Nutrient of the Month: Choline

Choline is a relative latecomer to the spotlight of nutrition, and though its essentiality was only recently established (in 1998), it is required for health from the most basic cellular development to the highest echelons of brain function. Insufficient intakes are common among children, older adults, and pregnant women, with around 90 percent of Americans not receiving the Adequate Intake level (which ranges from 125-550 mg); vegetarians may have especially low intakes. Humans can make small amounts of choline from S-adenosyl-methionine (SAMe), but diet must supply most bodily needs. Egg yolk is the richest food source of choline, and though it is most commonly found in animal foods like liver, meat, fish, fish eggs/caviar/roe, milk, and whey, plant foods such as soy, split peas, nuts, spinach, cruciferous vegetables, and shiitake mushrooms provide it in reasonable quantity.

The American Academy of Pediatrics considers choline one of 11 key neurodevelopmental nutrients for which deficiency cannot later be nutritionally corrected. It is so critical during brain and nervous system formation in a growing fetus that its biosynthesis in the liver is boosted by the high-estrogen environment of pregnancy, yet pregnancy and lactation may exhaust mothers’ choline reserves. A compelling study found that a high maternal choline intake (930 mg daily) in the third trimester of pregnancy related to lower cord plasma levels of the stress hormone cortisol and altered expression of genes controlling cortisol release, in effect “quieting” activity along this axis of the stress response. This same intake level in mothers showed benefits for these children’s executive cognitive function during childhood, as presented by Marie Caudill, PhD, RD and team at the 2018 American Society for Nutrition Annual Meeting.

A distinctive feature of choline is that it is not only used for 1) building the phospholipid
components of cell membranes, but also needed in 2) forming the neurotransmitter acetylcholine, which acts in the synaptic regions of neurons’ cell membranes; both of which are strongly implicated in cognitive health during aging. Choline helps maintain the integrity of membranes within mitochondria, and deficiency impairs cellular energy production while increasing oxidative stress. In older persons, lower circulating levels of eight choline-containing phospholipids (as well as two others) accurately predicts clinically significant worsening of cognitive function over the next few years.

Besides being incorporated into membranes, choline additionally influences virtually every cell by participating in the body’s ‘carbon economy’ of methylation, in which it works closely with folate, vitamin B12, and SAMe. Choline’s task of transferring single carbons as methyl groups facilitates proper tissue growth, but its methylation duties for DNA and histones (which control the configuration of DNA, and thus its availability for reading or epigenetic modification) demonstrate its involvement at the highest level of regulation of cell life—helping determine which cell programs run, which genes are expressed, which proteins get produced, and which cells grow.

This may partly explain why low choline intake increases overall cancer risk (and especially lung, breast, and nasopharyngeal forms), according to studies cited in a 2017 review by choline expert Dr. Steven Zeisel. Maternal intakes of methyl donors including choline influence the activity of DNA methyltransferases responsible for broad control over DNA methylation patterns at critical points in cell division, embryo development, and fetal growth—not just direct methylation, but all-around regulation of methylation! One of choline’s metabolites is another valuable methyl donor, betaine, and choline is also able to remethylate homocysteine (which in excess can harm blood vessels), thus sparing body stores of folate from that task. Choline deficiency places more metabolic stress on folate, leading to greater DNA damage and genomic instability.

Though choline is perhaps best known for growing and maintaining brains (and protecting against birth defects), it is interesting that in human and animal studies, an early sign of deficiency is elevated liver enzyme levels. Choline is needed for optimal fat metabolism and creation of VLDL lipoproteins, and choline shortage causes triglycerides to ‘back up’ in the liver, causing fatty infiltration of liver tissue and cell damage. In one study, over 75 percent of men and postmenopausal women on a low-choline experimental diet showed fatty liver and/or muscle damage (shown by significant increase in serum creatine phosphokinase levels), while less than half of premenopausal women were affected. Choline status can also impact susceptibility to inflammation. Compared to adults with the lowest choline intakes, those receiving the highest amounts daily had significantly lower levels of several prime biomarkers of inflammation: C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and resistin, and higher levels of the beneficial cardiometabolic marker adiponectin.

