Choline
Essential for Every Body

BALCHENM®
ENCAPSULATES

VitaCholine™
Choline is an essential nutrient; it is important for the healthy structure and function of the human body, acting as a biochemical building block, an agent of cell-to-cell communication and transportation, and part of a regulatory system for gene expression. Its role in cell structure and function, lipid metabolism, cell signaling and genetic regulation underlie its contribution to cognitive, cardiovascular, and hepatic health, as well as maintenance of vigor during strenuous exercise.

Choline’s demographic targets are as diverse as its therapeutic targets. It is an important component of the nutrition of prenatal and infant patients (via pregnant and lactating mothers), children, as well as athletic and geriatric segments of the population. However, awareness of choline and its benefits is low among US consumers, and measured dietary intakes reflect this. Choline was recently acknowledged by the USDA Dietary Guidelines Advisory Committee in its Report on the 2010 Dietary Guidelines for Americans.

Water-soluble choline salts, such as choline chloride and choline bitartrate, are versatile, stable, GRAS ingredients that can easily be incorporated into a variety of food and supplement products. Nutrient content and select health benefits of choline can be communicated to consumers by label claims on enriched and fortified products, offering a significant point of product differentiation.

**Choline’s material importance**

Choline’s necessity for human health is fundamental. Some of its effects are direct, in that it is a biosynthetic precursor of numerous molecules that are important for diverse structural and functional purposes in the human body (1). By its participation in several common biochemical reactions, including phosphorylation, base exchange, oxidation, one-carbon transfer, and acetylation, it generates important numerous intermediates for key metabolic processes. Other effects are indirect, in that it affects the balance of and need for many other partially compensatory metabolites to which it is closely related, via its influence on the activity of certain regulatory genes or the catalytic proteins they express.

Choline is ubiquitous in the body, as it is an important part of several biologically significant cell membrane phospholipids. One of these is phosphatidylcholine (PC), a primary structural component of the phospholipid membranes of all cells. The need for PC is extremely high in the first weeks and months of fetal development, as billions of cells are growing, dividing and differentiating. It continues to be necessary through the lifespan because of cellular turnover in certain tissues and organs. PC is also required in the construction of lipoprotein envelopes necessary for fat transport from the liver. It serves as a reservoir for free choline for tissues and organs that need it when the body is in a state of metabolic stress. Choline is also a precursor of the phospholipid sphingomyelin, which is part of the insulating lining of the body of neurons and itself a precursor of ceramide (2), which functions in intracellular signaling. By the mechanism of base exchange, PC can subsequently be converted to or from other important phospholipids involved in cell signaling and membrane structure and transport (3), namely phosphatidylethanolamine (PE), phosphatidylserine (PS), or phosphatidylinositol (PI)(4). Choline is a precursor of platelet-activating factor, which is a cellular messenger and an important mediator in numerous and diverse biological processes. It appears to be involved in different stages of reproduction (5), from fertilization and implantation, to the maturation of fetal lungs, and finally to hormonal action in the biochemical events preceding childbirth (1), for example.
Acetylation of choline generates acetylcholine, which is one of the body’s primary agents of neurotransmission. Comparatively little choline is converted to acetylcholine, as compared to its fate as a membrane phospholipid (6), however, it is important in that it is the only synthetic route to generate the acetylcholine molecule (7;8). The concentration of free choline available at the neuron terminal, the primary location of acetylcholine synthesis, is the limiting factor in this reaction. When neuronal communication accelerates during periods of high activity, the cells’ need for choline increases significantly. It is converted to acetylcholine directly, and via the breakdown of some of the choline-containing molecules described here (6;8-10).

Choline is readily converted by the body into the important osmolyte betaine in an irreversible oxidation process. It is significant in regulating the balance of influx and efflux of water in cells. By donation of one of its three methyl groups, it generates methionine, which is itself necessary for protein synthesis; the activity of this pathway spares the complementary nutrient folate for use in DNA synthesis (11), and concurrently reduces plasma homocysteine. Methyl groups [CH$_3$] are also important in that they function as so-called “epigenetic markers” that can activate or suppress the expression of genes and the activity of catalytic proteins. The changes in DNA that the placement of a methyl group brings about are heritable and retained over generations (12-15), implying a lifelong importance of choline’s biological activity.

