivity [6]. The relevance of DNA methylation in many physiological processes raises the question whether early nutritional intervention could protect the brain from insults or could improve memory function or attenuate symptoms that are linked to aging including decline in cognitive functions.

Memory formation however should not be reduced to a mere mechanism of encoding and retrieval. The process of remembering is not about forcing information into long-term storage but about how knowledge is experienced as a dynamic phenomenon. Studies on DNA methylation suggest that epigenetic modifications influence neuroplasticity and synaptic adaptability, reinforcing the idea that learning happens more effectively when the brain is actively engaged in constructing meaning, rather than passively absorbing information.

This perspective aligns with research showing that nutritional interventions, such as choline supplementation, may not only improve the biochemical processes underlying memory but also enhance the brain's ability to reconfigure its understanding of the world, creating deeper, more flexible cognitive structures.

Mounting evidence indicates that dysfunction and/or degeneration of the cholinergic system and dysregulation of Acetil choline (Ach) neurotransmission in specific brain regions are primarily involved in the etiology of cognitive disorders [7]. Ach is the main neurotransmitter that is released by cholinergic neurons in various areas of the brain to regulate cholinergic signaling or neurotransmission. Ach is synthesized and released by cholinergic neurons. These neurons play an instrumental role in cognitive, learning and memory functions and are vulnerable in neurodegeneration. Ach exerts its effects on cholinergic neuron function via its receptors. The two main Ach receptors are the cholinergic muscarinic Ach receptors (mAchRs) and the nicotinic Ach receptors (nAchRs). These receptors are differentially expressed in different brain regions. The binding of Ach to mAchR or nAchR differentially alters neuronal excitability and transmission. Cholinergic neurons that synthesize Ach are widely distributed in the brain with several inputs and outputs, connect different brain regions and require trophic factors such as NGF for survival and proper neurotransmission [8, 9]. It is then not surprising that a dysfunction of cholinergic neurons could impair their neurotransmission in affected brain regions. Among these brain regions, the basal forebrain cholinergic neurons are probably the best understood and studied so far and have been shown to exert a modulatory action on cortical neurons

function. These cholinergic neurons receive input from the prefrontal cortex, an important brain region that is involved in decision-making. In turn, forebrain and brainstem cholinergic neurons send neuronal projections into other several brain regions such as the hippocampus, amygdala, cerebral cortex and the thalamus. Interestingly, the striatum, which is considered part of the limbic system, is the only brain region with a large number of cholinergic interneurons and receive dopaminergic inputs from the thalamus, the cerebral cortex, and the brainstem [10]. Due to the extensive connections with other neurons in different brain regions, basal forebrain cholinergic neurons are particularly vulnerable to many brain diseases. These extensive bidirectional connections of cholinergic neurons with different brain regions could explain the wide range of physiological roles of the cholinergic system in learning, attention, memory, stress and hence emotional responses, sensation and sleep regulation. Hence, dysfunction of this cholinergic system would explain the wide range of symptoms that patients with neurodegenerative disorders often exhibit. The vulnerability of the cholinergic system with normal aging shows different but consistent findings compared to neurodegenerative disorders. The normal aging brain does not exhibit loss of cholinergic neurons but rather a decrease in their function that is decrease in signaling or neurotransmission. However, a number of studies demonstrated that this mark is indeed reversible and could be modulated by environmental factors including nutrition with long-lasting effects on health.

Choline

Choline (2-hydroxyethyl-trimethyl-ammonium) is an essential nutrient that has three methyl groups attached to the nitrogen atom of ethanolamine. Choline serves as an essential methyl donor in methylation reactions that occur via the betaine-methionine pathway. Choline acts as a precursor of several phospholipids in the mammalian brain such as phosphotidylcholine, phosphotidylethanolamine and sphingomyelin [11]. These choline-containing phospholipids have essential physiological functions including membrane biogenesis, cellular signaling, nerve cell myelination, cellular division and lipid transport, all are processes that are required for proper development and normal functioning of the brain. Choline is also a precursor for the neurotransmitter Ach.

