

## Choline Overview

Choline is an essential nutrient, a member of the B-vitamin family. It can be manufactured in the body (from the amino acid methionine), although some researchers feel that it is not made in sufficient amounts for optimal health. Folic acid and vitamin B12 are also needed to process choline properly. Choline plays a role in brain development (as an amine precursor for the neurotransmitter acetylcholine), liver function, and cardiovascular health. It is also used to enhance mental performance, memory and reaction time; for cancer prevention; to promote energy; and to delay fatigue. Choline is an important component of lipid transport and is a constituent of cell membranes. Therefore, it has functions in virtually every bodily system. It may reduce accumulation of fat in the liver.

Research shows that during pregnancy, choline intake of the mother may influence memory and brain development in the growing infant. Studies on choline and lecithin supplementation clearly show an increase in blood choline levels following supplementation with 1 – 5 grams of choline (or 5-15 grams of lecithin). Supplements have also been shown to improve marathon performance and endurance cycling ability (time to exhaustion), but may not be beneficial effect on shorter duration high-intensity exercise such as sprinting.

**Dietary Sources:** Food sources of choline include egg yolks (the major dietary source), organ meats and legumes. Choline is available in supplemental form as lecithin (or phosphatidylcholine) as well as purified choline capsules and as an ingredient in sports bars and drinks.

**Dosage:** The recommended amount of choline is 425mg/day for women and 550mg/day for men. The "average" diet supplies about 400 – 900mg of choline daily, which is presumed to be adequate. Choline was only designated as an essential nutrient by the Food and Nutrition Board of the National Academy of Sciences in April of 1998.

**Side Effects:** No adverse effects of choline supplements are noted at levels of 1-2 grams. Doses closer to 5 grams may be associated with side effects such as diarrhea, nausea, and abdominal discomfort. There have also been anecdotal reports of "fishy body odor" in people consuming high daily doses of choline or lecithin.

(Source: [www.supplementwatch.com](http://www.supplementwatch.com))

## Research Overview

The following studies are a brief review of the effects of choline.

1. Lecithin or choline administration can diminish the frequency of abnormal movements in patients with tardive dyskinesia
2. Both verbal and visual memory may be impaired in patients on long-term total parenteral nutrition and both may be improved with choline supplementation
3. Choline acts by increasing acetylcholine synthesis
4. Uptake of circulating choline into the brain decreases with age
5. Deprivation of choline during early development leads to compromised cognitive function and increased decline with age
6. Beneficial in endurance exercise
7. Low choline is associated with abnormal liver enzymes

Choline Abstracts (17)

Neurotransmitters 1. Dietary precursors and brain neurotransmitter formation. Fernstrom JD. *Annu Rev Med (UNITED STATES)* 1981, 32 p413-25

The rates of synthesis of serotonin, acetylcholine, and, under certain circumstances, dopamine and norepinephrine by brain neurons depend considerably on the availability to brain of the respective dietary precursors. This precursor dependence seems to be related to the fact that the enzyme catalyzing the rate-limiting step in the synthetic pathway for each transmitter is unsaturated with substrate at normal brain concentrations. Moreover, brain levels of the individual precursors rise following oral or parenteral administration of the pure compound or the ingestion of certain foods. Precursor-induced increases in brain transmitter formation seem to influence a variety of brain functions and behaviors, which suggests that transmitter release has been enhanced. It now appears that these precursors may become useful as therapeutic agents for the treatment of selected disease states, wherein the disease is related to reduced release of transmitter. Examples of Parkinson's disease (tyrosine), myasthenia gravis (choline or phosphatidylcholine), depression (tyrosine), and possibly abnormal appetite (tryptophan). Perhaps the future will bring the identification of still other neurotransmitters, whose rates of synthesis depend on precursor availability. Two potential candidates for which some information is already available are glycine (a spinal cord transmitter) and the prostaglandins (some of which may function as neuromodulators or transmitters) (48, 49). Each time a new precursor-product relationship is described, an opportunity becomes available for determining whether the precursor might be useful in treating disease states related to reduced transmitter release by neurons. The opportunities are worth exploring, since the use of a natural dietary constituent, even in purified form, is likely to produce fewer unwanted side-effects than are seen following administration of synthetic drugs.