<table>
<thead>
<tr>
<th>Role</th>
<th>Substance</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane phospholipid</td>
<td>Phosphatidylcholine</td>
<td>Structural component of the amphiphilic phospholipid membranes of all cells.</td>
</tr>
<tr>
<td></td>
<td>Sphingomyelin</td>
<td>Provides insulation along the length of a neuron.</td>
</tr>
<tr>
<td>Cell signaling</td>
<td>Phosphatidylinositol</td>
<td>Direct cell membrane traffic.</td>
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<tr>
<td></td>
<td>Ceramide</td>
<td>Secondary messenger by its interaction with proteins.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Role in processes of cell growth, aging, death.</td>
</tr>
<tr>
<td>Catabolism</td>
<td>Acetylcholine</td>
<td>Agent of message propagation between neurons.</td>
</tr>
<tr>
<td>Osmolyte Methyl donor</td>
<td>Betaine</td>
<td>Controls water transport in and out of cells.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contributes to the ‘methyl pool’ toward maintenance of the balance of choline, folate and B-vitamins.</td>
</tr>
</tbody>
</table>

Table 1. Biologically important choline derivatives (from references (1-6))
Choline’s importance at every age and stage

Choline nutrition for a bright beginning

Choline is indispensable in the proper development of the fetus, particularly the central nervous system. Maternal choline intake has been shown to have lifelong repercussions (13;15). Along with docosahexaenoic acid (DHA), choline is a necessary structural element of the phospholipid membranes of all brain cells (8;16). Reliable availability of choline in the prenatal period contributes to physiological changes in neurons that are theorized to correspond to an improved capacity for messaging between cells. In studies of choline-supplemented pregnancy, increased branching has been observed at the contact points between neurons in the part of the brain involved in learning and memory functions (16;17). By its influence on gene expression, choline is thought to regulate nerve cell reproduction and programmed death, a balance that is critical in the optimal growth and refinement of the connections that form between neurons (12;18-21). It may also activate a cell signaling sequence (19;22;23) which is thought to be important to the synaptic communication events that underlie learning and memory.

Adequate and/or enhanced maternal choline intake has been associated with long-lasting improvements in attention span, learning and memory in offspring of supplemented pregnancies (24-30). The benefits seen are dependent on the period and duration of supplementation (both pre- and post-natal > pre-natal only > post-natal only > control), and they appear to be lifelong (13). Performance enhancement in these offspring is most evident in their better execution of complex memory-related tasks, particularly those involving visuo-spatial and serial learning and memory (e.g. references (13;17;25-29;31)).

The close interrelationship between choline and the vitamin/coenzyme folate (32) makes them partially compensatory for one another and other methyl donors, such as methionine (33-35). However, they each have exclusive metabolic responsibilities as well. Adequate choline intake is important to ensure availability of these other molecules for these other critical purposes, particularly the synthesis of DNA and protein. Intervenational studies in animals and epidemiological observations in humans suggest that maternal dietary choline intake is potentially as important as folate is in attenuating the risk of neural tube defects in offspring (36-39).

STRUCTURE-FUNCTION CLAIMS

- Prenatal use of choline may lead to lifelong improvement of visuospatial memory in children born of the pregnancy.

- Supplementation with choline during infancy and childhood may lead to improved lifelong memory.
Get the message with choline

The communication that occurs between cells in the brain, and the ease with which it occurs, is a mechanistic basis of memory. Messaging is facilitated by better cell-to-cell contact between neurons and a greater availability and mobilization of neurotransmitters. It is also influenced by so-called secondary messengers and other bioactive metabolites (40). Mild memory loss is a normal consequence of aging for many individuals. Such cognitive decline may be the result of the breakdown of one or more elements of the cholinergic system, such as the uptake and interconversion of free choline and acetylcholine, maintenance of the myelin sheath and dendrites of neurons, and cellular decline in the hippocampus (41;42). This is compounded by the competing fates of free choline as both acetylcholine and phospholipids in aging neurons (43) and its participation in other biochemical processes (44). Choline administration may affect many of these, directly (as a source of an important precursor) or indirectly (by epigenetic or enzyme feedback mechanisms).

