14 Choline

14.1 Choline in health and disease
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14.1.1 Introduction
Choline is a water-soluble nutrient that is often grouped with the vitamin B complex. However, its functions suggest it is more than just another vitamin. Choline is crucial for the normal function of all cells (Zeisel and Blusztajn, 1994). It is needed for the structural integrity and signaling functions of cell membranes; it directly affects cholinergic neurotransmission; it is the major source of methyl groups in the diet; and it is required for lipid transport from liver and for normal muscle function (Zeisel and Blusztajn, 1994; Zeisel, 2006b). In early life, choline is crucial for fetal brain development; in later life, prolonged ingestion of a choline-deficient diet leads to fatty liver, and liver and muscle damage in humans (Zeisel, 2006b). Choline deficiency also reduces an individual’s ability to handle a methionine (Met) load, resulting in elevated homocysteine (Hcy), a risk factor for cardiovascular diseases (CVDs) (da Costa et al., 2005). Conversely, choline supplementation in animal models might mitigate or ameliorate the symptoms of fetal alcohol syndrome (Thomas et al., 2009), traumatic brain injury (Guseva et al., 2008), brain abnormalities in mouse models of Rett syndrome (Nag et al., 2008; Ward et al., 2009) and schizophrenia (Stevens et al., 2008). In this chapter, we focus on the new observations that enhance our understanding of the roles of choline in human health and disease.

14.1.2 Dietary and endogenous sources of choline
Foods contain several choline-containing compounds as well as betaine, a choline-metabolite which spares some choline requirements (Zeisel et al., 2003). Excellent sources of dietary choline are foods that contain membranes, such as eggs and liver. Recently, the US Department of Agriculture (USDA) developed the first database of choline content in foods (http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/Choline/ChoIn02.pdf last accessed 8-11-10). Average dietary choline intake on ad libitum diets for males and females are 8.4 mg/kg and 6.7 mg/kg choline per day, respectively (Fischer et al., 2005).

Also, choline can be formed endogenously (mainly in the liver) by the enzyme phosphatidylethanolamine-N-methyltransferase (PEMT) (Fig. 14.1). PEMT uses S-adenosylmethionine (SAM) converting phosphatidylethanolamine (PtdEtn) to phosphatidylcholine (PtdCho). This phospholipid is either incorporated into cell membranes or degraded to regenerate choline (Blusztajn et al., 1985). Mice that lack the PEMT gene rapidly develop fatty liver and severe liver damage, and die after 3 days of a choline-deficient diet; choline supplementation prevents this (Walkey et al., 1998).
PEMT-/- mice have lower choline pools in liver despite being fed sufficient or supplemental choline, suggesting that choline production by PEMT in the liver is a significant source of choline relative to dietary intake (Zhu et al., 2003).

**14.1.3 Choline absorption and metabolism**

Choline is found in foods as choline or choline esters, from which choline is freed by pancreatic enzymes. These choline esters include phosphocholine (PCho), glycerocephosphocholine (GPCho), phosphatidylcholine (PtdCho) and sphingomyelin (SM) (Zeisel and Blusztajn, 1994). Choline is absorbed in the small intestine; free choline enters the portal circulation and is mostly taken up by liver (Lekim and Betzing, 1976), whereas lipid-soluble PtdCho and SM enter via lymph and bypass the liver. Therefore, different forms of choline could have different bioavailability (Cheng et al., 1996). All tissues accumulate choline, but uptake by liver, kidney, mammary gland, placenta and brain is of special importance. Kidney accumulates choline and uses it to form betaine and GPCho, both of which are organic osmolytes that allow kidney to reabsorb water from the renal tubule (Burg and Ferraris, 2008).
A small portion of choline is acetylated to ACho by choline acetyltransferase, an enzyme that is highly concentrated in cholinergic nerve terminals, but also in non-nervous tissues such as placenta (Blusztajn and Wurtman, 1983). In brain, the availability of choline limits the rate of ACho synthesis (Cohen and Wurtman, 1975; Blusztajn and Wurtman, 1983; Ulus et al., 1989; Wecker, 1991). Choline taken up by brain might first enter a storage pool, perhaps as the PtdCho in membranes, before being converted to ACho (Blusztajn et al., 1986). This reservoir is important when particular cholinergic neurons fire frequently or when the uptake of choline from the extracellular fluid is inadequate (Cohen et al., 1995). Autopsy of individuals with Alzheimer’s disease showed abnormal phospholipid metabolism (Nitsch et al., 1992), suggesting the importance of phospholipid turnover to brain function.

