Altered Glucose Metabolism Autism

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Abstract

Studies looking at the metabolism in children with autism spectrum disorder have shown that each child examined was functionally deficient in both vitamin B2 and vitamin B12. Using lactic acid as a metabolic marker of glycolysis, it has been found that there is a biphasic alteration in glucose metabolism, which depends upon the degree of functional B2 deficiency. Initially, as functional B2 deficiency increases, there is a blockage at the metabolism of pyruvate, with a rise in lactic acid. As the deficiency increases still further, there appears to be reduction in the amount of glucose released from stored glycogen and lactic acid levels drop. The mechanism is discussed.

Keywords

Autism, functional B2 deficiency, glycolysis, glycogen, lactic acid

Introduction

Many tests are available to the clinician to study the metabolism of a subject. Arguably, one of the least invasive is the Organic Acids Test (OAT), which looks at metabolites in urine. Using this test, it is possible to look for functional vitamin deficiencies, through studying the elevations of various organic acids. Hence elevations in fatty acids such as glutaric acid, suberic acid, and sebacic acid are indicative of functional vitamin B2 deficiency, as the short, medium and long chain acyl-CoA dehydrogenase are dependent upon FAD for activity. Elevations in these fatty acids are often accompanied by elevation in lactic acid, which becomes raised when the enzyme pyruvate dehydrogenase, is deficient in FAD, one of the two active forms of vitamin B2. A more commonly known marker is methylmalonic acid, a marker for Adenosyl B12 deficiency (1). In addition, there are various neurotransmitter break-down products, such as Kynurenic acid, Quinolinic acid, and 5Hydroxyindole acetic acid, which become elevated in methylcobalamin deficiency (1).

Several studies have reported altered glucose metabolism in individuals with autism (2-9), however the mechanism has not been defined. The possibility exists that it is the known functional vitamin B2 deficiency, commonly observed in autism, that is responsible for this altered metabolism (10) an attempt to elucidate the mechanism, we have examined standard urinary OAT markers and compared the functional vitamin B2 deficiency marker, glutaric acid, with the pyruvate dehydrogenase deficiency marker, lactate.

Glucose metabolism starts following ingestion and absorption as which time, dietary glucose enters the circulation and is taken up via specific glucose transporters. When glucose is in excess in the circulation, insulin is released from the pancreas, binds to insulin receptors on appropriate cells and turns on inducible glucose transporters. Once inside the cell, glucose either enters the glycolysis pathway, or in glucose excess the glucose is polymerized and is stored as glycogen (Figure 1). Glucose that enters the glycolysis pathway is processed to generate 2 molecules of pyruvate, which in the presence of vitamin B2 (as FAD), vitamin B1 (as TPP) and lipoate, is processed by the enzyme pyruvate dehydrogenase to form acetyl CoA. In functional B2 deficiency, however, the pyruvate cannot be processed by pyruvate dehydrogenase, and is rapidly converted to lactic acid. The lactic

acid then down-regulates the expression of the glucose transporter and the cell can then become refractory to insulin. As serum glucose drops, glucose, stored as glycogen can be released to form glucose-1-phosphate by the action of the P5P-dependent enzyme glycogen phosphorylase. In functional B2 deficiency, however, Pyridoxal is not converted to Pyridoxal phosphate (P5P) and so glucose cannot be obtained from glycogenolysis (Figure 2). In this situation, serum glucose will be lower and a state of hypoglycaemia will result. Hypoglycaemia is common in children with autism (2-8) and is often preceded by gestational diabetes in the mothers (7, 9).

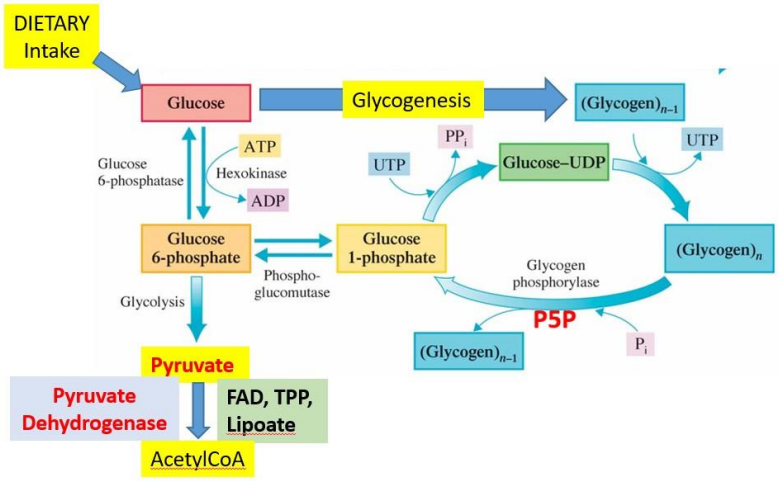


Figure 1. Fate of ingested glucose. In glucose deficiency, glucose enters the glycolysis pathway, and is processed to yield 2 molecules of pyruvate. In glucose excess, glucose is “polymerized” to form the storage macromolecule, Glycogen. Note the dependence of pyruvate dehydrogenase on the co-factors TPP, FAD and lipoate. Similarly note the dependence of glycogen phosphorylase on pyridoxal-5-phosphate.