The level of choline in the brain is directly affected by its levels in plasma, which is significantly influenced by intake of the nutrient (8;45;46). It crosses the blood-brain-barrier by facilitated diffusion, and moves from extracellular fluid into cells according to the existing concentration gradient (8;47;48). In states of dietary choline deprivation (49) or other metabolic stress, membrane phospholipids (phosphatidylcholine and sphingomyelin) may be catabolized by phospholipase enzymes in an effort to maintain levels of brain choline (50) and provide for its release into the hippocampus (51). It follows, then, that choline intake should be important, in maintenance of cell membrane integrity. An organism’s choline status can also up- or down-regulate the activity of other enzymes. It can affect the balance of enzymatic synthesis and breakdown of the neurotransmitter acetylcholine (52) by a mechanism that is dependent on dietary manipulation (53). It also appears to affect the release of acetylcholine into the synapse via a yet-uncharacterized mechanism involving activation of tyrosine hydroxylase, an enzyme in another common type of neuron (54;55).

If one of the elements of the cholinergic system that is modulated by choline intake (56) is indeed a major cause underlying memory loss, a hypothesis might follow that choline administration would be a useful compensatory therapy to restore this cognitive function in otherwise healthy elderly. Choline continues to be the subject of active interventional biomedical research (56-66), for its unique characteristics suggest its enormous importance in the maintenance of human cognitive health.

![Figure 2. Choline's role in neurotransmission](image)

**STRUCTURE-FUNCTION CLAIM**

- Choline may help memory problems associated with aging.
**Choline at the crossroads**

As a trimethylamine \((\text{CH}_3)_3\text{N}^+\) moiety, choline can substantially contribute to the pool of methyl groups that can be used for one-carbon transfer reactions with DNA and protein. Choline is oxidized in a two-step process and subsequently remethylates homocysteine to S-adenosylmethionine, a methyl donor necessary for the synthesis of DNA and RNA, the myelin insulation for neurons, and other biological materials (67;68).

Choline intake has been shown to have a direct inverse effect on levels of plasma homocysteine (69), a metabolically-generated amino acid to which various deleterious cytotoxic and vascular effects have been ascribed (70-73). Homocysteine is debated as a biomarker, by-product, risk-factor or active agent (74) of biochemical change, though it is widely believed to be associated with numerous health conditions (75), including age-related cognitive decline, occlusive cardiovascular disease (76;77), and negative outcomes in pregnancy, such as low birth weight, pre-eclampsia, placental abruption and recurrent pregnancy loss (78-81).

Choline works in synergy with other substances in the class of B-vitamins in homocysteine metabolism because of shared roles in methylation and amino acid synthesis (82;83). (It has been observed that drugs that disrupt the metabolic balance of choline and B-vitamins in the body tend to increase homocysteine levels (84).) Vitamin B$_2$ (riboflavin) is a key component of the cofactor flavin adenine dinucleotide (FAD) for the enzyme methylene tetrahydrofolate reductase (MTHFR), which catalyzes the first steps of the biosynthesis of sulfur-containing amino acids, including that of methionine via homocysteine (85). Vitamin B$_12$ (cobalamin) is a cofactor for methionine synthase, the enzyme which directly catalyzes this conversion (86). These relationships are important to acknowledge, as fluctuations in B-vitamins can shift the dynamics of reactions requiring free choline as well.

**STRUCTURE-FUNCTION CLAIM**

- Choline may help reduce levels of plasma homocysteine.