A major role for choline is the synthesis of membrane phospholipids. The predominant membrane phospholipid is PtdCho, from which SM, another phospholipid, is formed. Both PtdCho and SM play important roles in signal transduction because they are sources of lipid second messengers (Zeisel and Blusztajn, 1994). PtdCho is also required for the formation of lipoproteins, which deliver the triacylglycerol produced by liver to other tissues. Biosynthesis of PtdCho occurs by two pathways (Vance, 1990). First, choline is phosphorylated to PCho, which is then converted to cytidine diphosphocholine (CDP-choline). CDP-choline combines with diacylglycerol to form PtdCho. Alternatively, PtdCho can be synthesized from the PEMT pathway via three sequential methylation events using SAM as the methyl donor. As noted earlier, the PEMT pathway is most active in the liver, but has been identified in many other tissues, including brain and mammary gland (Blusztajn et al., 1985; Yang et al., 1988; Vance et al., 1997). Approximately 70% of the PtdCho in liver derives from the CDP-choline pathway, with the remainder from the PEMT pathway (DeLong et al., 1999). These two pathways produce different species of PtdCho, which have different physical properties and generate different signaling molecules (DeLong et al., 1999).

Choline contributes methyl groups after conversion to betaine (Niculescu and Zeisel, 2002). Choline is oxidized to betaine aldehyde and then to betaine by choline dehydrogenase (CHDH) and betaine aldehyde dehydrogenase (BADH), respectively, in the inner mitochondrial membrane (Lin and Wu, 1986). Liver and kidney are the major sites for choline oxidation. Because betaine cannot be reduced back to choline, the oxidation pathway commits choline to use for methylation pathway and diminishes the availability of choline for the alternative PtdCho synthesis pathway.

14.1.4 Choline, folate and methionine metabolism are inter-related

The methylation pathway of choline interacts with folate pathway at the step when Hcy is converted to Met (Finkelstein, 2000). Betaine:homocysteine methyltransferase (BHMT) uses betaine as the methyl donor, converting Hcy to Met. Alternatively, methionine synthase (MS) uses methyl-folate and vitamin B12 to convert Hcy to Met. Although little is known of its function, a novel enzyme BHMT-2 has been identified that uses S-methylmethionine (SMM), a derivative of Met, as a methyl donor to regenerate Met from Hcy (Szegedi et al., 2008). Methionine is the precursor for SAM, a methyl donor for various cellular events, including DNA and histone methylation. Perturbation of either MS or BHMT pathway, by nutrient deficiency or by mutations in genes involved in these pathways, results in elevated plasma Hcy concentration (Varela-Moreiras et al., 1995)
and in compensatory changes in the other methyl donor pathway (Selhub et al., 1991; Varela-Moreiras et al., 1992). It also results in a reduction of tissue concentration of SAM (Zeisel et al., 1989), which could have potential epigenetic effects (discussed later). That several parallel pathways are evolutionally conserved to regulate the level of Hcy and to ensure an adequate supply of SAM demonstrates the importance of these compounds.

14.1.5 Choline deficiency

Choline deficient humans develop fatty liver (Zeisel, 2000) owing to a lack of PtdCho limiting export of excess triglyceride from liver via very low density lipoprotein (VLDL) (Yao and Vance, 1988). Choline deficiency in humans is also associated with liver damage, characterized by elevated serum aminotransferases (Zeisel, 2000), enzyme that is released into blood stream when liver cells die. Choline deficiency in human can also present with muscle damage, characterized by elevated serum creatine phosphokinase (da Costa et al., 2004), or present with DNA damage and death in peripheral lymphocytes (da Costa et al., 2006b). Choline deficient humans are likely to accumulate Hcy, a risk factor for heart diseases, after a methionine rich diet (da Costa et al., 2005). In addition, women who have lower choline intakes during pregnancy have significantly increased risk of giving birth to a child with a neural tube defect (Velzing-Aarts et al., 2005). Women who have lower dietary intakes of choline could have an increased risk and mortality from breast cancer (Xu et al., 2008, 2009).