Choline has been identified by several studies conducted in animal models and in humans as an important nutrient that could program brain development during early life and affect the genome by causing epigenetic changes in a gene-specific manner or at a global scale in key brain regions that are associated with cognition, learning and memory. Choline is a nutrient that is required in optimal level throughout life to sustain normal functioning of many organs including the brain. It has both functional and structural roles. It is involved in the synthesis of acetylcholine, the neurotransmitter that is required for normal cholinergic neurotransmission in many brain regions [12]. It is also an essential structural component of cellular membranes and acts as a precursor for the formation of posphatidylcholine and sphingomyelin, the two main components of membrane phospholipids [12-14]. In addition to its role in cholinergic neurotransmission and in maintaining membrane structural and functional integrity, choline emerged recently as an epigenetic modulator of the genome by being a critical factor that alters the methylation status of DNA and histone proteins in the brain, two epigenetic processes that would alter brain function [15]. Several studies also showed that choline supplementation during sensitive periods of brain development such as prenatal, perinatal and early postnatal periods could have beneficial effects on learning, memory and on behavior during adulthood [12, 16-20].

Choline can donate its methyl groups by converting into betaine. In doing so, it can participate in folate-mediated one- carbon metabolism and participate in the formation of the major methyl-donor SAM (S-adenosyl-methionine). Methylation of genes or histones has been shown to modulate gene expression and function in a spatial and temporal manner in the brain. Variation in choline levels in the developing and the mature brain has been linked to many neurological disorders implicating the role of this nutrient in mental health.

Dietary choline deficiency decreases the levels of SAM in the brain resulting in a state of hypomethylation. Preclinical studies

demonstrated that supplementation of choline during prenatal life increased neurogenesis and angiogenesis in the fetal hippocampal region and improved performance in memory-related tasks that lasted for a lifetime [16, 21]. On the other hand, choline-deficient mice had a hypomethylated CDKN3 gene that resulted in an increase in the expression and activity by inhibiting the cell cycle progression and hence neurogenesis. Choline-induced changes in CDKN3 gene methylation status and function suggest that choline modulates the expression of cell cycle regulators and hence affects neurogenesis, cell proliferation and brain development and function [22]. These findings obtained in animal models were also confirmed in select human studies. It has been demonstrated that prenatal choline supplementation prevents neural tube defects [23]. Choline-related compounds such as CDP-choline have been shown to enhance some form of memory and cognitive functions with aging [24, 25].

Choline supplementation also resulted in anatomical changes in brain areas that are critical for learning and memory. For example, choline-supplemented rats showed an increase in the size of cholinergic neurons in the basal forebrain and in their ability to release Ach at synapses [26]. These studies indicate that the availability of the nutrient choline during early life such as prenatal or perinatal could program brain development and induce long-lasting positive effects on cognitive abilities during adulthood

Choline Intake

Choline can be created through *de novo* synthesis, but it is predominantly obtained from the diet, because the amount of biosynthesis that occurs in the body cannot sufficiently meet the daily requirements for humans, especially during critical periods of rapid development [12, 27-28].

The US Health and Medicine Division of the National Academies of Sciences, Engineering and Medicine set the adequate intake for total choline (AI), which depends on age and sex [28,29]:

- Children: 200 mg/day for children aged 1–3 years; 250 mg/day aged 4–8 years; and 375 mg/day aged 9–13 years;

- Adolescents aged 14–18 years: 400 mg/day (girls) and 550 mg/day (boys);

- Adults older than 19 years: 425 mg/day (women) and 550 mg/day (men); and

- Special groups: 450 mg/day for pregnant women or adolescents and 550 mg/day for lactating women or adolescents.