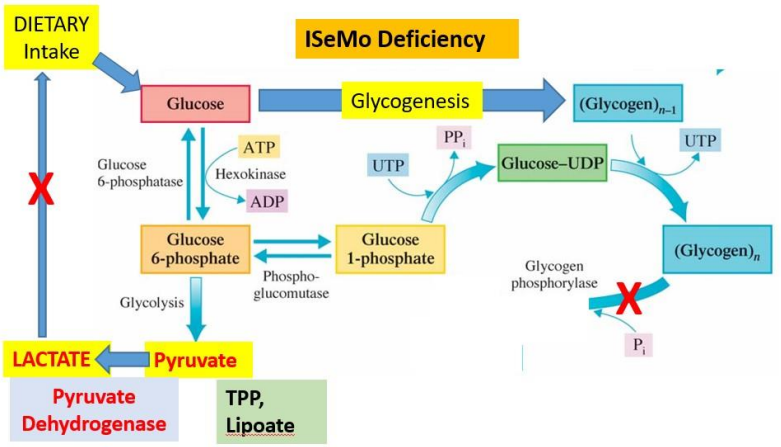


Figure 2. Fate of ingested glucose in functional vitamin B2 deficiency due to inadequate intake of Iodine or Selenium. In functional B2 deficiency, glucose enters the glycolysis pathway, and is processed to yield 2 molecules of pyruvate. Due the lack of FAD, pyruvate cannot be processed further, and isomerizes to lactic acid. In normal circumstances additional glucose can be released by glycogen phosphorylase, however, in functional deficiency of B2, there is a reduced production of P5P, and so Glycogenolysis is effectively blocked.

Methods

We have performed a restrospective analysis of urinary organic acids from 1400 children diagnosed with ASD and compared the functional B2 deficiency marker, glutaric acid, with markers such as lactic acid, and Kynurenic Acid (a breakdown product of tryptophan), the QA:KA ratio (a surrogate marker for functional B6 deficiency), and succinic acid (a surrogate marker for FMN deficiency). The levels of these urinary organic acid markers have been compared with urinary glutaric acid.

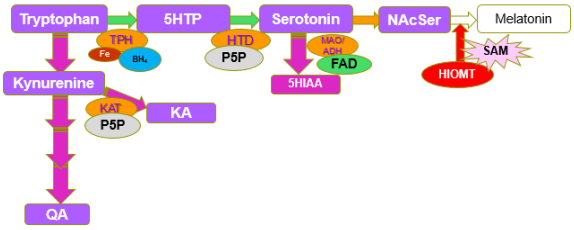


Figure 3. Altered Kynurenic acid pathway in Methylcobalamin deficiency. Production of Melatonin from NAcetylSerotonin, requires the S-Adenosylmethionine dependent enzyme, Hydroxy-indole-O-methyl transferase (HIOMT) enzyme. In methyl B12 deficiency, the tryptophan metabolites 5HTP, Serotonin, Kynurenine, and the Kynurenine metabolites, Kynurenic acid and Quinolinic acid increase. Critical in the degradation of the tryptophan metabolites are pyridoxal-5-phosphate (P5P) for the enzyme Kynurenineaminotransferase (KAT), with P5P also being required for the synthesis of serotonin from 5-hyroxytrytophane. Vitamin B2 (as FAD) is also required for the degradation of serotonin.

Results

Comparison of glutaric acid (a standard marker of vitamin B2 deficiency) with levels of lactic acid in the urine of ASD children reveals a bi-phasic pattern, which is characterized, initially, by a large rise in lactic acid levels, however, as glutaric acid rises about 0.5, there is a sudden drop in levels, suggesting that at this point, there is insufficient activity of glycogen phosphorylase to release glucose from stored glycogen, and thereby process it to pyruvate with the resultant build-up of lactic acid (Figure 3). In support of this hypothesis, there was a similar change in the levels of Kynurenic acid and the QA:KA ratio (markers of functional B6 deficiency) (Figs 4 and 5)

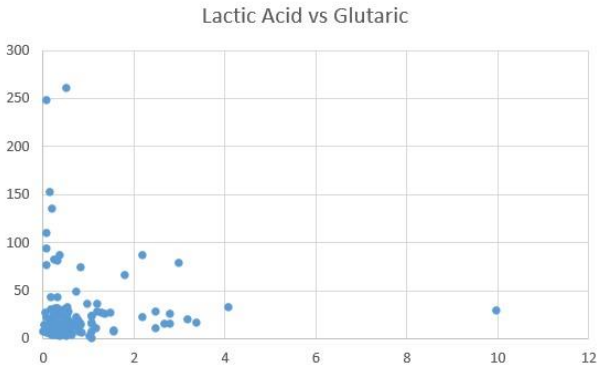


Figure 3. Comparison of urinary glutaric acid (x axis) with lactic acid levels (y axis).