2. Behavioral effects of dietary neurotransmitter precursors: Basic and clinical aspects Young SN. *Neuroscience and Biobehavioral Reviews (USA)*, 1996, 20/2 (313 323)

The levels and possibly function of several neurotransmitters can be influenced by the supply of their dietary precursors. The neurotransmitters include serotonin, dopamine, noradrenaline, histamine, acetylcholine and glycine, which are formed from tryptophan, tyrosine, histidine, choline and threonine. Tryptophan has been tested more than the other precursors in clinical trials and is currently available in some countries for the treatment of depression. Other uses for tryptophan and the therapeutic potential of other neurotransmitter precursors have not been tested adequately. Given the relative lack of toxicity of dietary components, further clinical trials with neurotransmitter precursors should be carried out.

3. Precursor control of neurotransmitter synthesis. Wurtman RJ, Hefti F, Melamed E. *Pharmacol Rev.* 1980 Dec;32(4):315-35.

Studies performed during the past decade have shown that the rates at which certain neurons produce and release their neurotransmitters can be affected by precursor availability, and thus by the changes in plasma composition that occur after ingestion of the precursors in purified form or as constituents of foods. Thus, tryptophan administration or a plasma ratio of tryptophan to other large neutral amino acids, thereby raising brain tryptophan levels, increasing the substrate saturation of tryptophan hydroxylase, and accelerating the synthesis and release of serotonin. Tyrosine administration or a high-protein meal similarly elevates brain tyrosine and can accelerate catecholamine synthesis in the CNS and sympathoadrenal cells, while the consumption of lecithin or choline increases brain choline levels and neuronal acetylcholine synthesis. The physiologic and biochemical mechanisms that must exist in order for nutrient consumption to affect neurotransmitter synthesis have been characterized and include: 1) the lack of significant feedback control of plasma levels of the precursor; 2) the lack of a real "blood-brain barrier" for the precursor, i.e. the ability of the plasma level of the precursor to control its influx into, or efflux from, the CNS; 3) the existence of a low-affinity (and thus unsaturated) transport system mediating the flux of the precursor between blood and brain; 4) low-affinity kinetics for the enzyme that initiates the conversion of the precursor to the transmitter; and, 5) the lack of end-product inhibition of the enzyme, in vivo, by its ultimate product, the neurotransmitter. The extent to which neurotransmitter synthesis in any particular aminergic neuron happens to be affected by changes in the availability of its precursor probably varies directly with the neuron's firing frequency. This relationship allows precursor administration to produce selective physiologic effects by enhancing neurotransmitter release from some but not all of the neurons potentially capable of utilizing the precursor for this purpose. It also allows the investigator to predict when administering the precursor might be useful for amplifying a physiologic process, or for treating a pathologic state. (for example, tyrosine administration raises blood pressure in hypotensive rats, lowers it in hypertensive animals, and has little effect on blood pressure in normotensive animals; the elevation in blood pressure probably reflects enhanced catecholamine release from sympathoadrenal cells, while the reduction in hypertensive animals probably results from increased catecholamine release within the brain-stem.) Such predictions are now being tested clinically in many institutions. Available evidence suggests that lecithin or choline administration can diminish the frequency of abnormal movements in patients with tardive dyskinesia.

Nutrition 4. Choline and human nutrition Zeisel SH, Blusztajn JK. *ANNU. REV. NUTR. (USA)*, 1994, 14:269-296

Choline is crucial for sustaining life. It modulates the basic signaling processes within cells, is a structural element in membranes, and is vital during critical periods in brain development. Choline metabolism is closely interrelated with the metabolism of methionine and folate. We believe that the normal human diet provides sufficient choline to sustain healthy organ function.

However, vulnerable populations may become deficient, including the growing infant, the pregnant or lactating woman, the cirrhotic, and the patient fed intravenously. Further studies of choline requirements in these groups are required.

