Choline: Needed for Normal Development of Memory

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Choline is a dietary component essential for normal function of all cells. It, or its metabolites, assures the structural integrity and signaling functions of cell membranes; it is the major source of methyl-groups in the diet (one of choline's metabolites, betaine, participates in the methylation of homocysteine to form methionine); and it directly affects nerve signaling, cell signaling and lipid transport/metabolism. In 1998, the National Academy of Sciences, USA, issued a report identifying choline as a required nutrient for humans and recommended daily intake amounts. Eggs are an excellent dietary source of choline.

Pregnancy and lactation are periods when maternal reserves of choline are depleted. At the same time, the availability of choline for normal development of the brain is critical. When rat pups received choline supplements (in utero or during the second week of life), their brain function changed, resulting in the lifelong memory enhancement. This change in memory function appears to be due to changes in the development of the memory center (hippocampus) in the brain. The mother's dietary choline during a critical period in brain development of her infant influences the rate of birth and death of nerve cells in this center. These changes are so important that we can pick out the groups of animals whose mothers had extra choline even when these animals are elderly. Thus, memory function in the aged rat is, in part, determined by what the mother ate. This is not the first example of a critical nutrient that must be present at a specific time in brain development. If folate isn't available in the first few weeks of pregnancy, the brain does not form normally. Thus, we suggest that pregnancy is a period when special attention has to be paid to dietary intake.

Key teaching points:

- Choline has been identified as a required nutrient.
- Studies indicate that choline plays a role in development of memory.
- Choline intake during pregnancy may be important for brain development.
- Eggs are a good source of choline in the diet.

The Institute of Medicine (IOM) of the US National Academy of Sciences recently made recommendations for dietary choline requirements [1]. Choline in the diet is important for many reasons: it is needed for synthesis of the phospholipids in cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid-cholesterol transport and metabolism [2]. Most choline in the body is found in phospholipids such as phosphatidylcholine and sphingomyelin. Though representing a smaller proportion of the total choline pool, important metabolites of choline include platelet-activating factor, acetylcholine, choline plasmalogens, lysophosphatidylcholine, phosphocholine, glycerophosphocholine and betaine. There are several comprehensive reviews of the metabolism and functions of choline [1–3].

Male humans [4] and many species of animals, including the baboon, fed a choline deficient diet deplete choline stores and develop liver dysfunction [5–9]. Some humans (male and female) fed with total parenteral nutrition (TPN) solutions devoid of choline, but adequate for methionine and folate, develop fatty liver and liver damage that resolves when a source of dietary choline is provided [10–15]. Fatty liver occurs because choline is required to make the phosphatidylcholine portion of the very-low-density lipoprotein (VLDL) particle that is needed to export triacylglycerol from the liver

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[16,17]. Animals fed a choline deficient diet may also develop growth retardation, renal dysfunction and hemorrhage, or bone abnormalities [8,18,19]. There is no doubt that cells in culture absolutely require choline [20] and die by programmed cell suicide when deprived of this nutrient [21–23]. The exact amount of choline that the human diet must contain to sustain life is modulated by the pathway (most active in the liver) for the *de novo* biosynthesis of the choline moiety via the sequential methylation of phosphatidylethanolamine using S-adenosylmethionine as the methyl donor [24]. This ability to form choline moiety *de novo* means that some of the demand for choline can, in part, be met by using methyl-groups derived from one carbon metabolism (via methyl-folate and methionine). Because of this metabolic interrelationship, choline deficiency depletes cells of methyl-folate and methionine, and increases intracellular S-adenosylhomocysteine and homocysteine concentrations [25,26]. As our understanding of the importance of folate and homocysteine nutrition increases, there should be increased interest in how choline interacts with folate and homocysteine metabolism.

The IOM recommended an Adequate Intake (AI) estimation for choline in the diet. The IOM report cautioned, 'this amount will be influenced by the availability of methionine and methyl-folate in the diet. It may be influenced by gender, and it may be influenced by pregnancy, lactation, and stage of development. Although AIs are set for choline, it may be that the choline requirement can be met by endogenous synthesis at some of these stages.' The IOM recommendations are shown in Table 1.