There are a number of other markers that associated with low functional vitamin B2 that show a similar profile to that for lactic and glutaric.

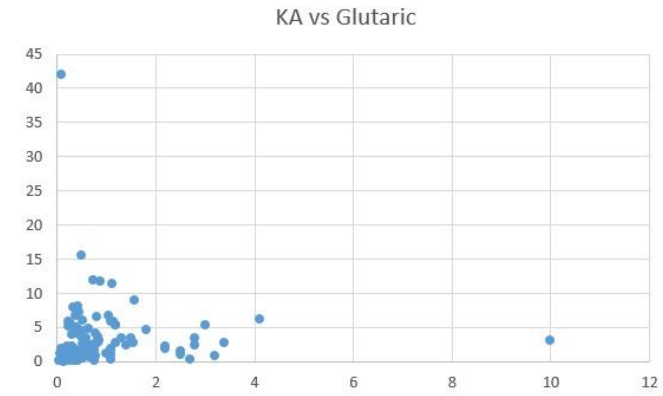


Figure 4. Comparison of urinary glutaric acid (x axis) with Kynurenic acid levels (KA; y axis).

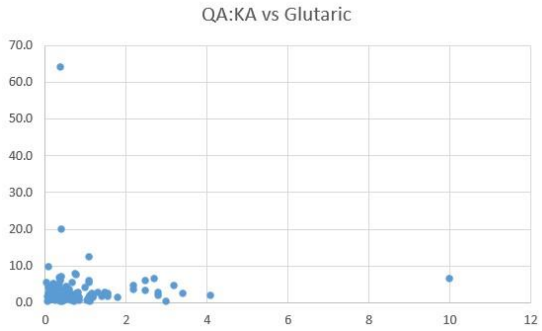
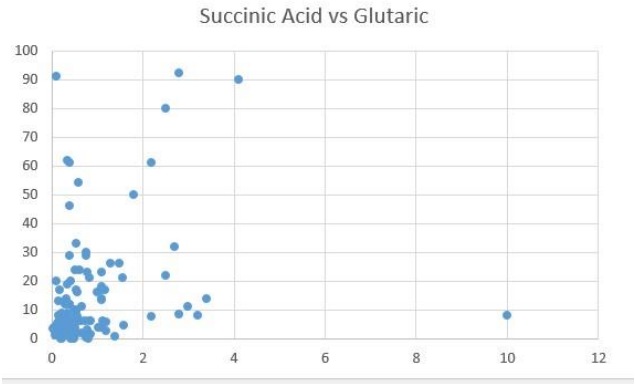


Figure 5. Comparison of urinary glutaric acid (x axis) with the QA:KA ratio (y axis)

Metabolism of succinic acid in the citric acid cycle is dependent upon the FMN-dependent enzyme succinate dehydrogenase and the activity of the enzyme decreases as FMN levels drop, and there is a resultant increase in urinary succinic acid (Figure 6).



Discussion.

Hypoglycaemia is common in autism (11-13), however, the mechanism does not appear to be understood. Examination of OAT data from over 1400 children has shown that they are all functionally deficient in both vitamin B2 (10) and vitamin B12 (1, 14-17). The data presented above would support the notion that it is the functional vitamin B2 in autism that causes the hypoglycaemia. Hence if functional B2 is sufficiently bad, then metabolism of glucose via glycolysis is reduced, and release of glucose from glycogen is also reduced. This would then be associated with

poor energy metabolism in the brains of the children with autism, compounding the observed developmental delay. Analysis of “mean” serum glucose levels may not reveal these correlations as the elevated lactic acid would be "normalized" by the much lower lactic acid seen in extreme functional B2 deficiency. Potentially, given that storage of glycogen is an important back-up energy source in the brain, these children would have much lower energy conversion in the brain, which would then be “starved” of energy, potentially contributing to the developmental delay seen in these children. These findings could potentially mean that in those individuals with extreme functional B2 deficiency, there is the potential for these children to develop glycogen storage disease if untreated.

Summary

A common feature of children with autism is that they can be shown to be metabolically deficient in functional vitamin B2, with the result that they have a reduced ability to process fats, sugars and protein for energy. The effect on glucose metabolism appears to be related to the extent of deficiency that the children have. Hence in moderate functional B2 deficiency, metabolism of glucose via the glycolysis pathway is restricted with the result that urinary lactic acid levels rise. In severe deficiency, however, the metabolism of stored glycogen is affected such that glucose is not released from glycogen stores, and so interprandial blood glucose levels are reduced, resulting in hypoglyaecemia in these individuals. Potentially this then contributes to the state of mental delay seen in these children.

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Conflict of Interest

The authors declare that they have no conflicts of interest with the contents of this article