## Liver

5. Choline may be an essential nutrient in malnourished patients with cirrhosis Chawla RK, Wolf DC, Kutner MH, Bonkovsky HL. *GASTROENTEROLOGY (USA)*, 1989, 97/6 (1514-1520)

Elemental diets designed for nutritional support in protein-calorie malnutrition are often deficient in choline, a nonessential nutrient. Previously, malnourished patients on these diets were found to be at risk of developing plasma choline deficiency. We have now estimated the prevalence of this deficiency by determining fasting plasma levels of choline among cirrhotic and noncirrhotic malnourished male subjects maintained on regular hospital mixed food or elemental parenteral and enteral formulas. Plasma choline concentrations (microM, average plus or minus SD) were as follows: (i) mixed foods, 11.3 plus or minus 4.3 for cirrhotic (n = 22) and 9.3 plus or minus 2.4 for noncirrhotic (n = 12) patients; (ii) parenteral formula, 5.3 plus or minus 1.6 for cirrhotic (n = 5) and 8.6 plus or minus 5.2 for noncirrhotic (n = 16) subjects; and (iii) enteral formula, 6.1 plus or minus 1.2 for cirrhotic (n = 5) and 11.7 plus or minus 1.9 for noncirrhotic (n = 4) subjects. The level for healthy normal subjects eating mixed foods was 12.0 plus or minus 2.2. The prevalence of plasma choline deficiency, i.e. plasma levels greater than or equal to 2 SD below the normal average, was as follows: parenteral formula, all cirrhotic and 10 of 16 noncirrhotic subjects; enteral formula, all cirrhotic and none of the noncirrhotic subjects. The reversibility of choline deficiency was examined in a longitudinal study of three phases involving 10 patients - 5 with alcoholic cirrhosis (all on enteral formula); 5 noncirrhotic (1 on enteral and 4 on parenteral formula). During phase 1 (3-day equilibration period; ad libitum regular hospital diet), plasma choline levels were within the normal range for all subjects. During phase 2 (2 wk, choline depletion phase, elemental formulas), choline levels were subnormal in all cirrhotic subjects (5.1  $\pm$  2.0 microM) on enteral formula and all noncirrhotic patients on parenteral formula (5.9 plus or minus 1.3 microM). During phase 3 (2 wk, choline repletion phase, elemental formula + 6 g choline/day), the levels normalized in all patients (cirrhotic 11.4 plus or minus 3.1 microM and noncirrhotic 11.9 plus or minus 3.2 microM). Analyses of abdominal computed tomographic scans and plasma liver chemistries in the cirrhotic subjects during the three phases suggested a correlation between plasma choline deficiency and hepatic steatosis and abnormal liver enzyme levels in some patients. Therefore, choline may be an essential nutrient in malnourished cirrhotic patients and its deficiency may be associated with adverse hepatic effects.

6. Male rats fed methyl and folate deficient diets with or without niacin develop hepatic carcinomas associated with decreased tissue NAD concentrations and altered poly(ADP ribose) polymerase activity Henning SM, Swendseid ME, Coulson WF. *Journal of Nutrition (USA)*, 1997, 127/1 (30-36)

Folate is an essential cofactor in the generation of endogenous methionine, and there is evidence that folate deficiency exacerbates the effects of a diet low in choline and methionine, including alterations in poly(ADP ribose) polymerase (PARP) activity, an enzyme associated with DNA replication and repair. Because PARP requires NAD as its substrate, we postulated that a deficiency of both folate and niacin would enhance the development of liver cancer in rats fed a diet deficient in methionine and choline. In two experiments, rats were fed choline and folate deficient, low methionine diets containing either 12 or 8% casein (12% MCFD, 8% MCFD) or 6% casein and 6% gelatin with niacin (MCFD) or without niacin (MCFND) and were compared with folate supplemented controls. Liver NAD concentrations were lower in all methyl deficient rats after 2-17 mo. At 17 mo, NAD concentrations in other tissues of rats fed these diets were also lower than in controls. Compared with control values, liver PARP activity was enhanced in rats fed the 12% MCFD diet but was lower in MCFND fed rats following a further reduction in liver NAD concentration. These changes in PARP activity associated with lower NAD concentrations may slow DNA repair and enhance DNA damage. Only rats fed the MCFD and MCFND diets developed hepatocarcinomas after 12-17 mo. In Experiment 2, hepatocarcinomas were found in 100% of rats fed the MCFD and MCFND diets. These preliminary results indicate that folic acid deficiency enhances tumor development. Because NAD in these animals was also low, further studies are needed to clearly define the role of niacin in methyldeficient rats.

