Review

CellPress

Maternal choline supplementation: a nutritional approach for improving offspring health?

Xinyin Jiang[1], Allyson A. West[2], and Marie A. Caudill[2]

[1] Department of Health and Nutrition Sciences, Brooklyn College, Brooklyn, NY 11210, USA
[2] Division of Nutritional Sciences, Cornell University, Ithaca 14853, NY, USA

The modulatory role of choline on the fetal epigenome and the impact of *in utero* choline supply on fetal programming and health are of great interest. Studies in animals and/or humans suggest that maternal choline supplementation during pregnancy benefits important physiologic systems such as offspring cognitive function, response to stress, and cerebral inhibition. Because alterations in offspring phenotype frequently coincide with epigenetic modifications and changes in gene expression, maternal choline supplementation may be a nutritional strategy to improve lifelong health of the child. Future studies are warranted to elucidate further the effect of choline on the fetal epigenome and to determine the level of maternal choline intake required for optimal offspring physiologic function.

Choline and its role in fetal development

The essential nutrient choline participates in several vital biological functions (see Figure I in Box 1) with key roles in fetal development [1]. During development, choline phospholipids (i.e., phosphatidylcholine and sphingomyelin) are required in large amounts for membrane biogenesis, myelination of nerve axons, cell division, tissue expansion, and lipid transport [2]. In addition, the choline-derived neurotransmitter, acetylcholine, is essential for proper organization and function of the developing brain through its effects on neurogenesis and synapse formation [3]. Notably, large amounts of acetylcholine are produced and accumulate in human placenta (see Glossary) where it functions as a signaling molecule to influence cellular differentiation and proliferation as well as parturition [4]. Finally, betaine, an oxidized metabolite of choline, is a source of methyl groups for the production of *S*-adenosylmethionine (SAM), which serves as a substrate for DNA and histone methyltransferases (Box 1), and is thus required for the establishment and maintenance of the fetal epigenome [5–10].

During pregnancy, maternal choline intake can affect metabolic and physiologic function of the offspring through a variety of inter-related mechanisms. With the overall goal of examining whether maternal choline supplementation

Glossary

Adequate intake (AI): a recommended average daily nutrient intake level that is established when a Recommended Dietary Allowance (RDA) cannot be determined due to insufficient data. The main criterion for establishing the choline AI was prevention of liver damage.
Angiogenesis: the process of growing new blood vessels. Placental angiogenesis is complex with several angiogenic factors, including sFLT1 and VEGF, playing important roles. Perturbations in placental angiogenesis can impair placental and maternal vasculature function with downstream adverse effects on fetal and maternal health.
Down syndrome: also known as trisomy 21, is a genetic disorder resulting from the triplication of chromosome 21. The disorder is associated with aberrant neurological symptoms, which result in intellectual disability and early onset dementia.
Hippocampus: a part of the brain that plays an important role in information consolidation, short- and long-term memory formation, attention and spatial navigation.
Hypothalamic–pituitary–adrenal (HPA) axis: the neuroendocrine feedback interactions between the hypothalamus, the pituitary gland, and the adrenal glands that regulate several bodily functions, including stress reactivity, digestion, immune system function, and energy expenditure.
Insulin-like growth factor 2 (IGF2): a growth factor that promotes placental and fetal cellular growth and division. It is encoded by an imprinted gene which is expressed only from the paternal allele. In mice, *Igf2* expression is regulated by CpG methylation of the differentially methylated region 2 (DMR2) located within the last coding exon of *Igf2*. DMR2 methylation generates an active chromatin conformation which increases *Igf2* gene expression.
One-carbon metabolism: the transfer of activated one-carbon units (e.g., methyl groups). Choline functions in one-carbon metabolism as a source of methyl groups through its oxidative products betaine, dimethylglycine, and sarcosine. Other nutrients with important roles in mediating the transfer of one-carbon units include methionine, folate, vitamin B12, vitamin B6, and riboflavin.
Placenta: a fetus-derived tissue connecting the fetus to the maternal uterine wall. The placenta exchanges nutrients, metabolic substrates, and respiratory gases between maternal and fetal circulation. In addition, the placenta is an endocrine organ that secretes several hormones, including corticotropin releasing hormone (primate placentas).
Preeclampsia: a serious medical condition of pregnancy characterized by high blood pressure and proteinuria. Preeclampsia and its complications may persist into the post-partum period; treatments to control preeclampsia include antiplatelet and antihypertensive medications. The pathogenesis of preeclampsia is not entirely clear; however, an imbalance between pro- and anti-angiogenic factors in the maternal vasculature may play a role.
Schizophrenia: a brain disorder characterized by psychotic behaviors, hallucinations, delusions, and impaired cognitive function. The etiology of schizophrenia is complex and likely includes both genetic and environmental components. Brain chemistry, structure, and function are altered with schizophrenia.
Sensory gating: describes the capacity of the brain to filter out repeat and/or unimportant environmental stimuli. Cerebral inhibition, a measure of sensory gating, is evaluated by comparing the electrophysiologic response to a pair of repeated auditory stimuli, with a weaker response to the second stimulus versus the initial stimulus, indicating cerebral inhibition. Diminished sensory gating/cerebral inhibition (i.e., inability to ignore repeat stimuli) is a trait associated with schizophrenia and inattention.

