Editorial

Betaine a potent mediator of metabolic programming?

Volume 2 Issue 1 - 2015

Xinyin Jiang
Department of Health and Nutrition Sciences, City University of New York, USA

Correspondence: Xinyin Jiang, Department of Health and Nutrition Sciences, Brooklyn College, City University of New York, 2900 Bedford Ave. Brooklyn, NY 11210, USA, Tel (718)9512738, Fax (718)9514670, Email xinyinjiang@brooklyn.cuny.edu

Received: December 23, 2014 | **Published:** January 23, 2015

Editorial

Metabolic programming is described as the long-lasting impacts that the antenatal environment exerts on the biological functions and health outcomes of an individual organism in later life. The potential role of betaine as a mediator of metabolic programming has garnered much more attention recently. Betaine, or trimethylglycine, is a bioactive product present in a variety of foods such as wheat, spinach, sugar beets and seafood. It can also be derived from the oxidation of choline, a semi-essential nutrient. Betaine serves as a major osmolyte and methyl donor in the body. To serve as a methyl donor, betaine donates one of its labile methyl groups to homocysteine, which remethylates homocysteine to methionine. After methionine is converted to the universal methyl donor S-adenosylmethionine, the betaine-derived methyl group is used for methylation reactions such as DNA and histone Methylation.[1] DNA and histone methylating reactions are major epigenetic events, which produce heritable changes in gene expression without altering DNA sequence. As epigenetics is considered as the cornerstone mechanism by which prenatal nutrition exerts its lasting influence on offspring health, betaine is speculated to affect the process of metabolic programming by serving as an epigenetic modifier.

Altered betaine status during pregnancy has been observed for a long time. Plasma concentrations of betaine decline until gestational week 20and then remain stable in humans. Plasma betaine is a strong negative predictor of homocysteine in the second half of pregnancy, suggesting the increased use of betaine in the methylation cycle.[2] Only a handful of studies have examined the relationship between betaine status and birth outcomes in humans, including a prospective study showing a positive correlation between maternal plasma betaine concentrations in the second trimester of pregnancy and better infant cognitive test scores at 18months of age.[3] The specific effects of betaine intake or supplementation on fetal metabolic programming remain largely unexplored.

Three recent studies investigated the influence of maternal betaine supplementation on fetal growth and lipid and glucose metabolism in rodent models, which shed light on the role of betaine in metabolic programming. The study by Alirezaei et al.,[4] evaluated the nutritional impact of betaine on the weight and length of rat offspring. Female Sprague-Dawley rats were given ethanol (4g/kg body weight), betaine (1.5% w/w of diet), betaine plus ethanol or normal saline for 1month before mating. Betaine supplemented pups had significantly higher weight and length than other pups on embryonic day 19, which suggests that betaine is a fetal growth-promoting factor. Two studies by Cai et al. investigated the effects of maternal betaine supplementation on hepatic expression of cholesterol metabolic genes and gluconeogenic genes in newborn piglets.[5,6] Sows were supplemented with 3g/kg of betaine or fed with a control diet throughout pregnancy in both studies. Messenger RNA and protein expression of several cholesterol metabolic genes such as 3-hydroxy-3-methylglytaryl CoA reductase (HMGCR) and gluconeogenic genes such as phosphoenolpyruvate carboxykinase (PEPCK) in newborn piglets was found to be altered by maternal betaine supplementation. Interestingly, such alterations in gene/protein expression were associated with changes in corresponding promoter DNA and histone methylation marks, indicating that the programming effect of betaine was indeed mediated by serving as a methyl donor. Relevant human studies on betaine and prenatal programming are still lacking, although supplementation of choline, the precursor of betaine, has been shown to increase placental DNA methylation and reduce fetal stress reactivity.[7]

The questions remain as to what biological pathways are susceptible to prenatal betaine exposure that we should explore in future studies and whether there are additional mechanisms besides epigenetic modifications which explain the effects of betaine. Based on the three aforementioned studies, glucose tolerance and lipid homeostasis seem to be responsive to prenatal betaine administration, and indeed, the crosstalk between betaine and macronutrient metabolism in non pregnant animals has been utilized since manyyears ago when betaine was added as a feed additive to increase yield of leaner meat in livestock.[8] Such effect of betaine as a "carcass modifier" may be explained by the sparing of methionine from the methylation cycle for somatic protein production.[1] Betaine has also been shown to improve non-alcoholic fatty liver disease and insulin resistance in adult animals by facilitating fat export from the liver, decreasing fatty acid synthesis, activating components of insulin signaling, and maintaining normal mitochondrial function.[8] These mechanisms beyond epigenetic modifications may also be relevant to the betaine-mediated metabolic programming at birth and in adulthood.

In conclusion, betaine is a promising mediator of metabolic programming by serving as a methyl donor and influencing several aspects of macronutrient metabolism. Future studies should be focused on further delineating the long-term impacts of betaine on pathways susceptible to metabolic programming. Human studies are warranted to confirm findings from animal models and determine the efficacy of prenatal betaine supplementation in improving health outcomes, such as lowering incidence of type 2diabetes and obesity in the long term.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

References

1. Craig SA. Betaine in human nutrition. *Am J Clin Nutr.* 2004;80(3):539–549.
2. Molloy AM, Mills JL, Cox C, et al. Choline and homocysteine interrelations in umbilical cord and maternal plasma at delivery. *Am J Clin Nutr.* 2005;82(4):836–842.
3. Wu BT, Dyer RA, King DJ, et al. Early second trimester maternal plasma choline and betaine are related to measures of early cognitive development in term infants. *PLoS One*. 2012;7(8):e43448.
4. Alirezaei M, Jelodar G, Niknam P, et al. Nutritional effects of betaine on weight and length of rat offspring. *Comp Clin Pathol.* 2014;23:551–556.
5. Cai D, Jia Y, Song H, et al. Betaine supplementation in maternal diet modulates the epigenetic regulation of hepatic gluconeogenic genes in neonatal piglets. *PLoS One*. 2014;9(8):e105504.
6. Cai D, Jia Y, Lu J, et al. Maternal dietary betaine supplementation modifies hepatic expression of cholesterol metabolic genes via epigenetic mechanisms in newborn piglets. *Br J Nutr*. 2014;112(9):1459–1468.
7. Jiang X, Yan J, West AA, et al. Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans. *FASEB J.* 2012;26(8):3563–3574.
8. Zeisel SH. Metabolic crosstalk between choline/1-carbon metabolism and energy homeostasis. *Clin Chem Lab Med.* 2013;51(3):467–475.