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Mathematical modeling of the methionine cycle and transsulfuration pathway in individuals with autism spectrum disorder

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ABSTRACT

Previous research has shown a connection between metabolic abnormalities in the methionine cycle and transsulfuration pathway and autism spectrum disorder. Using clinical data from a case-control study investigating measurements of transmethylation and transsulfuration metabolites, a steady-state model of these metabolites in liver cells was developed and participant-specific parameters were identified. Comparison of mean parameter values and parameter distributions between neurotypical study participants and those on the autism spectrum revealed significant differences for four model parameters. Sensitivity analysis identified the parameter describing the rate of glutamylcysteine synthesis, the rate-limiting step in glutathione production, to be particularly important in determining steady-state metabolite concentrations. These results may provide insight into key reactions to target for potential intervention strategies relating to autism spectrum disorder.

1.Introduction

Autism spectrum disorder (ASD) is a general diagnosis for a group of neurodevelopmental disabilities that appear in the early years of childhood, typically before the age of two (American Psychiatric Association, 2013). Although the disorder can be associated with a large array of symptoms, the two primary criteria for diagnosis of ASD are difficulties with social interaction and communication and the display of restricted, repetitive behaviors (American Psychiatric Association, 2013). The Center for Disease Control's most recent estimate of ASD prevalence among children in the United States is 1 in 68 (Christensen et al., 2016). This is a substantial increase from its 1996 estimate of 1 in 294 (Yeargin-Allsopp et al., 2003), and even more so from international estimates in the early 1970s of approximately 1 in 2300 (Gillberg and Wing, 1999).

The significant rise in ASD prevalence has prompted research into certain risk factors for the disorder. While there is clearly a genetic component involved in the development of ASD (Abrahams and Geschwind, 2008; Bailey et al., 1995; Rai, 2016), recent twin studies indicate that heritability of the disorder is potentially lower than previously estimated (Gaugler et al., 2014; Hallmayer et al., 2011). Environmental factors are also suggested to contribute to increased ASD susceptibility through a variety of mechanisms (Rossignol et al., 2014). For example, a recent study found significant correlations between the concentrations of organic pollutants, such as pesticides, in the blood of children and the severity of ASD-associated behaviors in those children with the disorder potentially also affected by a child's genetic susceptibilities (Boggess et al., 2016). The results of another study indicated a significant association between maternal antidepressant treatment before pregnancy and ASD risk in children (Castro et al., 2016). Correlations have also been found between concentrations of certain toxic metals in blood and urine and ASD severity (Adams et al., 2012, 2016). While there is an ongoing debate on what factors contribute to ASD (and in what capacity), these findings provide evidence that the factors involved in ASD risk are much more complex than just genetic predisposition alone.

Recent research has also pointed to a critical connection between incidence of ASD and irregularities in folate-dependent one-carbon metabolism and transsulfuration. Several studies have found evidence for reduced methylation capacity and increased oxidative stress in people with ASD compared to age-matched controls (Adams et al., 2011; James et al., 2006; Melnyk et al., 2012). Since the metabolic pathways directly responsible for these abnormalities are the methionine cycle and transsulfuration pathway, these results suggest that some dysfunction in these pathways might be associated with ASD. While the methionine cycle is found in all cells in the body, transsulfuration is limited to the liver, pancreas, small intestine, kidney, and brain (Finkelstein and Martin, 2000; Vitvitsky et al., 2006). Combined,

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these pathways have many diverse functions in the human body, including the regulation of gene expression through addition of methyl groups to DNA (Ulrey et al., 2005), myelin protein stabilization in nerve cells (Miller, 2003), and synthesis of glutathione, one of the body's major antioxidants (Wu et al., 2004). Glutathione plays an important role in detoxification and removal of reactive oxygen species in the body. In mammals, glutathione is found in all tissue types, with high concentrations found in the liver (Lu, 1999) where it is primarily synthesized. The main function of glutathione is antioxidant defense against reactive oxygen species, including free radicals (Fang et al., 2002), and detoxification of environmental toxins, including heavy metals (Adams et al., 2011). Metabolic abnormalities and deficiency of glutathione can result in increased intracellular oxidative stress. Studies suggest that elevated levels of oxidative stress are associated with the pathophysiology of a number of diseases, including Alzheimer's disease (Markesbery, 1997), diabetes (Giugliano et al., 1996), and cystic fibrosis (Roum et al., 1993), as well as ASD (James et al., 2006). Although the link between glutathione, oxidative stress, and disease has been well-studied, exact explanations for why these relationships exist have yet to be found (Ballatori et al., 2009).