Memory 7. Habituation of exploratory activity in mice: effects of combinations of piracetam and choline on memory processes. Platel A, Jalfre M, Pawelec C, Roux S, Porsolt RD. *Pharmacol Biochem Behav (UNITED STATES)* Aug 1984, 21 (2) p209-12

The effects of various piracetam + choline combinations on an experimental model of memory were investigated. Mice were given two sessions in a simple photo-cell activity cage and the decrease in activity at the second session (habituation) served as an index of retention. Retention was facilitated by post-session administration of 2000 mg/kg piracetam IP and 50 mg/kg piracetam + 50 mg/kg choline IP. Similar injections of choline alone (10 to 200 mg/kg IP), piracetam alone (10 to 1000 mg/kg IP) or other combinations of piracetam and choline were without effect. These results, consistent with those reported elsewhere, suggest that piracetam can interact with choline to facilitate memory processes.

8. Profound effects of combining choline and piracetam on memory enhancement and cholinergic function in aged rats. Bartus RT, Dean RL 3rd, Sherman KA, Friedman E, Beer B. *Neurobiol Aging (UNITED STATES)* Summer 1981, 2 (2) p105-11

In an attempt to gain some insight into possible approaches to reducing age-related memory disturbances, aged Fischer 344 rats

were administered either vehicle, choline, piracetam, or a combination of choline and piracetam. Animals in each group were tested behaviorally for retention of a one trial passive avoidance task, and biochemically to determine changes in choline and acetylcholine levels in hippocampus, cortex and striatum. Previous research has shown that rats of this strain suffer severe age-related deficits on this passive avoidance task and that memory disturbances are at least partially responsible. Those subjects given only choline (100 mg/kg) did not differ on the behavioral task from control animals administered vehicle. Rats given piracetam (100 mg/kg) performed slightly better than control rats ( $p$  less than 0.05), but rats given the piracetam/choline combination (100 mg/kg of each) exhibited retention scores several times better than those given piracetam alone. In a second study, it was shown that twice the dose of piracetam (200 mg/kg) or choline (200 mg/kg) alone, still did not enhance retention nearly as well as when piracetam and choline (100 mg/kg of each) were administered together. Further, repeated administration (1 week) of the piracetam/choline combination was superior to acute injections. Regional determinations of choline and acetylcholine revealed interesting differences between treatments and brain area. Although choline administration raised choline content about 50% in striatum and cortex, changes in acetylcholine levels were much more subtle (only 6-10%). No significant changes following choline administration were observed in the hippocampus. However, piracetam alone markedly increased choline content in hippocampus (88%) and tended to decrease acetylcholine levels (19%). No measurable changes in striatum or cortex were observed following piracetam administration. The combination of choline and piracetam did not potentiate the effects seen with either drug alone, and in certain cases the effects were much less pronounced under the drug combination. These data are discussed as they relate to possible effects of choline and piracetam on cholinergic transmission and other neuronal function, and how these effects may reduce specific memory disturbances in aged subjects. The results of these studies demonstrate that the effects of combining choline and piracetam are quite different than those obtained with either drug alone and support the notion that in order to achieve substantial efficacy in aged subjects it may be necessary to reduce multiple, interactive neurochemical dysfunctions in the brain, or affect activity in more than one parameter of a deficient metabolic pathway.

#### 9. Verbal and visual memory improve after choline supplementation in long-term total parenteral nutrition: a pilot study.

Buchman AL, Sohel M, Brown M, Jenden DJ, Ahn C, Roch M, Brawley TL. Division of Gastroenterology and Hepatology, Northwestern University, Chicago, Illinois 60611, USA. a-buchman@nwu.edu

JPEN J Parenter Enteral Nutr. 2001 Jan-Feb;25(1):30-5.

