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Altered Neurotransmitter Metabolites in Vitamin B12 Deficiency

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Abstract

Vitamin B12 deficiency is often associated with neuronal symptoms such as difficulty sleeping, anxiety and depression. Using the Organic Acid Test as a tool it has been possible to examine various neurotransmitter markers to determine how they are altered in functional vitamin B12 deficiency, and therefor try to correlate these alterations with the symptoms. Depending upon the extent and type of functional vitamin B12 deficiency it has been found that lack of methyl B12 activity causes a dramatic increase in the levels of serotonin, dopamine and nor-epinephrine. Potentially the excess dopamine is causative for the increase in anxiety, whilst excess serotonin would eventually cause depression, and the lack of melatonin production, sleep issues. The findings have significant implications in the treatment of anxiety, depression and sleep disorders.

Keywords: Vitamin B2; Vitamin B12; Neurotransmitters; Anxiety; Depression; Autism; Developmental Delay; Organic acids test.

Introduction

Vitamin B12 deficiency has been associated with many symptoms including weakness, fatigue, loss of vision, loss of sensation and dementia. Accompanying these symptoms many persons report other symptoms, such as difficulty sleeping, intestinal issues, depression, anxiety and mood changes [1, 2, 3, 4, 5, 6]. Measurement of vitamin B12 deficiency has generally been performed by simple analysis of levels in serum, however, recently it has become apparent that functional vitamin B12 deficiency may occur with normal or elevated serum vitamin B12, which may present as Paradoxical B12 deficiency, in which case additional measurements of biochemical markers, such as Methylmalonic Acid and homocysteine may be required to confirm the diagnosis of deficiency. More recently, in preliminary studies, it was established that there are other markers of functional vitamin B12 which can be identified through the use of an Organic Acids Test of urine [6]. In those preliminary studies, correlative data has shown that functional B12 deficiency is most often caused by functional vitamin B2 deficiency. These studies have been extended to examining the synthetic pathways for melatonin and epinephrine, both of which require a terminal methylation step during synthesis, and as such are dependent upon functional MethylB12 for activity.

Methods

Study sample Data analysis was carried out under the Australian National Health and Medical Research Council guidelines (NHMRC). Under these guidelines, all data was deidentified and steps were taken to ensure the anonymity and confidentiality of the data. Deidentification has consisted of absolute anonymity and confidentiality of the data, such that no specifics such

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as gender, ethnicity, Country of Origin, etc., is associated with any data point in the study. As such per the NHMRC guidelines: [7] 1. The research does not carry any risk to the participants 2. The benefits of the research are many and will be of considerable benefit to any past, current or future participants, and as such represent no harm. 3. The data is from over 1600 participants collected over 6 years and as such it would be impracticable to obtain consent from the participants. Further the participants had been notified at the time of analysis that data presented for analysis might potentially be used in research – but would be totally de-identified (which it has been). 4. There is no known reason why any of the participants would not have consented if they had been asked 5. Given the total de-identification of the data, there is absolute protection of their privacy 6. Data is only housed in one location and has only been assessed by one person, and as such the confidentiality of the data can be assured. 7. No financial benefits from the data are anticipated, rather the data will be used to help prevent and treat those to whom the data applies. 8. The waiver is not prohibited by State, Federal or International Law.

A retrospective analysis was performed upon data submitted to us for analysis from a cohort of individuals with various conditions, including autism spectrum disorder, chronic fatigue syndrome, healthy controls, and hypothyroidism. The data was submitted from countries including USA, Canada, United Kingdom, Ireland, Germany, Spain, France, Italy, Bulgaria, India, Sweden, Bulgaria, Serbia, Dubai, Croatia and Australia. No selection was made in the acceptance of data, with no data being rejected. Data is presented regardless of sex, or age. Ages varied from 1 year old to seventy-two years old. Metabolic analysis was performed on Organic Acid Test Data (1620 sets, Great Plains Laboratories, Lenexa, KS, USA), which had been submitted to us for interpretation. Data was tabulated in an Excel spreadsheet, and processed using the standard plotting functions in the program.

Results

Individual data is plotted as Scattergrams (Figures 1-6). Data comparisons were made between Methyl Malonic Acid, a standard marker of Adenosylcobalamin deficiency, glutaric acid, a marker of functional B2 deficiency, and the neurotransmitter metabolites homovanillic acid (HVA), Vannillyl mandelic acid (VMA), 5-hydroxyindole acetic acid (5HIAA), Quinolinic Acid (QA), and Kynurenic Acid (KA), as well as the ratio of QA:KA.