Almost no information is available about the choline content of foods. Eggs have an especially high choline moiety content (about 300 mg choline/egg, mostly in the form of phosphatidylcholine). Both commercially available infant formulas and bovine milk contain choline and choline-containing compounds [27]. Plasma choline concentration varies in response to diet [28] and can rise as much as two-fold after a two-egg meal. Fasting plasma choline concentrations vary from 7 to 20 μM, with most subjects having concentrations of 10 μM. Individuals that have starved for up to seven days have diminished plasma choline, but levels never drop below approximately 50% of normal [29].

Table 1. Recommended Adequate Intakes (AI) for Choline [1]

Population	Age	AI
AI for Infants	0 to 6 months	125 mg/day, 18 mg/kg
	6 to 12 months	150 mg/day
AI for Children	1 through 3 years	200 mg/day
	4 through 8 years	250 mg/day
	9 through 13 years	375 mg/day
AI for Males	14 through 18 years	550 mg/day
	19 and older	550 mg/day
AI for Females	14 through 18 years	400 mg/day
	19 years and older	425 mg/day
AI for Pregnancy	All ages	450 mg/day
AI for Lactation	All ages	550 mg/day

Pregnancy may be a time when dietary supplies of choline are especially limiting. Though female rats are resistant to choline deficiency, pregnant rats are as vulnerable to deficiency as are males [30]. During pregnancy, large amounts of choline are delivered to the fetus across the placenta [31], and this depletes maternal stores of choline [32]. At birth, humans and other mammals have plasma choline concentrations that are much higher than those in adults [33]. The need for choline is likely to be increased during lactation because so much must be secreted into milk (human milk contains 1.5 to 2 mM choline moiety per liter [27]). Lactating rats are more sensitive to choline deficiency than are non-lactating rats [30].

Ensured availability of choline appears to be important to infants because organ growth - extremely rapid in the neonate - requires large amounts of choline for membrane biosynthesis [34,35]. During development, there is a progressive decline in blood choline concentration that begins *in utero*. In fact, plasma or serum choline concentrations are sevenfold higher in the fetus and neonate than they are in the adult [33,34]. This decline in serum choline concentration occurs during the first weeks of life in the rat and the human [36]. High levels of choline circulating in the fetus presumably ensure enhanced availability of choline to tissues. Neonatal rat brain efficiently extracts choline from blood [37,38]. Supplementing choline during the perinatal period further increases blood and brain choline metabolite concentrations [39]

An interesting effect of dietary choline deficiency in rats has never been studied in humans. Choline availability during embryogenesis and perinatal development of the rat and mouse may be especially important. There are two sensitive periods in rodent brain development during which treatment with choline (about 1 mmol/day) produces long-lasting enhancement of spatial memory that is lifelong [40–49]. The first occurs during embryonic days 12 to 17 (rats give birth on day 21), and the second during postnatal days 16 to 30. Choline supplementation during these critical periods elicits a major improvement in memory performance at all stages of training on a 12-arm radial maze. Though all animals were cross-fostered with untreated mothers, even when the rats are old these memory changes persist and can be used to easily identify which rats got more or less choline during the perinatal period; the normal age-associated decrement that occurs in rat memory seems to be delayed in the choline supplemented group ([44], Warren Meck, personal communication). Pups from mothers fed a choline deficient diet during this same period of pregnancy have diminished memory function [44,47]. During embryogenesis, progenitors of neurons and glia divide, many migrate to new locations, and unnecessary cells die by apoptosis [50–52]. These early developmental events determine the future structure and function of the brain. The choline-induced spatial memory facilitation correlates with changes in the birth, death and migration of cells in the hippocampus during fetal brain development [53–56], with altered distribution and morphology of neurons involved in memory storage within the brain

[41,46], with biochemical changes in the hippocampus [57] and with electrophysiological changes in the hippocampus [45]. Are these findings in rats likely to be true of humans? We do not know. Human and rat brains mature at different rates; the rat brain is comparatively more mature at birth than is the human brain, but in humans hippocampal development may continue for months or years after birth [58]. A controlled human study is needed, but until then it seems prudent to ensure that dietary intake of choline is adequate during pregnancy. Two eggs per day contain approximately the dietary requirement for choline, and until more foods are analyzed for choline content, pregnant women might want to include eggs in their diets.

ACKNOWLEDGMENTS

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