This paper seeks to contribute to our understanding of how metabolites of the methionine cycle and transsulfuration pathway interact by creating a mathematical model where the probability density functions (PDFs) of the parameter values are determined from clinical data. Detailed models of the methionine cycle and transsulfuration pathway exist (Duncan et al., 2013a, 2013b; Reed et al., 2008, 2004) that include complex nonlinear formulas for the rates of each of the reactions, as well as inhibitory and excitatory effects of metabolites on enzymes. These models have a large number of parameters which cannot all be estimated by measuring only a small number of metabolites in the blood. Instead, we chose to develop a smaller model of the pathways with unidirectional linear kinetics. This model does not have the biological detail of the larger models, but it has the advantage of having only 8 parameters (the kinetic rate constants), which can be determined from clinical data. Estimation of the PDFs of these parameters for both neurotypical study participants and participants with ASD, as well as performing sensitivity analysis on the model, allows for identification of important reactions that could potentially be manipulated for future intervention strategies for ASD.

2.Materials and methods

2.1.Plasma metabolite data

The clinical data used in this model come from the Integrated Metabolic and Genomic Endeavor (IMAGE) study at Arkansas Children's Hospital Research Institute (Melnyk et al., 2012). The IMAGE study protocol was approved by the University of Arkansas for Medical Sciences' Institutional Review Board, and parents provided written informed consent. Data for 82 neurotypical study participants (control) and 93 participants on the autism spectrum (case) were used for the model in this work. These data reflect plasma concentrations of transmethylation and transsulfuration metabolites, as well as those of tyrosine, nitrotyrosine, and chlorotyrosine, quantified with high performance liquid chromatography (HPLC) (Melnyk et al., 1999, 2000). Amounts of cytosine, 5-methylcytosine, and 8-oxo-deoxyguanosine in DNA were also quantified using a HPLC-ultraviolet system and HPLC electrochemical detection (Helbock et al., 1998). The interested reader is referred to Melnyk et al. (2012) for further information regarding data collection and experimental procedures.

2.2.Model development

The components and structure of the methionine cycle and transsulfuration pathway can be found in the public literature (Reed et al., 2008). The mathematical model developed here is based upon the structure of these metabolic pathways in liver cells, where 8 metabolites measured in the clinical study are modeled. The model consists of the component balances of the individual metabolites at steady state, is based on mass action kinetics, and can be mathematically described as a set of linear algebraic equations. Molar concentrations of metabolites (c), participant-specific rate parameters (p), and efflux rate constants (f) represent the inputs to the system.

A compartmental model, where the concentrations of the metabolites within each compartment are considered to be well-mixed, is used. There are potentially fluxes of components into and out of each compartment, resulting in a net flux rate. Similarly, reactions within each compartment can result in the concentration of a metabolite being increased or decreased. This is represented by the general component balance:

$$\frac{d}{dt}\begin{pmatrix}\text{amount of}\\ \text{metabolite } i \text{ in}\\ \text{compartment}\end{pmatrix} = \begin{pmatrix}\text{net flow rate of}\\ \text{metabolite } i \text{ into or}\\ \text{out of compartment}\end{pmatrix} + \begin{pmatrix}\text{net rate of production}\\ \text{or depletion of metabolite}\\ i \text{ in compartment}\end{pmatrix}. \quad (1)$$

The structure of the metabolic reactions described by the mathematical model is shown in Fig. 1. Methionine, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), and homocysteine make up the methionine cycle. Cysteine, glutamylcysteine, glutathione (GSH), and glutathione disulfide (GSSG) are the modeled components of the transsulfuration pathway. Cystathionine, an intermediate in the reaction of homocysteine converting to cysteine, was omitted from the transsulfuration pathway due to lack of available measurements for it.

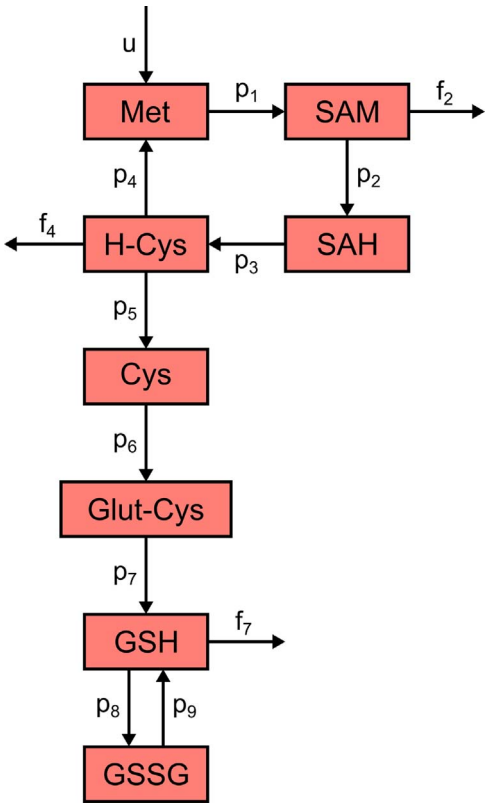

Fig. 1. The structure of the methionine cycle and transsulfuration pathway as described by the mathematical model. Met: methionine, SAM: S-adenosylmethionine, SAH: S-adenosylhomocysteine, H-Cys: homocysteine, Cys: cysteine, Glut-Cys: glutamylcysteine, GSH: glutathione, GSSG: glutathione disulfide. The p variables represent participant-specific rate parameters, while the f variables correspond to flux rate constants. Variable u is a zero-order, participant-dependent methionine influx used to keep the system at steady state.

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