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![Figure 3. Choline: An important metabolic intermediate and precursor](image-url)
Keeping the mind and body finely tuned

As has been discussed, choline is absolutely necessary for the optimal structure and function of the biological apparatus of the human body, from the level of cells, to that of whole tissues and organs. Choline need is thought to be exaggerated in physically active individuals who, by engaging in intensive exercise, run down their internal stores of the nutrient (87-89). Its functionality for this group of consumers may be collectively related to its role as the precursor of neurotransmitters, membrane phospholipids, cellular osmolytes, as well as its value in methyl-group donation (90).

When choline is depleted and dietary sources are insufficient to replenish it, membrane phospholipids must be sacrificed and broken down to ensure choline supply to the brain (8); this may compromise muscle tissue in the process (91). Maintenance of the nervous system during intense exercise is certainly critical, as it drives the continued activation of muscles and delays the onset of so-called “central fatigue,” which is associated with long periods of sustained muscular exertion (92). Decreased choline and acetylcholine may be associated with delays in transmission of muscle contraction impulses (87). Ingestion of choline increases the synthesis of acetylcholine and its release from neurons in the muscles and the heart, and at the neuromuscular junction (93;94).

Choline is also important, of course, as it is the direct precursor of betaine, a metabolite which has been extensively studied for ergogenic effects in athletes. Administration of choline will affect betaine levels (8;95). It is converted to betaine in a two-step enzymatic process in which energy equivalents (as cellular adenosine triphosphate (ATP)) are collaterally generated. Interventional studies with supplementary betaine have been conducted in humans (e.g. reference (96)); improvement in subjects’ strength and power performance has been observed, though not unilaterally. Any of betaine’s biological effects, i.e. as an osmoprotectant against dehydration, a methyl donor/precursor to creatine, complement to B-vitamins, could conceivably contribute to the physiological effect; the mechanistic picture is still in development (97).

Choline nutrition studies in active individuals indicate that the type, duration and intensity of physical activity (90) are important factors controlling choline expenditure and dictating potential benefits of supplementation. Further research is warranted in mechanistic studies (e.g. references (98-100)) and controlled interventional studies (e.g. the relationship between plasma homocysteine levels, exercise, and choline/betaine intake) with carefully chosen metrics to fully understand the role of choline in this special case of metabolic stress.

**STRUCTURE-FUNCTION CLAIM**

*Choline may reduce fatigue and increase vigor during strenuous exercise.*
Wrapping it up

Free choline is an important component of the structure of very low density lipoproteins, the cellular packaging system designed to remove excess lipid material from the liver (101-103). The choline that is used by the liver for this purpose is synthesized by a liver-specific pathway (PEMT, discussed earlier), a partially compensatory general pathway common to all cells, or else it is obtained from the diet (44;104). Choline deficiency, then, results from the convergence of less-than-optimal dietary habits and enzyme impairment at the individual genetic level (105-107), and is compounded by hormonal status (108-110). It is not surprising that changes in folate status or choline status can induce changes in one another, as they are closely interrelated with some common metabolic responsibilities (111;112).

The effect of choline deficiency in humans has been most unmistakably illustrated in individuals on controlled diets, such as total parenteral nutrition (TPN) (113). Plasma free choline is observed to decrease significantly with administration of TPN that is inadequate in choline, but sufficient in complementary B-vitamins (114;115). Longer-term deficiency, in TPN patients (116-118) as well as otherwise healthy individuals, is associated with the clinical onset of liver dysfunction, as indicated by abnormally high serum activity of serum transaminases (alanine- and aspartate aminotransferases), enzymes which are released from hepatic cells when they are damaged (116). These are considered to be a general surrogate indicator of hepatocyte damage and steatosis (accumulation of excess fat), which cannot ordinarily be easily observed (119). The etiology of liver dysfunction (120) is thought to be related to the rupture of cell membranes caused by steatosis, as well as the induction of apoptosis (controlled cell death) (121) and compensatory uncontrolled cell division in liver tissue (119;122;123). Choline deficiency studies in animals have demonstrated the induction of carcinoma in liver tissue, without the influence of carcinogens, with sustained deprivation of this nutrient (120;124).

