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Review Article

Metabolism-Based Treatments for Autism Spectrum Disorder and Co-Morbidities

Ning Cheng1* and Jong M. Rho2

¹Department of Developmental Neurosciences, Alberta Children's Hospital Research Institute (ACHRI), Cumming School of Medicine, Canada ²Departments of Pediatrics, Clinical Neurosciences, Physiology & Pharmacology, University of Calgary, Canada

Abstract

Autism spectrum disorder (hereafter referred to as "ASD") has broad and heterogeneous clinical manifestations and has been associated with a plethora of possible etiological factors. As such, it has been a challenge to investigate underlying neurobiological mechanisms and to develop effective treatments. Recent studies have increasingly implicated mitochondrial dysfunction as a cause of ASD. Mitochondria are integrally involved in many cellular functions and hence susceptible to many pathophysiological insults. This could explain in part how a wide range of genetic and environmental factors can lead to the consistent behavioural phenotype observed in autistic individuals. Derangements in mitochondrial structure and function - while not unique to diseases such as ASD - nevertheless provide a scientific rationale for experimental therapeutics. Meanwhile, the ketogenic diet (KD), used for nearly a century to treat medically intractable epilepsy, has been shown to enhance mitochondrial function through a multiplicity of mechanisms. This review provides the clinical and basic laboratory evidence for the use of metabolism-based therapies such as the KD in the treatment of ASD, as well as emerging co-morbid models of epilepsy and autism. Future research directions aimed at validating such therapeutic approaches and identifying novel mechanistic targets are also discussed.

INTRODUCTION

Mitochondrial and metabolic dysfunction in ASD

Owing to the premise that a combination of both genetic and environmental factors can contribute to the development of ASD, it has been hypothesized that numerous variables might influence converging signalling pathways and networks, perturbations of which might lead to ASD [1,2]. Identifying central nodes of these cellular networks and pathways would then provide insights into the pathophysiology of ASD, and form the basis of therapeutic approaches for different forms of the disorder. A candidate for such central nodes is the mitochondrion, which is integrated into many cellular pathways. For example, in addition to their well-known role in ATP production, mitochondria are also critically involved in cellular metabolism, intracellular calcium signalling, generation of reactive oxygen species, and apoptosis [3-7]. Mitochondria are also involved in the regulation of innate and adaptive immunity [8]. To varying degrees, all of these factors have been implicated in ASD. Furthermore, mitochondria are known be affected by many of the same endogenous and exogenous risk factors for ASD, such as toxins, drugs, immune activation, and metabolic disturbances [9]. Thus,

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*Corresponding author

Ning Cheng, Department of Developmental Neurosciences, Alberta Children's Hospital Research Institute (ACHRI), Cumming School of Medicine, HMRB 285, 3330 Hospital Dr. N.W.Calgary, Alberta T2N 4N1, Canada, Tel: 403-210-6952; Email: ncheng@ucalgary.ca

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understanding the role of mitochondrial dysfunction in ASD may help unify our understanding of this complex and heterogeneous disorder. Mitochondria play a vital role especially in the nervous system, which has inherently very high energy demands. In addition, mitochondria are in involved in various aspects of neurodevelopment such as the proliferation, differentiation and maturation of neural stem cells, formation of dendriticarbors and spines, developmental and synaptic plasticity, and the determination of cell survival and death [10-14] .Thus, it is not surprising that there are now multiple lines of evidence from clinical, genetic and biochemical studies – in both humans and animal models – supporting a role for mitochondrial dysfunction in the etiology of ASD [15,9,16-18].

Clinical evidence is increasingly pointing to the involvement of mitochondrial disease and dysfunction in ASD. The prevalence of mitochondrial disease in the ASD is estimated to be 5.0%, 500 times higher than that found in the general population ($\approx 0.01\%$). The prevalence of abnormal values of biomarkers related to mitochondrial function in the ASD population may be even higher, suggesting that as many as 30% of children with ASD may show evidence of mitochondrial dysfunction [18]. Additionally,

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the rate of ASD is higher among children with mitochondrial disease [19]. Together, these findings suggest that mitochondrial dysfunction likely represents a significant subclass of ASD, far more than initially believed.

Along similar lines, common co-morbidities of ASD also implicate mitochondrial dysfunction. For example, epilepsy - a common co-morbidity associated with ASD - has also been thought to not infrequently arise from mitochondrial dysfunction. The reported prevalence of epilepsy in ASD population ranges from 5% to 38%, which is much higher than the 1%–2% prevalence in the general population [20]. Further, seizures have been reported to occur in about 35 to 60% of individuals with biochemically-confirmed mitochondrial disease [21]. Thus, shared symptoms suggest a common etio-pathology for ASD and epilepsy. Similarly, gastrointestinal dysfunction, another frequent co-morbidity of ASD [22] is also commonly reported in mitochondrial disease [23], Taken together, we believe that mitochondria may act as a point of convergence for many mechanistic domains within neurobiology that have been implicated in ASD. However, the exact mechanisms of metabolic dysfunction in ASD remain largely unknown and whether it is a cause or result of the disrupted neurodevelopment observed in ASD is not clear.

Ketogenic diet as a promising therapy for ASD

The ketogenic diet (KD) is a special high-fat, low-carbohydrate diet, which has been shown to be remarkably effective in the treatment of patients with medically intractable epilepsy [24], and was designed to reproduce the biochemical changes seen upon fasting [25]. Recently, dietary and metabolic therapies have been attempted in a wider variety of neurological diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis, neuro trauma, and brain cancer [26-29].