**BACKGROUND:** Previous investigations have demonstrated that choline deficiency, manifested in low plasma-free choline concentration and hepatic injury, may develop in patients who require long-term total parenteral nutrition (TPN). Preliminary studies have suggested lecithin or choline supplementation might lead to improved visual memory in the elderly and reverse abnormal neuropsychological development in children. We sought to determine if choline-supplemented TPN would lead to improvement in neuropsychological test scores in a group of adult, choline-deficient outpatients receiving TPN. **METHODS:** Eleven subjects (8 males, 3 females) who received nightly TPN for more than 80% of their nutritional needs for at least 12 weeks before entry in the study were enrolled. Exclusion criteria included active drug abuse, mental retardation, cerebral vascular accident, head trauma, hemodialysis or peritoneal dialysis, (prothrombin time [PT]  $>2x$  control), or acquired immune deficiency syndrome (AIDS). Patients were randomly assigned to receive their usual TPN regimen ( $n = 6$ , aged 34.0  $\pm$  12.6 years) over a 12-hour nightly infusion or their usual TPN regimen plus choline chloride (2 g) ( $n = 5$ , aged 37.3  $\pm$  7.3 years). The following neuropsychological tests were administered at baseline and after 24 weeks of choline supplementation (or placebo): Weschler Adult Intelligence Scale-Revised (WAIS-R, intellectual functioning), Weschler Memory Scale-Revised (WMS-R, two subtests, verbal and visual memory), Rey-Osterrieth Complex Figure Test (visuospatial functioning and perceptual organization), Controlled Oral Word Association Test (verbal fluency), Grooved Pegboard (manual dexterity and motor speed), California Verbal Learning Test (CVLT, rote verbal learning ability), and Trail Making Parts A & B (visual scanning, psychomotor speed and set shifting). Scores were reported in terms of standard scores including z scores and percentile ranks. Mean absolute changes in raw scores were compared between groups using the Wilcoxon rank sum test, where  $p$  values  $< .05$  constituted statistical significance. **RESULTS:** Significant improvements were found in the delayed visual recall of the WMS-R (7.0  $\pm$  2.7 vs -3.3  $\pm$  5.7,  $p = .028$ ), and borderline improvements in the List B subset of the CVLT (1.0  $\pm$  0.8 vs -2.0  $\pm$  2.4,  $p = .06$ ) and the Trails A test (-3.8  $\pm$  8.1 vs 3.7  $\pm$  4.5 seconds,  $p = .067$ ). No other statistically significant changes were seen. **CONCLUSIONS:** This pilot study indicates both verbal and visual memory may be impaired in patients who require long-term TPN and both may be improved with choline supplementation.

#### Cholinergic neurons

#### 10. Choline and cholinergic neurons.

Blusztajn JK, Wurtman RJ.

Science. 1983 Aug 12;221(4611):614-20.

Mammalian neurons can synthesize choline by methylating phosphatidylethanolamine and hydrolyzing the resulting phosphatidylcholine. This process is stimulated by catecholamines. The phosphatidylethanolamine is synthesized in part from phosphatidylserine; hence the amino acids methionine (acting after conversion to S-adenosylmethionine) and serine can be the

ultimate precursors of choline. Brain choline concentrations are generally higher than plasma concentrations, but depend on plasma concentrations because of the kinetic characteristics of the blood-brain-barrier transport system. When cholinergic neurons are activated, acetylcholine release can be enhanced by treatments that increase plasma choline (for example, consumption of certain foods).

11. Free choline and choline metabolites in rat brain and body fluids: sensitive determination and implications for choline supply to the brain.

Klein J, Gonzalez R, Koppen A, Loffelholz K. Department of Pharmacology, University of Mainz, Germany.

Neurochem Int. 1993 Mar;22(3):293-300.

In the central nervous system, choline is an essential precursor of choline-containing phospholipids in neurons and glial cells and of acetylcholine in cholinergic neurons. In order to study choline transport and metabolism in the brain, we developed a comprehensive methodical procedure for the analysis of choline and its major metabolites which involves a separation step, selective hydrolysis and subsequent determination of free choline by HPLC and electrochemical detection. In the present paper, we report the levels of choline, acetylcholine, phosphocholine, glycerophosphocholine and choline-containing phospholipids in brain tissue, cerebrospinal fluid and blood plasma of the untreated rat. The levels of free choline in blood plasma (11.4 microM), CSF (6.7 microM) and brain intracellular space (64.0 microM) were sufficiently similar to be compatible with an exchange of choline between these compartments. In contrast, the intracellular levels of glycerophosphocholine (1.15 mM) and phosphocholine (0.59 mM) in the brain were considerably higher than their CSF concentrations of 2.83 and 1.70 microM, respectively. In blood plasma, glycerophosphocholine was present in a concentration of 4.58 microM while phosphocholine levels were very low or absent (< 0.1 microM). The levels of phosphatidylcholine and lyso-phosphatidylcholine were high in blood plasma (1267 and 268 microM) but very low in cerebrospinal fluid (< 10 microM). We concluded that the transport of free choline is the only likely mechanism which contributes to the supply of choline to the brain under physiological conditions.