While choline deficiency is common, there has been concern over the gut microbiome’s production of trimethylamine oxide (TMAO) from choline metabolism, and TMAO’s potential ties with cardiovascular disease. While elevated circulating TMAO levels have been linked to vascular damage and dysfunction, it is not clear yet whether this is indicative of causation or if TMAO is an ‘innocent bystander’ biomarker; generous dietary provision of choline has been more closely related to lower cardiovascular risk rather than higher risk. TMAO is also produced from betaine and carnitine—which likewise actively support functional health yet are also present in meager amounts in many diets. One preliminary study suggests that the microbiota in individuals with less gut microbiome diversity and a higher Firmicutes-to-Bacteroidetes ratio may produce more TMAO.

Most of the US population doesn’t get enough choline, and fatty liver is on the rise. In choline-deficient individuals, several genetic polymorphisms influence risk for liver disease, fetal neural tube defects, muscle damage, and other choline deficiency-related conditions. Though estrogen greatly increases choline synthesis, around half of women possess a gene variant that negates this estrogenic influence, and these women—and during pregnancy, their progeny—depend heavily on sufficient dietary provision of choline.

Choline is an exquisite example of a well-connected, pleiotropic nutrient—involved in gene regulation and in healthy structure and function of the brain, mitochondria, cell
membranes, liver, blood vessels, stress and inflammatory response patterns, and even our "second brain," the gut microbiome. This nutrient is so frequently overlooked that a team of researchers has recently developed helpful menus for choline-focused Mediterranean-style and vegetarian eating patterns that are easy to use.

We're Closing In On Sellout Status!

Alert! Urgent! It's time to act! We're not trying to be dramatic, but registrations for the 2019 Thought Leaders Consortium have been coming in at a brisk pace. Because we like to keep this conference to 400 attendees or less, we very intentionally select a mid-sized venue. Every tracking metric we are using indicates that we are going to reach our capacity well ahead of this year's event. The PLMI room block at the Hyatt Regency Lake Washington is nearly 100% booked. This year, we will close registration when the last seat is spoken for and we will not be establishing a waitlist. Have you been meaning to register? Is it on your to-do list and you just haven't gotten to it yet? Are there details you want to look into or questions you'd like us to address? This is a great week to finalize your plans.

Conference Overview >>
5 Things We Want You to Know >>
Speaker Gallery >>
Program Schedule >>
Conference Registration >>

Questions? Please contact Annette Giarde, Operations Manager: annettegiarde@plminstitute.org

"The Right Molecules in the Right Concentrations"

Long before the decoding of the human genome and discovery of genetic polymorphisms that influence the functionality of essential proteins, Dr. Abram Hoffer's work in nutrition showed that generous supplementation with certain micronutrients produced unexpected improvements in function for certain people. Dr. Linus Pauling called this orthomolecular medicine because it demonstrated that establishing "the right molecules in the right concentrations" to create the "optimum molecular environment" for health entailed appreciating each person's unique biochemical individuality. This summary of results from the orthomolecular approach to schizophrenia, published shortly after the Human Genome
Project began, was written by Dr. Hoffer’s son, L. John Hoffer, MD, PhD.

Now, other nutritional deficiencies and genetic variants that affect oxidative stress, nutritional status, and neurotransmitter balance are known to interfere with neuropsychiatric function and contribute to conditions like schizophrenia. A 2017 meta-analysis of essential nutrition in schizophrenia found that, in some cases, B vitamin supplementation led to significant improvements, which is further supported by the results of a 2018 trial that employed methylfolate in schizophrenia. Altered methylation function and homocysteine metabolism due to common genetic polymorphisms has been implicated in schizophrenia, and other research suggests that these may negatively affect status and utilization of vitamin B12 and docosahexaenoic acid in this population. Another extensive meta-analysis also found that serum levels of vitamin D and folate each related inversely to degree of psychotic symptomatology at first diagnosis, and that vitamin C levels were significantly lower in those diagnosed compared to healthy controls.

One small Japanese study on schizophrenia has found that supplementation with the Brassica vegetable phytonutrient sulforaphane improved subjects’ scoring on a visual recognition measure of cognitive function; the researchers noted that antipsychotic drugs employed in schizophrenia can increase oxidative stress, and they cite a previous study suggesting that sulforaphane may aid neurons’ protective systems. Though these results are preliminary, they build on other research addressing gene-nutrient-environment interactions that may relate to altered function in schizophrenia.