Figure 5. Very low density lipoprotein

<table>
<thead>
<tr>
<th>STRUCTURE-FUNCTION CLAIM</th>
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</thead>
<tbody>
<tr>
<td>• Choline may promote healthy liver function.</td>
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</tbody>
</table>
Meeting the body's need for choline

When free choline is needed in a tissue or organ, it is either biosynthesized, extracted from circulation (8;44), or scavenged from local endogenous supply. It is subsequently stored as the free base or, more commonly, in a phosphorylated form such as phosphocholine (128). In this way, it can be most easily used for the variety of biological purposes that have been enumerated here.

Biosynthesis and dietary needs

The efficiency of endogenous choline production varies with age, gender, and hormonal status, and is itself influenced by diet. All cells synthesize choline via the cytidine diphosphocholine (CDP-choline) mechanism (6;44), known as the Kennedy pathway. Another mode of choline biosynthesis is via the sequential methylation of phosphatidylethanolamine, catalyzed by phosphatidylethanolamine N-methyltransferase (PEMT)(104;129). PEMT exists in abundance primarily in the liver, presumably to satisfy the needs incurred there in phospholipid synthesis and to supplement the CDP-choline pathway in times of metabolic stress (104). As the efficiency of this enzyme is estrogen-regulated (110;130), it is not surprising that certain segments of the population, particularly estrogen-deficient men and post-menopausal women, are most likely to become choline deficient with inadequate dietary intake (109).

Despite the abundant estrogen in circulation during gestation, pregnant women are also at increased risk for choline deficiency (131) because of the drain on choline imposed by the fetus (132;133). Choline availability to the fetus (12;134;135), and later, to the nursing infant, is directly affected by efficiency of PEMT activity (136) and maternal dietary habits (8;137;138).

Choline is considered an essential nutrient for humans (119) because these biosynthetic mechanisms do not ordinarily produce quantities sufficient to sustain normal organ function, even in a healthy human body. Deprivation of dietary choline is first manifest by a decrease in plasma choline. Sustained deprivation will lead to an increase in plasma homocysteine, an accumulation of fat in vacuoles of liver cells (steatosis), and damage to liver cell membranes (109). As deprivation devolves into dietary deficiency, cell suicide is activated in lymphocytes (139), damage is sustained by muscle cells, and organ dysfunction begins (91).

Dietary administration of choline easily reverses these symptoms of deficiency (129). In fact, current dietary recommendations for choline are based on the daily dosage necessary to prevent these abnormalities in most individuals, i.e. 7 mg/kg body weight/day (119). Based on data from studies of choline-deprived humans and animals, the Dietary Reference Intakes (DRIs) were developed for choline nutrition in healthy individuals (119) and published by the Food and Nutrition Board of the Institute of Medicine (US) in 1998.

In the years following the publication of the IOM’s findings, evidence has mounted that current DRIs are an inadequate estimate of actual choline need in the US population. While DRIs are predicated on dietary intake related to the appearance of easily observable clinical markers of liver dysfunction, they may not address other important and undesirable endpoints, such as elevated plasma homocysteine (140). Additionally, nutrigenomic and metabolomic research techniques (141) have begun to supplement and supplant some traditional, and more limited, methodologies in dietary intake and genetic analysis (106;110;136;142). The broad “population view” of choline nutrition, which was statistically necessary in the formulation of the DRIs (143), has obscured important, but previously unrealized, genetic differences that exist within the population (142).

Dietary intake is especially critical to individuals with loss-of-function variations in their genes for choline metabolism, particularly PEMT (110;129). The dietary choline requirement is also apparently increased in individuals with certain variations in genes involved in B-vitamin metabolism and one-carbon transfer, especially the gene encoding the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) (109;144). Adequacy of folate nutrition is evidently inextricably linked to choline need (11;34;35;108;111;144).
Dietary intake and supplementation

There are numerous widely available, nutrient-dense food sources that are especially choline-rich (135;145), including beef liver, egg yolks and wheat germ. According to current US food regulations, foods containing 55 mg of choline per serving may be declared a Good Source of this nutrient on their labels. Likewise, those containing 110 mg of choline per serving are an Excellent Source, and may be labeled as such.