Corresponding author: Caudill, M.A. (mac379@cornell.edu).
Keywords: choline; development; epigenetics; fetus; programming.

1043-2760/$ – see front matter
 http://dx.doi.org/10.1016/j.tem.2014.02.001

Box 1. The role of choline in methylation

To serve as a methyl donor, choline is first oxidized to betaine via a two-step reaction mediated by choline dehydrogenase and betaine aldehyde dehydrogenase (Figure I). One of the three methyl groups associated with betaine is subsequently transferred to homocysteine, forming methionine and dimethylglycine in a reaction catalyzed by betaine homocysteine *N*-methyltransferase (BHMT). The methionine produced by homocysteine remethylation can then be converted to *S*-adenosylmethionine (SAM), which is the universal methyl donor that transfers its methyl group to various molecules, including DNA, proteins, and lipids, using over 50 methyltransferases. Because *BHMT* is only expressed in liver and to a lesser extent kidney, the use of betaine/choline as a methyl donor mainly occurs in these two organs. However, choline-derived methyl groups are made available to other tissues following their uptake of plasma methionine and SAM – which were initially generated via the hepatic or renal BHMT reaction [32,36,37].

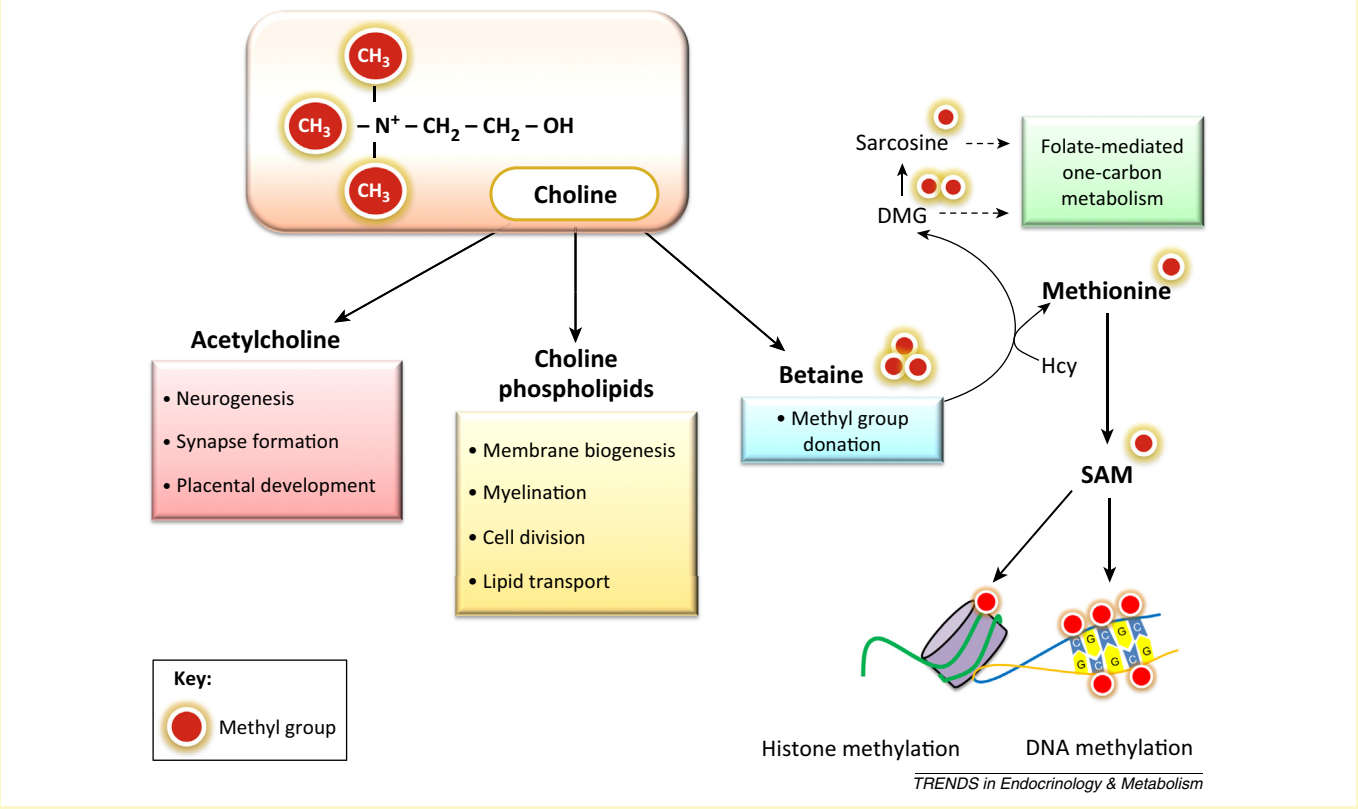

Figure I. Biological functions of choline. Choline is the substrate for the synthesis of acetylcholine, phospholipids (e.g., phosphatidylcholine and sphingomyelin), and betaine. The functions of these choline derivatives are listed in their respective boxes. Betaine donates a methyl group to homocysteine (Hcy) to form methionine, which is converted to the universal methyl donor *S*-adenosylmethionine (SAM) and dimethylglycine (DMG). SAM-derived methyl groups are used for the synthesis of several metabolites (e.g., creatine, neurotransmitters, hormones, phosphatidylcholine) and for the methylation of DNA and histones. DMG and its demethylated derivative, sarcosine, may then be used as a source of one-carbon units for folate-mediated one-carbon metabolism.