In 2016, the European Food Safety Authority established the following recommendations for adequate intake levels for choline [6]:

- Children: 140 mg/day for children aged 1–3 years; 170 mg/day aged 4–6 years; 250 mg/day aged 7–10 years; and 340 mg/day aged 11–14 years;

- Adolescents: 400 mg/day aged 15–17 years; and

- Special groups: 480 mg/day for pregnant women.

Choline is present in a wide variety of foods: peanuts, liver, wheat germ, beans, fish and vegetables, with eggs and meat products being the food products with the richest content in choline [10]. The United States Department of Agriculture (USDA) developed—and is constantly upgrading—a database that provides researchers and consumers with data about the choline content in foods [30].

Early life is a critical period that is characterized by rapid cellular growth and differentiation. Exposure to environmental fac-

tors during this critical period could program brain development and result in long-lasting changes in brain function. So, a healthy diet is a foundation for a good mental health throughout our life and particularly vital during early life when the brain is undergoing excessive neurogenesis, neuronal differentiation and migration and establishment of neuronal networks. Diet that is rich in components that participate in the one-carbon metabolism and the folate cycle is essential for normal development of the brain. These components include choline, betaine, methionine, folic acid, Vit-B12, and Vit-B6 and participate in methylation reactions to regulate neuronal gene expression by epigenetic mechanisms. These findings suggest that providing favorable environmental factors including an optimal diet during critical period of brain development could boost the activity of the brain later in life. In addition, the observations that dynamic processes such as methylation and histone modifications could also happen in the mature brain and alter its function prompt the idea that nutritional intervention that includes choline and other nutrients may protect cognitive functions with aging.

Several studies have tried to assess choline intake and its food sources among different population groups from different parts of the world [27, 31-37]. One study assessed the choline intake of the European population considering the European Food Safety Authority European Comprehensive Food Consumption Database and the United States Department of Agriculture Nutrient Database. It included data from surveys performed between 2000 and 2012 in nine European countries: The Netherlands, Finland, Sweden, Italy, Germany, France, Ireland, and the UK. Average choline intake ranges were 151–210 mg/day among toddlers (1 to 3 years old), 177–304 mg/day among other children (3 to 10 years old), 244–373 mg/day among adolescents (10 to 18 years old), 291–468 mg/day among adults (18 to 65 years old), 284–450 mg/day among elderly people (65 to 75 years old), and 269–444 mg/day among very elderly people (>75 years old) [27].

After ingestion of choline-rich foods, plasma levels of choline are elevated; most of the dietary choline that reaches the liver can be converted in an irreversible reaction into betaine via the enzymatic activity of choline oxidase [12]. Circulating choline can cross the blood brain barrier (BBB) via carriers or transport proteins that are located at BBB and be metabolized further in the brain or could be oxidized mainly in the liver into betaine to serve as a major source of methyl groups for the formation of methionine and SAM, major methyl-donors for methylation pathways in this organ. A small portion of dietary choline is usually acetylated to Acetyl-CoA to generate Ach by the Ach-synthesizing enzyme choline acetyltransferase, so that changes of choline levels in the blood would then affect its levels in the brain and how much of it will be used for the synthesis of Ach by neurons.

In addition to obtain choline from diet, choline can also be synthesized *de novo* from phosphocoline by a series of complex chemical reactions that have been shown to occur primarily in the liver and to a lesser extent in other tissues including the brain [12]. For these reasons, choline is metabolized in the blood and there's no difference between the various chemical forms of choline (e.g. bitartrate or alfoscerate) for their activity and metabolism.

Indeed, although choline is derived from the diet, several people do not get the optimal requirements that are needed for intake which is 7.5 mg daily per kg of body weight, a value that has been shown to vary between individuals in response to several factors such as sex, age, genetic polymorphisms and environmental factors [38, 39]. For example, at least 75% of American adults consume less than the recommended Adequate Intake levels [40] and a recent National Health and Nutrition Examination Survey (NHANES) found that only 4% of men and 2% of women over the age of 71 years meet the AI value [41] so that a specific supplementation could be required.

