Neuroscience and Biobehavioral Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

One-carbon metabolism in neurodevelopmental disorders: Using broad-based nutraceutics to treat cognitive deficits in complex spectrum disorders

Q1 Laura Schaevitz [a], Joanne Berger-Sweeney [a], Laura Ricceri [b,*]

[a] School of Arts and Sciences, Tufts University, MA, USA
[b] Section of Neurotoxicology and Neuroendocrinology, Dept Cell Biology and Neuroscience, Istituto Superiore di Sanità, Rome, Italy

ARTICLE INFO

Article history:
Received 12 November 2013
Received in revised form 7 March 2014
Accepted 15 April 2014

Keywords:
Folate supplementation
Choline supplementation
Neurodevelopment

ABSTRACT

Folate and choline, two nutrients involved in the one-carbon metabolic cycle, are intimately involved in regulating DNA integrity, synthesis, biogenic amine synthesis, and methylation. In this review, we discuss evidence that folate and choline play an important role in normal cognitive development, and that altered levels of these nutrients during periods of high neuronal proliferation and synaptogenesis can result in diminished cognitive function. We also discuss the use of these nutrients as therapeutic agents in a spectrum of developmental disorders in which intellectual disability is a prominent feature, such as in Fragile-X, Rett syndrome, Down syndrome, and Autism spectrum disorders. A survey of recent literature suggests that nutritional supplements have mild, but generally consistent, effects on improving cognition. Intervening with supplements earlier rather than later during development is more effective in improving cognitive outcomes. Given the mild improvements seen after treatments using nutrients alone, and the importance of the genetic profile of parents and offspring, we suggest that using nutraceutics early in development and in combination with other therapeutics are likely to have positive impacts on cognitive outcomes in a broad spectrum of complex neurodevelopmental disorders.

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* Corresponding author.
E-mail address: laura.ricceri@iss.it (L. Ricceri).

http://dx.doi.org/10.1016/j.neubiorev.2014.04.007
0149-7634/© 2014 Published by Elsevier Ltd.

1. Background

Our knowledge about the underlying anatomical and neurochemical basis of intellectual disability has come, in part, from the study of individuals and animal models with known genetic mutations that impair cognitive function such as Fragile-X, Rett syndrome, and Down syndrome. Research suggests that, despite disparate affected neurochemical and anatomical pathways, developmental disorders with intellectual disability share several common features including reduced cortical plasticity and early abnormalities in the development of the cerebral cortex (Berger-Sweeney, 2003).

Nutritional factors can impact both the structural development and function of the brain including the cerebral cortex (Anjos et al., 2013). The cerebral cortex in humans is established in utero and continues during the first few years of postnatal life through rapid proliferation of progenitor cells. Beginning at around two years of age, there is large-scale synaptogenesis and reorganization of neural networks in the cortex that continues throughout the teenage years (Huttenlocher and Dabholkar, 1997). Two nutrients, folate and choline, intimately involved in regulating DNA integrity, synthesis, biogenic amine synthesis, and methylation through one-carbon metabolism, likely play important roles in these proliferative and synaptogenic processes. In this review, we discuss the evidence that folate and choline play an important role in normal cognitive development (inadequate intake resulting in diminished cognitive function) and the potential relevance for use of these nutrients as therapeutic agents in developmental disorders in which intellectual disability is prominent (e.g. Fragile-X, Rett syndrome, Down syndrome, and Autism spectrum disorders).

1.1. Folate and methionine cycles

The folate and methionine cycles (Fig. 1) represent a biochemical network playing a pivotal role in DNA synthesis, selected amino acid synthesis and methylation of large (DNA, RNA, proteins, polysaccharides, phospholipids) and small (e.g. glycine) molecules. Folate is a metabolic co-factor that carries one-carbon groups. Folate can be acquired naturally in fresh fruit and vegetables or in two synthetic forms, folic acid (the synthetic oxidized monoglutamyl form of folate used in vitamin supplements and food fortification) and folinic acid (a vitamer that can be transported more readily across the blood-brain barrier and is more similar biologically to natural folate). After being absorbed in the intestines folate and folinic acid are biologically active, whereas folic acid must be reduced by dihydrofolate reductase (DHFR) to dihydrofolate (DHF) and subsequently to tetrahydrofolate (THF) and 5-mTHF (the predominant form of cytoplasmic folate). Dihydrofolate reductase also functions to salvage dihydrobiopterin into tetrahydrobiopterin, a critical co-factor for synthesis of several neurotransmitters including serotonin and the catecholamines. 5-mTHF transfers a methyl group to homocysteine yielding methionine, a reaction catalyzed by methionine synthetase (MS) and requiring the B12-derived coenzyme cobalamine. Homocysteine can also be methylated by an alternative pathway utilizing betaine-homocysteine methyltransferase (BHMT); this enzyme [which has been found only in liver and kidney in adult mammals (McKeever et al., 1991)] uses as a substrate betaine, in part derived by choline oxidation catalyzed by choline dehydrogenase (CHDH) that is found exclusively within mitochondria.

Methionine (from homocysteine or from the diet) is then converted to S-adenosyl methionine (SAM) by methionine S-adenosyltransferase (MAT); methylation reactions occur when a methyl group is transferred from SAM to a methyl acceptor molecule. SAM is a universal donor of one-carbon units for many different methylation reactions via specific methyl transferases, including methylation of DNA, phospholipids (conversion of phosphatidyl-ethanolammine to phosphatydil-choline), synthesis and activation of neurotransmitters (e.g. norepinephrine-epinephrine conversion requires SAM as methyl donor), and of creatine, a key component in energy metabolism. After methyl donation, SAM is converted to S-adenosyl-homocysteine (SAH); since SAH inhibits further methylation reactions, the SAM/SAH ratio is an indicator of methylation potential (e.g. a low ratio indicates reduced methylation potential and vice versa) (Grillo and Colombatto, 2008).

Methylation of DNA, through the addition of methyl groups to cytosine residues in CpG dinucleotides, alters transcription of associated genes by changing the ease at which transcriptional machinery can access the DNA. DNA methylation, therefore, is an important mechanism through which epigenetic programming occurs. Epigenetics refers to changes in gene expression that do not alter the DNA sequence. Patterns of DNA methylation regulate a number of essential processes throughout life. During early embryonic development, epigenetic programming regulates essential processes such as X-chromosome inactivation, imprinting and differentiation of cells into tissue subtypes (Feng et al., 2007; Li, 2002) that affect developmental organization of the brain. In the adult, changes in DNA methylation patterns regulate gene transcription in response to neuronal activity and neurotransmitter availability (Axelrod, 1971; Lubin et al., 2011) that affect synaptic plasticity. Altering methylation potential and thereby changing

Please cite this article in press as: Schaevitz, L., et al., One-carbon metabolism in neurodevelopmental disorders: Using broad-based nutraceutics to treat cognitive deficits in complex spectrum disorders. Neurosci. Biobehav. Rev. (2014), http://dx.doi.org/10.1016/j.neubiorev.2014.04.007