may be a nutritional strategy for improving offspring health, this article will assess: choline-mediated changes on the fetal epigenome and on gene expression and thus fetal development; the supply of, and demand for, choline during pregnancy; and the impact of maternal choline supplementation on offspring physiologic systems.

Maternal choline affects the fetal epigenome and developmental programming

The prenatal period is associated with the establishment and maintenance of the epigenome (Box 2). Following conception, DNA methylation patterns of gametes are mostly abolished, and *de novo* methylation is required to establish an appropriate gene-silencing pattern. DNA methylation is tightly linked to histone modifications through the activities of methyl-binding proteins and histone-modifying proteins which, together with DNA methylation, orchestrate the spatial- and time-sensitive epigenomic alterations that occur during fetal development [11].

The fetal epigenome exhibits substantial plasticity: it can be altered by various maternal environmental factors including nutrition (e.g., starvation, methyl donor supply, protein availability) [12–14], maternal stress [15], seasonality [16], pollutants and chemicals (e.g., bisphenol A, lead, arsenic, or pesticides) [17–20], and substance abuse (e.g., alcohol and tobacco) [21,22]. The environmental conditions of the fetus can profoundly influence its biology and long-term health, a process known as developmental programming of adult disease. The pathways most sensitive to programming by *in utero* exposures include those related to cardiovascular diseases [23], type 2 diabetes [24,25], obesity [26], immunological diseases [27], and neural function [28]. Interestingly, developmental programming of adult disease differs between male and female offspring with males often exhibiting greater sensitivity to the maternal *in utero* environment [29–31].

Maternal choline supply during pregnancy has been shown to modify the epigenome of fetal liver [8,10] and brain [5,6,10] in animals, as well as the placenta and fetal