In animals, choline deficiency results in liver cell proliferation, apoptosis, and transformation into cancer cells (Newberne and Rogers, 1986). Choline deficiency compromises renal function, with abnormal concentrating ability, free water reabsorption, sodium excretion, glomerular filtration rate, renal plasma flow, and gross renal hemorrhage (Zeisel and Blusztajn, 1994). These signs appear to be owing to the lack of betaine, a choline derivative and an organic osmolyte crucial for normal renal function. Finally, choline deficiency during fetal development has been shown to affect learning and attentional processes throughout the lifespan (Meck et al., 1988, 1989; Meck and Williams, 1997abc).

14.1.6 Factors influencing choline requirement

There are not sufficient data to set an Estimated Average Requirement (EAR), and thus no calculation for a Recommendation Dietary Allowance (RDA) for choline. Instead, in 1998, the Food and Nutrition Board of the US Institute of Medicine established an adequate intake (AI) for choline of 550 mg/day for men and 425 mg/day for women and a tolerable upper intake limit (UL) for adults at 3.5 g/day (Institute of Medicine and National Academy of Sciences USA, 1998). The requirement increases to 450 mg/day and 500 mg/day for pregnancy and lactation, respectively. The main criterion for establishing the AI for choline is to prevent liver damage, whereas the UL is to prevent effects of excess choline such as hypotension and fish body odor. Factors such as gender, menopausal status, pregnancy, lactation and genetic mutation can affect choline requirement. As more information becomes available, we expect that these recommendations could be revised upwards, because approximately 10% of subjects in a human study needed
approximately 850 mg choline/day (2× as much as the requirement) to avoid fatty liver, liver and muscle damage (Fischer et al., 2007).

14.1.6.1 Gender, menopausal status, pregnancy and lactation

Fifty-six percent of premenopausal women did not develop signs of choline deficiency when deprived of dietary choline for up to 42 days, whereas most adult men and postmenopausal women did (da Costa et al., 2004, 2005; Fischer et al., 2007). Premenopausal women require less dietary choline because estrogen induces the PEMT gene, thereby enhancing the de novo biosynthesis of choline moiety (see earlier discussion of PEMT). Estrogen binds to its receptors, ERα and ERβ, which bind to estrogen response elements (EREs) in the promoters of the PEMT gene, resulting in an up-regulation in PEMT mRNA expression and increased hepatic enzyme activity (Ressegue et al., 2007). Estrogen as the mediator of increasing PEMT activity in women is important, particularly during pregnancy when the fetus develops; estrogen concentration rises from 1 to 60 nM during pregnancy (Sarda and Gorwill, 1976; Adyemo and Jeyakumar, 1993), suggesting that capacity for endogenous synthesis of choline should be highest at the end of pregnancy when choline is most needed by the fetus.

Pregnancy and lactation are stages that demand high dietary choline intake and leave mothers extremely vulnerable to choline deficiency. During pregnancy, placenta stores choline as ACho and delivers large amounts of choline to the fetus (Leventer and Rowell, 1984). In utero, the fetus is exposed to very high choline concentrations, with a progressive decline in blood choline concentration in the offspring until adult levels are achieved after the first weeks of life (McMahon and Farrell, 1985). Plasma or serum choline concentrations are 6–7× higher in the fetus and newborn than they are in adults (Zeisel and Wurtman, 1981; Ozarda Ilcol et al., 2002). High circulating choline in the neonate ensures the availability of choline to tissues. The neonate has a particularly high capacity for choline transport across the blood-brain barrier to the brain (Cornford and Cornford, 1986). There is also a novel form of PEMT in neonatal brain (not in adult brain) (Blusztajn et al., 1985), accompanied by sufficient SAM to enable PEMT to maintain high rates of activity (Hoffman et al., 1979). These multiple mechanisms for providing choline to fetal brain suggest the importance of choline during fetal development.

14.1.6.2 Gene polymorphism and choline requirement

Although premenopausal women are more resistant to choline deficiency, a significant portion of them (44%) still develop organ dysfunction when deprived of choline, suggesting individual differences in susceptibility to choline deficiency. In fact, some men and women require more than 850 mg/70 kg per day choline in their diet, whereas others require less than 550 mg/kg per day (Fischer et al., 2007). Genetic variation probably underlies the differences in dietary requirements. Choline is involved in several metabolic pathways, and mutations of genes (single-nucleotide polymorphism; SNP) in these pathways can influence the metabolism choline and an individual’s choline requirement.