There are a number of mechanisms through which the KD may provide neuroprotective activity. Two hallmark features of biochemical changes after the KD treatment are the rise in ketone body production by the liver through fatty acid oxidation and a reduction in blood glucose levels [29]. Specific polyunsaturated fatty acids such as arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid might themselves regulate neuronal membrane excitability [30], reduce inflammation [31,32], or decrease the production of reactive oxygen species (ROS) by mitochondria [33]. Additionally, ketone bodies have been shown to possess neuro protective properties through improved bioenergetics. They have been reported to raise ATP levels and reduce ROS production through enhancement of NADH oxidation and inhibition of mitochondrial permeability transition [34,35]. Furthermore, the KD has been shown to stimulate mitochondrial biogenesis [36,37]. The second major biochemical feature of the KD is the reduction in cellular glycolysis. In addition to suppressing seizures, glycolytic restriction - for example, with the use of 2-deoxyglucose, an inhibitor of phosphor glucose isomerase also improves mitochondrial function and decreases oxidative stress, reduces activity of pro-apoptotic factors, and inhibits inflammatory mediators such as interleukins and tumor necrosis factor alpha [38,39]. Beyond enhancing bioenergetics and mitochondrial function, the KD has also been shown to modulate the metabolism of γ -amino butyric acid (GABA) and acetylcholine, two major neurotransmitters [38], as well as purines (such as ATP and adenosine) that have neural modulatory roles [40-42]. In addition, the KD has also been reported to regulate energysensing pathways such as those involving the insulin-like growth factor and the mammalian target of rapamycin [43,44]. As mentioned above, mitochondrial and metabolic dysfunction may play key roles in the pathophysiology of ASD. Based on research showing that the KD provides numerous neuroprotective effects through modulation of mitochondrial and metabolic pathways, it is reasonable to hypothesize that the diet could provide beneficial effects for autistic individuals.

The effects of the KD on ASD patients and animal models of ASD

To date, there have been limited trials of treating autism patients with the KD. Results from these studies show that more than 50% of ASD patients who received KD treatment showed average-to-significant clinical improvement according to the Childhood Autism Rating Scale, while the remaining exhibited only minor benefits [45-47]. Although patient numbers in these studies were very limited, they collectively suggest that the KD could be an effective therapy for ASD, particularly for core symptoms. Animal models of human diseases have contributed much to our understanding of their pathophysiological mechanisms, and to the development of therapeutic agents. The same appears to hold true for preclinical models of ASD. In an animal model of succinic semialdehyde dehydrogenase (SSADH) deficiency, which is often associated with autistic behaviours, Nylen and colleagues found that KD treatment normalized electroencephalogram activity and certain electrophysiological properties of several brain regions. Behaviourally, KD-treated mutant animals experienced significantly fewer seizures compared to mutant animals fed only the control diet [48] .In another study, Mantis and collaborators found that abnormal motor behaviours and anxiety in a mouse model of Rett syndrome were mitigated through restriction of a standard diet or feeding with the KD in restricted amounts [49]. More recently, using the BTBR T+tf/J (BTBR) mouse model of autism, Ruskin and colleagues investigated the effects of the KD on the core behavioural deficits that define autism [50]. These investigators found that the BTBR mice showed increased sociability in a threechamber test, decreased self-directed repetitive behaviour, and improved social communication in a food preference assay after 3 weeks of KD treatment [50]. These results strongly indicate, and for the first time in an animal model of ASD, that the KD can ameliorate core behavioural symptoms of autism. As mentioned earlier, both genetic and environmental risk factors contribute to the development of ASD. Anotable example of an environmental risk factor linked to ASD is exposure to valproic acid (VPA) during pregnancy.VPA is a broadly efficacious medication for epilepsy, mood disorders and migraine prophylaxis. Utilizing this model, Ahn and collaborators found that the KD restored impaired play behaviours of juvenile rats exposed to VPA prenatally, but did not change the disrupted pattern of play responses [51]. Interestingly, the authors also found that prenatal exposure to VPA altered mitochondrial respiration, and the KD was able to partially reverse these changes [51].

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Future research directions using metabolism-based treatments

Although strong evidence exists that mitochondrial and metabolic dysfunction may play important roles in the pathophysiology of ASD, the exact mechanisms remain undefined and many questions remain. For example, is mitochondrial dysfunction a cause or by-product of the disrupted neurodevelopment observed in ASD? Can impaired mitochondrial function define a sub-type of the otherwise heterogeneous patient population? Is the severity of mitochondrial and/or metabolic disturbance correlated with any behavioural abnormalities and/ or co-morbidities? When mitochondrial function is improved, can it ameliorate the general clinical features of ASD? Answering these fundamental questions will require the collective efforts of basic, translational and clinical researchers, and scientists with diverse expertise in neurosciences with a particular focus on metabolic aspects of ASD, as well as their relationships with both genetic and environmental risk factors.

Similarly, although the KD has thus far shown promising results from limited studies in both patients and animals, a mechanistic understanding of its effects in models of ASD is lacking. Borrowing from the rich literature on the KD treatment for epilepsy, shifts in energy metabolism and the direct actions of the ketone bodies on the mitochondria are two of the promising candidate mechanisms. In addition, the optimum formulation of the KD needs to be established, which may be distinct from those used in epilepsy. Moreover, method of implementing the KD in ASD population needs to be more thoroughly investigated, considering food selectivity and restricted flexibility often observed in people with ASD[52]. For example, in the study carried out by Evangeliou and colleagues [45], seven out of thirty patients could not tolerate the KD, whereas five other patients discontinued it after a few months. Last, but not the least, the potential side-effects of KD treatment in patients with ASD should be carefully investigated, particularly when metabolic disorders or problems with the digestive system are also present.

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