Acetylcholine

12. Brain acetylcholine: control by dietary choline.

Cohen EL, Wurtman RJ.

Science. 1976 Feb 13;191(4227):561-2.

Acetylcholine concentrations in whole rat brain or in various brain regions and free choline concentrations in blood serum and brain vary with dietary choline consumption. The increases in brain acetylcholine after treatment with physostigmine (an inhibitor of acetylcholinesterase) or after consumption of a diet high in choline are additive, suggesting that choline acts by increasing acetylcholine synthesis.

Neurochemical effects

13. Neurochemical effects of choline supplementation.

Wecker L.

Can J Physiol Pharmacol. 1986 Mar;64(3):329-33.

Whether or not the brain can use supplemental choline to enhance the synthesis of acetylcholine (ACh) is an important consideration for assessing the merits of using choline or phosphatidylcholine (lecithin) for the treatment of neuropsychiatric disorders postulated to involve hypochocholinergic activity. While it is well documented that administered choline is incorporated into ACh, the ability of supplemental choline to increase the synthesis and release of ACh has been questionable. Studies in my laboratory have demonstrated that acute or chronic choline supplementation does not, by itself, enhance the levels of ACh in brain under normal biochemical and physiological conditions. However, supplemental choline prevents the depletion of ACh in brain induced by numerous pharmacological agents that increase the firing of cholinergic neurons. Since the levels of free choline in brains from supplemented rats were not different from controls prior to drug challenge, evidence suggested that the observed effects of choline were mediated by alterations in the mobilization of choline from choline-containing compounds. Studies investigating the release of choline from brain indicated that more choline was released per unit time in tissues from choline-supplemented rats than from controls. In addition, brain tissue from choline-supplemented rats had increased concentrations of total lipid phosphorus as compared with controls. Hence, although choline supplementation does not alter the levels of ACh in brain under normal conditions, it does appear to support ACh synthesis during drug-induced increases in neuronal activity, an effect most likely mediated by alterations in the metabolism of choline-containing phospholipids.

Decreased in older adults

14. Decreased brain choline uptake in older adults. An in vivo proton magnetic resonance spectroscopy study.

Cohen BM, Renshaw PF, Stoll AL, Wurtman RJ, Yurgelun-Todd D, Babb SM. Brain Imaging Center, McLean Hospital, Belmont, MA 02178, USA.

JAMA. 1995 Sep 20;274(11):902-7.

**OBJECTIVE**--To test the hypothesis that uptake of circulating choline into the brain decreases with age, because alterations in metabolism of choline may be a factor contributing to age-related degenerative changes in the brain. **DESIGN**--Cohort comparison in younger and older adults. **PARTICIPANTS**—Subjects were chosen consecutively from lists of healthy volunteers screened by medical and psychiatric interviews and laboratory tests. Younger adults (n = 12) were between the ages of 20 and 40 years (mean age, 32 years), and older adults (n = 16) were between the ages of 60 and 85 years (mean age, 73 years). **INTERVENTIONS**--After fasting overnight, subjects received choline, as the bitartrate, to yield free choline equal to 50 mg/kg of body weight. Blood was drawn for determination of plasma choline concentration by high-performance liquid chromatography, and proton magnetic resonance spectroscopy (1H-MRS) was performed to determine the relative concentration of cytosolic choline-containing compounds in the brain at baseline and after ingestion of choline. **MAIN OUTCOME MEASURES**--Plasma choline and cytosolic choline-containing compounds in the brain, estimated as the ratio of the choline resonance to the creatine resonance on 1H-MRS scans of the basal ganglia, were compared following blinded analyses of data from subject cohorts studied at baseline and 3 hours after choline ingestion. **RESULTS**--Levels of plasma choline and cytosolic choline-containing compounds in brain were similar at baseline in younger and older subjects. Following ingestion of choline, plasma choline concentration increased by similar proportions (76% and 80%) in both younger and older subjects. Brain cytosolic choline--containing compounds increased substantially in younger subjects (mean increase, 60%; P < .001 vs baseline). Older subjects showed a much smaller increase in brain choline-containing compounds (mean, 16%; P < .001 vs the increase in younger subjects). **CONCLUSION**--Uptake of circulating choline into the brain decreases with age. Given the key role of choline in neuronal structure and function, this change may be a contributing factor in onset in late life of neurodegenerative, particularly dementing, illnesses in which cholinergic neurons show particular susceptibility to loss.