Only a few reports investigate whether SNPs in the genes involved in one-carbon metabolism have roles in choline requirements (Kohlmeier et al., 2005; da Costa et al., 2006a). Premenopausal women with 5,10-methylenetetrahydrofolate dehydrogenase (MTHFD1 rs2236225) SNP were 15× more susceptible to choline deficiency
than non-carriers (Kohlmeier et al., 2005). This variant increases the use of choline perhaps by limiting the availability of methyl-folate for Hcy remethylation and increasing the demand for choline as a methyl-group donor. In addition, individuals with PEMT rs12325817 or CHDH rs12676 SNPs were much more susceptible to choline deficiency, and women harboring these SNPs were affected more than were men (da Costa et al., 2006a). Conversely, CHDH rs9001 had a protective effect (da Costa et al., 2006a). SNPs in the PEMT gene might alter endogenous synthesis of choline, and SNPs in CHDH could change the utilization of the choline moiety.

Genetic variance can influence the efficiencies of choline pathways and have effects on choline requirement. It is important to take genetic variation into consideration when setting a dietary choline requirement.

14.1.7 Choline and developing brain

In early pregnancy, choline is needed for normal neural tube closure. Inhibition of choline uptake and metabolism is associated with the development of neural tube defects (NTDs) in mice (Fisher et al., 2001, 2002). This might also be true in humans. In California, women with low dietary folate intake, those who consumed the lowest amount of periconceptional dietary intake of choline had 4× the risk of having a baby with a NTD than did women who consumed the highest amount (Shaw et al., 2004). It is further shown in folate fortified population that low intake of choline is a risk factor, whereas high intake of choline is a protective factor for NTDs (Shaw et al., 2009).

Although no human studies are available, animal studies have shown that choline is crucial for the development of the hippocampus, the memory center of brain. Choline supplementation to pregnant rodent dams during later pregnancy and in the early postnatal period (the periods when neurogenesis and synaptogenesis occur) results in memory changes that extend throughout the life-span of the offspring pups, and prevents the memory decline normally observed in aged rats (Meck et al., 1988; Meck and Williams, 1997a,b,c, 1999, 2003; Williams et al., 1998). Interestingly, offspring of rat dams treated with supplemental choline during late pregnancy had greater improvement in memory (compared with controls) than did offspring of mothers supplemented during the early postnatal period (Meck et al., 1988), suggesting that late pregnancy might be a more sensible window for the effect of choline supplementation. Rats born of choline supplemented dams also had enhanced memory precision (less interference of new memory in current tests by the memory from previous tests) and were able to process memory more efficiently (Meck and Williams, 1997a,b,c; Meck and Williams, 1999). Also, supplemental choline in utero enhanced electrical properties of brain such as long-term potentiation (LTP) in the offspring (Pyapali et al., 1998). Remarkably, the memory enhancement by choline supplementation during these crucial periods lasted throughout the life-span. Adult rodents have a decrement in memory as they age; however, offspring exposed to extra choline in utero did not show this decline in cognitive function (Meck and Williams, 1997a,b,c; Meck and Williams, 2003). Also, choline exposure, in utero, attenuated age-related declines in exploratory behavior (Glenn et al., 2008).

The association between pre- and postnatal choline supplementation and brain function in humans has not yet been studied. However, the evidence from the animal studies could provide insights to how choline supplementation during these critical windows...
(pre- and early postnatal) can affect brain development and memory function. Moreover, prenatal or postnatal choline supplementation has also been explored as a potential therapeutic agent for several cognitive diseases using rodent models (see below).

### 14.1.8 Choline and other cognitive diseases

Fetal alcohol syndrome (FAS) occurs in 1 in every 750 infants born each year in the USA (Clarren et al., 2001). Rats exposed to alcohol neonatally had poor performance on memory tasks, and this was ameliorated by either prenatal or postnatal choline supplementation (Thomas et al., 2004, 2009). Rett syndrome is a neurodevelopmental disorder in the autism spectrum of disease, and is sometimes associated with mutations in the methyl-CpG-Binding protein 2 (MeCP2) gene (Nag et al., 2008; Ward et al., 2009). It is the second leading cause of mental retardation in girls (Nag et al., 2008; Ward et al., 2009). In mouse models of Rett syndrome (where the gene MeCP2 has been deleted), prenatal or postnatal choline supplementation attenuated the motor coordination deficits and improved neuronal integrity, proliferation and survival (Nag et al., 2008; Ward et al., 2009). Choline supplementation might ameliorate the symptoms of traumatic brain injury (TBI) (Guseva et al., 2008), status epilepticus (Yang et al., 2000; Holmes et al., 2002; Wong-Goodrich et al., 2008) and schizophrenia (Stevens et al., 2008) in rodent model systems. Again, no equal experiments in humans are found.