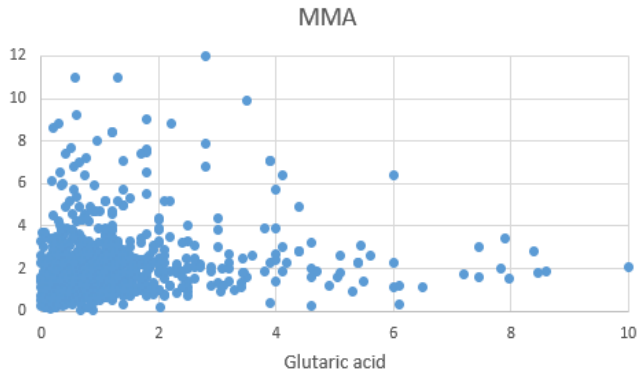

Figure 1: Scattergram of MMA values plotted against Glutaric acid.

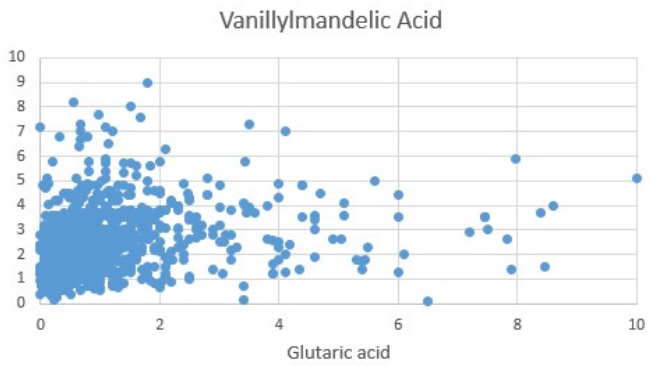

Figure 3: Scattergram of Vanillylmandelic Acid (VMA) values plotted against Glutaric acid.

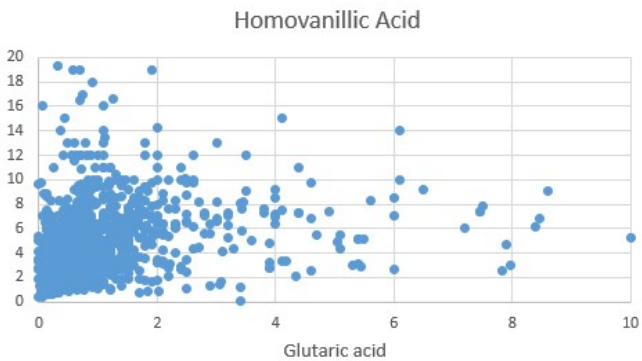

Figure 2: Scattergram of Homovanillic Acid (HVA) values plotted against Glutaric acid.

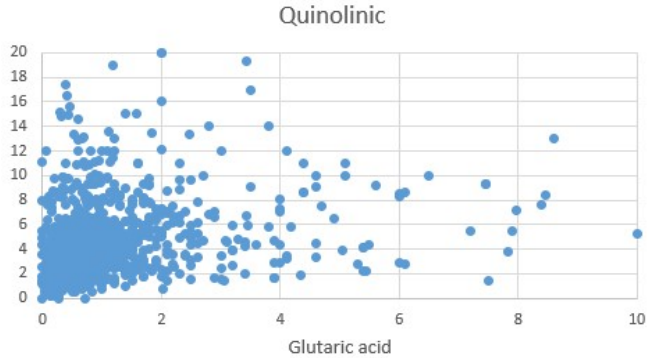

Figure 4: Scattergram of Quinolinic Acid (QA) values plotted against Glutaric acid

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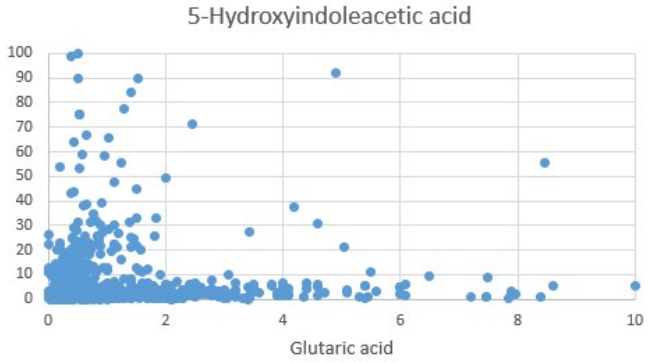

Figure 5: Scatter gram of 5-Hydroxyindoleacetic acid (5HIAA) values plotted against Glutaric acid.