Neuroprotective Effects of Choline Intake in Adults

Animal studies have shown that choline supplementation is neuroprotective. Researchers have shown that prenatal supplementation of choline improved memory function in rats well into adulthood [42-44]. Teather and Wurtman [45] examined the effects of dietary supplementation of cytidine [5]- diphosphocholine, a source of choline, on memory impairment in aged rats and found supplementation to be protective against age-related memory deficits.

In 1995 Ladd et al. [46] analyzed the relationship between precursors of Ach and memory. They enrolled 80 college students in a double-blind mixed design to test the effect of phosphatidylcholine (PCh) on explicit memory. Dose of placebo and PCh was compared at two levels (10 and 25 g) as was time of ingestion (60 and 90 min. 25 g of PCh). With the higher dose of PCh, which supplies 3.75 g of choline, significant improvement in explicit memory, as measured by a serial learning task, was detected at 90 min post-ingestion and slight improvement was observed 60 min post-ingestion. Further analyses indicated that this improvement may have been due to the responses of slow learners. This was the first study to test the effect of a single dose of PCh on explicit memory in normal human subjects. These results could be applied to long-term dietary habits.

Oxidizedcholine forms the methyl donor betaine for the conversion of homocysteine to methionine [47–49], and Elias et al. [50] reported that high homocysteine concentrations are related to both cognitive impairments in nondemented samples and an increased risk of Alzheimer's disease (AD). Finally, concurrent choline intake was positively correlated with the performance of subjects on verbal and visual memory tasks [1, 12], and inversely correlated with white-matter hyperintensity volume, a brain magnetic resonance imaging measurement that is associated with impaired cognitive function and AD [51]. One possible explanation for the effect of concurrent choline intake on cognition in adults lies in its function as a precursor of the phospholipid phosphatidylcholine, a major constituent of all biological membranes, including those in neurons and glial cells.

Again, from a Phenomenic Learning standpoint, the role of choline in cognitive function is not solely about strengthening memory storage, but rather about improving the fluidity of thought and the ability to perceive connections between different concepts. Enhanced cholinergic signaling may facilitate a more organic and effortless integration of knowledge, allowing individuals to recall information not by mechanical memorization, but because the learning process itself has been deeply meaningful and naturally organized.

This aligns with findings suggesting that cognitive improvements linked to choline are not just quantitative (e.g., remembering more items) but also qualitative—allowing for more nuanced reasoning, better pattern recognition, and a stronger ability to navigate complex information landscapes. This is particularly relevant in the context of lifelong learning and the preservation of cognitive abilities as the brain ages.

Choline bitartrate (CB) is one of the most common kinds of choline supplements and is known to be more absorbable than other forms [12]. Equally important, preclinical studies have reported a choline-sparing effect of Vitamin B12 (B12) supplementation, evidencing that patients with B12 deficit exhibit lower blood concentrations of choline [12]. On these grounds, Mone et al. [52] decided to test the effects of combining CB and B12 on cognitive impairment in hypertensive elders with cognitive frailty (CF). From January 2023 to December 2023, they evaluated (Cerebrain® FORTE oral vials)137 consecutive hypertensive elders with CF. Of the screened patients, 27 did not fulfill the criteria and 11 did not give the consent to participate; a total of 99 patients successfully completed the study. Patients were randomly assigned to CB + B12, Choline Alphoscerate, or no nutraceuticals and followed-up for 3 months. A the end of this period the MoCA score was measured again and showed a beneficial effect of CB + B12 treatment on cognitive impairment ($p < 0.001$ vs baseline). Patients receiving choline alphoscerate presented a significant salutary effects on cognitive impairment ($p < 0.005$ vs baseline). Yet, the difference at follow-up between the two active treated groups was statistically significant, favoring CB + B12 ($p < 0.05$). This data show a very promising effect of the combination CholineBT+VitB12 and further study, evaluating the long term benefit either, are welcomed in order to assess other possible benefit that this supplementation could have.

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