### 14.1.9 Choline and epigenetics

The mechanism whereby choline manipulation during pregnancy results in permanent changes in memory of the fetus remains unknown. In adults, it is thought that increased dietary choline intake results in increased the synthesis and release of ACho. However, this is not likely to be the case in fetuses, because choline supplementation to dams resulted in the accumulation of PCho and betaine in the fetal brain rather than choline and ACho (Garner et al., 1995).

The term ‘epigenetics’ defines heritable changes in gene expression that are not coded in the DNA sequence itself. Epigenetic mechanisms can be mediated by DNA methylation and histone modifications that are read as signals that change gene expression. DNA methylation occurs predominantly at the cytosine bases followed by a guanosine (CpG) and when it occurs in the promoter regions (regions that regulate DNA expression) the expression of the associated gene is altered (Bird, 1986; Jeltsch, 2002). Although there are exceptions, increased DNA methylation is usually associated with gene silencing, whereas decreased methylation is associated with increased gene expression (Fukuyama et al., 2005). Histones are proteins around which DNA is tightly wound, forming the dynamic structure called chromatin. Chromatin can either be in an inactive state or in an active state in which transcription factors can pass through histones and bind to DNA (Quina et al., 2006). Histone acetylation predominantly promotes active chromatin, whereas histone methylation can be associated with both transcriptionally active and inactive chromatin (Kim et al., 2009). Furthermore, the degree of methylation (mono-, di- or tri-methylation) results in different effects on chromatin state (Rice et al., 2003).

Methylation of DNA and histones requires SAM as the methyl-donor for the methylation of cytosines in DNA and lysine and arginine residues in histones, respectively.
The availability of SAM is directly influenced by dietary choline. In rodents, choline deficiency or disturbance of choline pathways results in depletion of SAM and elevation of $S$-adenosylhomocysteine (SAH) (Zeisel et al., 1989). The SAM:SAH ratio modulates methylation enzyme activity; low SAM:SAH ratio inhibits the activities of DNA and histone methyltransferases. In cell and rodent models, methylation of genes that inhibit cell cycling is decreased during choline deficiency, resulting in over-expression of the inhibitory genes causing decreased progenitor cell proliferation and increased apoptosis in the fetal hippocampus (Niculescu et al., 2004, 2005). Gestational choline availability also affects histone methylation in the developing embryo, resulting in changes in gene expressions, primarily genes that regulate methylation and neuronal cell differentiation (Davison et al., 2009).

There are other examples where methyl groups in maternal diets have permanent effects on their offspring via epigenetic effects. Feeding pregnant Psudoagouti Avy/a mouse dams a methyl-supplemented diet altered epigenetic regulation of agouti expression in their offspring, as indicated by increased agouti/black mottling of their coats (Loff et al., 1998; Cooney et al., 2002). In another example, methyl donor supplementation to dams increased DNA methylation of the fetal gene $\text{axin fused (Fu)}$ and reduced the incidence of tail kinking in offspring by 50% (Waterland et al., 2006). It is clear that the dietary manipulation of methyl donors (either deficiency or supplementation) can have a profound impact upon gene expression and, consequently an impact on normal physiological processes and on human diseases.

### 14.1.10 Choline and cancer

Choline is the only nutritional deficiency that causes liver cancer without any known carcinogen (Newberne and Rogers, 1986). In rodents, choline deficiency results in a higher incidence of spontaneous hepatocarcinomas (liver cancer) (Newberne and Rogers, 1986). Several mechanisms are suggested for its carcinogenic effects. Choline deficiency increases lipid peroxidation in the liver (Rushmore et al., 1984), which is a source of free radicals in the nucleus that could modify DNA and cause carcinogenesis. Choline deficiency perturbs protein kinase C (PKC) signaling, resulting in altered cell proliferation signals and cell apoptosis and eventually in carcinogenesis (da Costa et al., 1993). Epigenetic alterations also might mediate the mechanisms that underlie the etiology of cancers. Methyl deficiency results in hypomethylation of some genes but also paradoxically hypermethylation of CpG islands in specific genes (e.g., tumor suppressor genes) that are associated with gene silencing (Jones and Baylin, 2002; Feinberg and Tycko, 2004), leading to tumor development. Histone modifications also occur in methyl deficiency in various models of cancer (Pogribny et al., 2007; Dobosy et al., 2008; Davison et al., 2009).