#### PREVENTION OF MEMORY LOSS FROM GESTATION

15. Metabolic imprinting of choline by its availability during gestation: implications for memory and attentional processing across the lifespan.

Meck WH, Williams CL. Department of Psychological and Brain Sciences, Duke University, 9 Flowers Drive, Box 90086, 27708-0086, Durham, NC, USA

Neurosci Biobehav Rev. 2003 Jun;27(4):385-99.

A growing body of research supports the view that choline is an essential nutrient during early development that has long-lasting effects on memory and attentional processes throughout the lifespan. This review describes the known effects of alterations in dietary choline availability both in adulthood and during early development. Although modest effects of choline on cognitive processes have been reported when choline is administered to adult animals, we have found that the perinatal period is a critical time for cholinergic organization of brain function. Choline supplementation during this period increases memory capacity and precision of the young adult and appears to prevent age-related memory and attentional decline. Deprivation of choline during early development leads to compromised cognitive function and increased decline with age. We propose that this organizational effect of choline availability may be due to relatively permanent alterations in the functioning of the cholinergic synapse, which we have called 'metabolic imprinting'.

#### REDUCES URINARY CARNITINE EXCRETION

16. Choline supplementation reduces urinary carnitine excretion in humans.

Dodson WL, Sachan DS. Department of Nutrition, University of Tennessee, Knoxville 37996-1900, USA.

Am J Clin Nutr. 1996 Jun;63(6):904-10. Comment in: Am J Clin Nutr. 1997 Feb;65(2):574-5.

Two experiments were conducted to determine the effects of supplementary choline and/or pantothenate on the carnitine and lipid status of free-living humans. Analyses of carnitine and cholesterol fractions, triacylglycerols, and creatinine were determined in serum and/or urine. In experiment 1, adults receiving 13.5 mmol choline plus 1.4 mmol pantothenate/d had a significant decline in urinary carnitine excretion and renal clearance with nonesterified carnitine (NEC) declining the most dramatically, 84%.

Additionally, serum NEC and total carnitine concentrations decreased significantly. No changes were observed in any of the serum lipids examined. In experiment 2, subjects took 0.20 mmol and 0.02 mmol/kg choline or pantothenate, respectively. Choline, but not pantothenate, supplementation significantly decreased urinary carnitine excretion, renal clearance, and fractional clearance of NEC. We conclude that supplementary choline maintained serum carnitine concentrations by conserving urinary carnitine. Moreover, these observations merit additional investigation to determine metabolic and functional consequences of choline and carnitine interactions in humans.

17. J Nutr. 2003 Jan;133(1):84-9. Carnitine and choline supplementation with exercise alter carnitine profiles, biochemical markers of fat metabolism and serum leptin concentration in healthy women. Hongu N, Sachan DS. Department of Nutrition and Agricultural Experiment Station, The University of Tennessee, Knoxville, TN 37996-1900, USA.

We sought to determine the effects of supplementary choline, carnitine and a combination of the two with or without exercise on serum and urinary carnitine and biochemical markers of fatty acid oxidation in healthy humans. Nineteen women were placed in three groups: 1) placebo, choline or carnitine preloading period of 1 wk followed by 2) supplementation with choline plus carnitine during wk 2-wk 3 and 3) all groups exercised in wk 3. Although there were no changes in the placebo group, serum and urinary carnitine decreased in the choline-supplemented group during wk 1. Introduction of carnitine to the choline group restored serum and urinary carnitine. Serum and urinary carnitine increased during wk 1 in the carnitine-supplemented group and, although the introduction of choline to this group depressed serum and urinary carnitine, they remained significantly greater than control. Serum beta-hydroxybutyrate and serum as well as urinary acylcarnitine were elevated by the supplements. A mild exercise regimen increased the concentration of serum beta-hydroxybutyrate, and serum and urinary acylcarnitines; it also decreased serum leptin concentrations in all groups. The effects of supplements were sustained until wk 2 after cessation of choline plus carnitine supplementation and exercise. We conclude that the choline-induced decrease in serum and urinary carnitine is buffered by carnitine preloading, and these supplements shift tissue partitioning of carnitine that favors fat mobilization, incomplete oxidation of fatty acids and disposal of their carbons in urine as acylcarnitines in humans.

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