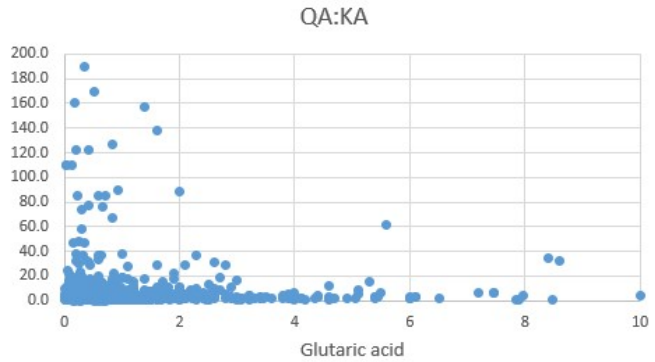

Figure 6: Scattergram of QA:KA ratio values plotted against Glutaric acid.

Discussion

It is apparent from the data that as functional vitamin B2 deficiency increases, as measured by urinary glutaric acid, so too does the standard vitamin B12 deficiency marker, MMA, supporting the role for functional vitamin B2 in the maintenance of vitamin B12 activity. Hence, during methylation of homocysteine to regenerate methionine, the enzyme methionine synthase donates the methyl group to homocysteine and becomes the inactive Co(I)B12. Incoming 5-methyltetrahydrofolate (5MTHF), then is used to regenerate MethylCo(III)B12. 5MTHF is "supplied" either from dietary sources or from the reduction of 5,10,methylene-THF by the FAD-dependent enzyme 5-methylenetetrahydroflate reductase. In the absence of FAD, there is reduced available 5MTHF within the cell. If levels of 5MTHF are low, Co(I) B12 is rapidly converted to inactive Co(II)B12, which requires the FMN/FAD dependent enzyme Methionine Synthase Reductase (MTRR) plus S-Adenosylmethionine (SAM), to regenerate MethylCo(III)B12.

{MTRR-FMN/FAD/NADPH}Co(II)B12-MTR + SAM => {MTRR-FMN/FAD/NAD}Co(III)B12-MTR + SAH

In the absence of FMN/FAD there is an accumulation of inactive Co(II)B12, and the reduced production of SAM, with a concomitant reduction in methylation reactions within the cell. Thus, as functional vitamin B2 decreases, vitamin B12 is gradually inactivated to Co(II)B12, and hence markers such as MMA and homocysteine will rise. Potentially this is why there is an association between symptoms of vitamin B12 deficiency in those with hypothyroidism [8].

Role of Methylcobalamin in the production of Adrenalin

The final step in the production of Epinephrine (adrenalin), is the methylation of Nor-epinephrine by phenylalanine-N-Methyl Transferase using S-Adenosylmethionine as the methyl donor. In functional B12 deficiency, the efficiency of this step is reduced, and so the two precursors accumulate inside the cell. In the OAT, increased levels of Homovanillic acid (HVA) and Vanillyl Mandelic acid (VMA) were measured (Figures 1, 2), representing decreased methylation. The levels of HVA and VMA may be somewhat compromised in functional B2 deficiency, as the reactivity of MAO decreases. Linkage of FAD to MAO, occurs via a covalent bond, during synthesis of MAO, whereas linkage of FAD and FMN to MTHFR and MTRR is ionic, and the activity of these two enzymes are greatly compromised as levels of FAD decrease, particularly in the non-wild-type phenotypes. Hence, theoretically there should be a greater reduction in the production and regeneration of methylCo(III)cobalamin as the levels of FMN and FAD decrease. Lack of methylation due to B12 insufficiency would explain the adrenal fatigue and POTS associated with vitamin B12 deficiency [9, 10].