However, many of these Good and Excellent natural sources of choline are limited in the current American diet because of their high fat or cholesterol content (146) or lack of palatability. Indeed, recent population studies suggest that a significant portion of the US population does not consume dietary choline at current recommended levels (147), contrary to the limited earlier data from certain smaller-scale investigations (148). The choline shortfall is more apparent in certain ethnic groups (146) and specific subpopulations. For example, there is evidence that approximately 90 percent of pregnant women in the U.S. have usual intakes below the choline AI level (147).

Dietary supplements, choline-rich meal-replacement products, and the discretionary fortification of foods and beverages, are appropriate ways to deliver necessary choline to consumers. Water-soluble choline salts are very easily added to virtually any processed food product, liquid, tablet or capsule, exhibiting excellent stability and high bioavailability. They have broad regulatory acceptability worldwide. In the US, choline fortified foods may be labeled with nutrient content claims, according to guidelines in the table below.

Oral administration of choline readily affects serum choline levels; certain organs and tissues will take it up before it is metabolized in the gut (46;95;149;150). For example, it is converted to betaine in the kidney, where it offers osmoprotection against the components of nascent urine. Free choline can readily traverse the blood-brain-barrier by facilitated diffusion from plasma (8;47;48). Once it is in the extracellular fluid, it can enter any cell in which it is needed by a non-specific, low affinity uptake mechanism, depending on the concentration gradient that exists between the plasma and the extracellular fluid (8). When choline reaches the upper small intestine, it is transported by a carrier (151) in a concentration-regulated mechanism, and it subsequently enters the portal circulation (95), where it can be picked up by the liver. Excess choline is converted to trimethylamine by the action of intestinal flora (152).

Table 3. Choline nutrient content claims*

<table>
<thead>
<tr>
<th>Claim</th>
<th>Conditions of use</th>
<th>Choline Content (mg Choline/RACC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Source of Choline, Contains/Provides Choline, Plus Choline, Fortified/Enriched with Choline, More Choline, Added Choline, Extra Choline</td>
<td>Product must contain 10-19% of the Daily Consumption Value of choline per Reference Amount Customarily Consumed (RACC)</td>
<td>≥55 mg</td>
</tr>
<tr>
<td>Excellent Source of Choline, High/Rich in Choline</td>
<td>Product must contain ≥20% of the Daily Consumption Value of choline per RACC</td>
<td>≥110 mg</td>
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</table>

*According to the Food and Drug Administration Modernization Act of 1997 (FDAMA), nutrient content claims are allowed in food and supplement labeling when they are based on current, published, authoritative statements from certain federal scientific bodies, including the National Academy of Sciences. All are based on an adult Daily Consumption Value, and may not be used in products intended for consumers under 4 years of age.
Conclusion

Choline biochemistry underlies many important processes in human nutrition. It is a material requirement of cells for membrane structure and metabolic control, and its presence is integral in maintaining a balance of key biochemistry needed for cell growth, function and repair. It is indispensable for its enabling roles in metabolism and mobilization of other micro- and macronutrients, including vitamin cofactors, amino acids and lipids. Though it is known to be the linchpin for many converging biological processes, its importance is currently underappreciated.

Dietary intake of choline is known to affect the availability of the nutrient to the tissues and organs whose viability depend on it, and it is absolutely necessary, as the body does not produce enough, even under ideal conditions. However, current population dietary trends appear to indicate that choline awareness and intake are less than optimal in most individuals. Choline chloride and choline bitartrate are the highly soluble, stable, bioavailable forms of choline that have been incorporated into numerous nationally-branded foods, beverages, and supplements in recent years. These product categories are the ideal vehicle to deliver to choline’s many important lifelong nutritional benefits -- with a strong, clear message on the label.

This article is for informational purposes only and is not meant to be construed as authoritative legal or medical advice. Balchem makes no representations as to its accuracy and assumes no liability or responsibility for the content of this article.

Choline supplements are not intended to diagnose, treat, cure or prevent any disease.

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