Only a handful of epidemiologic studies explore how choline and betaine intakes alter cancer risk at the population level. The Long Island Breast Cancer Study Project found that high choline consumption reduced breast cancer risk (Xu et al., 2008), and high choline and betaine consumption reduced breast cancer mortality (Xu et al., 2009). Moreover, individuals with single nucleotide polymorphisms in genes of choline metabolism ($\text{PEMT rs12325817 SNP}$) had higher risk of developing breast cancer, whereas people with a polymorphism in choline metabolism gene $\text{BHMT rs3733890}$ had lower breast cancer mortality. These data suggest the importance of nutrients and
genetic interactions in the etiology of cancer. Alternatively, the Nurse’s Health Study II found no association between choline intake and breast cancer risk (Cho et al., 2007a), but a positive association between choline intake and colorectal cancer risk (Cho et al., 2007b), suggesting different etiologies between breast and colorectal cancer. More research is warranted.

### 14.1.11 Choline and heart disease

Choline and betaine might benefit heart health by reducing plasma Hcy, a risk factor for heart disease (Zeisel, 1981). Dietary choline intake was inversely related to circulating Hcy concentrations in the Framingham Heart Study (Cho et al., 2006) and in the Nurse’s Health Study (Chiuve et al., 2007), suggesting a protective effect of choline intake. However, when looking at the association between dietary choline intake and heart disease incidence, no association was found in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (Dalmeijer et al., 2008), and a marginal positive association was found in the Atherosclerosis Risk in Communities (ARIC) study (Bidulescu et al., 2007). It is important to note that in the ARIC study, the majority of individuals in the cohort had choline intake below the AI (Bidulescu et al., 2009). Hence, the effects of choline supplementation on heart disease risk remains unclear. Some human studies suggested that betaine supplementation increases plasma low-density lipoprotein (LDL)-cholesterol and triacylglycerol concentrations (McGregor et al., 2002; Schwab et al., 2002; Olthof et al., 2005), effects that might counterbalance its Hcy lowering effects. However, the changes in serum lipid concentrations were not associated with higher risk of heart disease. Moreover, the rise in LDL concentration could be an artifact of increasing VLDL and triacylglycerol excretion from fatty liver to plasma, which is not an adverse outcome (for a critical review see Zeisel, 2006b). The relation between choline and heart health warrants more study.

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14.2 Choline in fetal programming

Jan Krzysztof Blusztajn

14.2.1 Introduction

The fields of basic and applied nutritional sciences have evolved from a traditional focus on deficiency states to a broader interest in improving health and quality of life. There are several challenges and novel concepts associated with this paradigm. These include: (1) nutrigenetics – how the genome of an organism governs its response to a nutrient; (2) nutrigenomics – how the nutrient interacts with the genome to modulate gene expression patterns; and (3) nutriepigenomics – how a nutrient influences the epigenome and thus modulates gene expression patterns. This chapter aims to illustrate some of these concepts using the nutrient, choline, as an example. With the recent advances in the studies of human genome and the possibility of correlating gene polymorphisms (particularly single nucleotide polymorphisms, SNPs) with phenotype, considerable progress in the field of human choline nutrigenetics is being made. This information is summarized here. In many other areas, the only available data derive from studies in animal models. In particular, this chapter will: (1) present information on how dietary choline during pregnancy in rodents influences (‘programs’) the phenotype of offspring; and (2) propose that a nutriepigenomic mechanism is probable.

14.2.2 Choline, an essential nutrient for humans

Choline was added to the list of essential nutrients recently. It was only in 1998 that the Food and Nutrition Board (FNB) of the Institute of Medicine of the National Academy of Sciences of the United States of America recognized that for the maintenance of normal health, humans needed to obtain choline from the diet and issued guidelines on its daily intake (FNB, 1998). Because at that time, and perhaps to this day, there were insufficient data to generate Reference Daily Intake (RDI) values, the FNB issued Adequate Intake (AI) recommendations (Table 14.1). The AI calls for the average intake of 7.5 mg of choline daily per kg of body weight. Notably, the AI is increased for pregnant and breastfeeding women to satisfy the needs of the fetus and baby whose choline is supplied via placenta (Garner et al., 1995) and milk (Zeisel et al., 1986; Holmes-McNary et al., 1996), respectively. The AI values were established primarily to ensure that dietary choline is sufficient to prevent liver dysfunction associated with low choline consumption.