Role of vitamin B12 in the production of Melatonin

Synthesis of Melatonin, is a multi-step process, culminating in the methylation of NAcetyl-Serotonin, by the enzyme Hydroxy-Indole-O-Methyl Transferase, which uses S-Adenosylmethionine as the methyl donor. As methylation rate drops, the cell responds by increasing the uptake of tryptophan and producing more 5HTP => Serotonin => N-Acetylserotonin. This is accompanied by an increase in the rate of the Kynurenine pathway. The degradation products 5-hydroxyindole acetic acid (5HIAA), Kynurenic Acid (KA) and Quinolinic Acid (QA), become elevated as the rate of melatonin production decreases and the cell tries to compensate. Of note in the production of these degradation products is the reliance of FAD, for the activity of MAO, but more importantly the reliance of the enzymes,

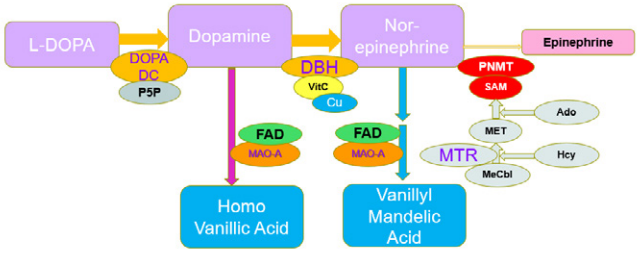

Figure 7: Synthetic pathway for Epinephrine synthesis with degradation products

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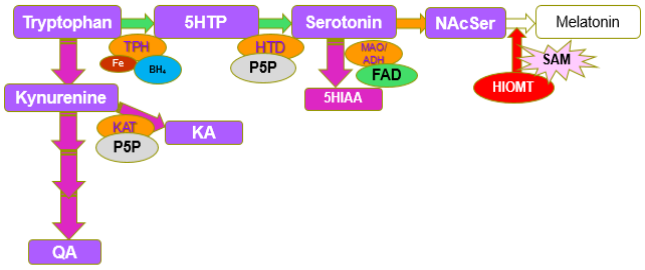

Figure 8:

hydroxytryptophan decarboxylase (HTD), and Kynurenine Amino transferase on the active form of vitamin B6, Pyridoxal-5-phosphate (P5P). P5P must first be synthesized by the FMN-dependent enzyme pyridoxal kinase. Hence in a deficiency of FMN, the synthesis of both serotonin, and kynurenic acid is compromised. Lack of activity of HTD would in turn further increase the production of KA and QA, however the lack of P5P would then reduce the formation of KA and hence the ratio of QA:KA should increase. Lack of methylation due to B12 insufficiency would explain the lack of sleep that has been associated with vitamin B12 deficiency [11, 12, 13, 14, 15]. In addition, the upregulation of serotonin production in B12 insufficiency would also explain the depression, which is the second most common symptom associated with vitamin B12 deficiency [16, 17, 18, 19, 20, 21, 22].

Conclusion

Functional vitamin B12 deficiency has a dramatic effect on the efficacy of the synthesis of Melatonin and epinephrine, which is dependent upon the mechanism by-which the functional VB 12 deficiency occurs. In overt B12 deficiency, there is a compensatory increase in the levels of serotonin, and dopamine and nor-epinephrine, which in turn leads to build up the metabolites, 5HIAA, QA and KA (in the melatonin-related pathway), and VMA and HVA in the epinephrine pathway. If, the functional B12 deficiency, is due to a deficiency in FMN and FAD, as the deficiency becomes overt, the levels of serotonin may be reduced dramatically as too KA, 5HIAA and an increase in the QA:KA ratio. Eventually, if the B2 deficiency is great enough levels of VMA and HVA tend to plateau out. It would thus be expected that the symptoms of absolute B12 deficiency and functional B12 deficiency, mediated by functional B2 deficiency would be somewhat different in nature, and so may explain the wide range of symptoms associated with functional B12 deficiency. Arguably, the most important outcome of these findings will be in their application to the treatment of conditions such as depression and anxiety, which are currently treated with SSRIs. Clearly, in functional B12 deficiency, there is actually a huge over-production of serotonin, which would ultimately lead to down-regulation of serotonin receptors. In that case, rather than treat with SSRIs, these conditions should be treated by correcting the functional vitamin B12 deficiency, which is the cause of the conditions. Potentially this would be of considerable economic benefit to both the patients and to the health budgets of many countries.

Compliance with Ethical Standards

We declare that there are no potential conflicts of interest. Research did no involve human participants and/or animals. No Informed consent is required, all data is “blinded” and as such is anonymous.

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