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GENERAL

Methylcobalamin and its importance

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Introduction

Methylcobalamin, the most active form of vitamin B12 is a water-soluble vitamin which is essential for the healthy functioning of the brain and nervous system, production of blood, and management of stress and fatigue. Dietary sources of vitamin B12 includes milk products such as milk, cheese, and yoghurt; beef; fish; chicken; eggs; certain nutritional yeast products; certain types of soy milk; and breakfast cereals that have been fortified with the vitamin (Yadav et al., 2021).Fatty acid synthesis, energy production, DNA synthesis, and control are just a few of the metabolisms that vitamin B12 is typically engaged in.Adenosylcobalamin (AdoCbl), methylcobalamin (MeCbl), hydroxocobalamin (OHCbl), and cyanocobalamin (CNCbl) are some analogues of vitamin B12. CNCbl and OHCbl are inactive in mammalian cells whereas AdoCbl functions as a cofactor of methylmalonyl Co-A mutase and MeCbl functions as a cofactor of methionine synthase, to produce methionine from homocysteine, that is necessary for the methylation cycle, which involves methylating DNA or proteins (Zhang et al., 2013).

Methylcobalamin also called by the names mecobalamin or methyl B12 is an essential nutrient as it cannot be synthesized in our body and needs to be supplied through diet. MeCbl possess an octahedral Cobalt (III) center with methyl alkyl bonds which are produced in lab by reduction of CNCbl using sodium borohydride in alkaline solution followed by reaction with methyl iodide. Deficiency of vitamin B12 can lead to a variety of health problems including blood deficiencies like anemia, depression, irritability, psychosis, hyperhomocysteinemia and at last cardiovascular disorders(Gupta and Sana, 2015).

Pharmacology

General mechanism:

Methylcobalamin is a cofactor of methyltransferase class of enzyme, methionine synthase and hence MeCbl catalyze the transfer of methyl group from methylenetetrahydrofolate to homocysteine to form methionine and tetrahydrofolate (Zhang and Ning, 2008).

Pharmacokinetics:

Methylcobalamin can be administered orally, intramuscularly, intravenously, intrathecal, sublingually (Zhang and Ning, 2008) and intranasal (Gupta and Sana, 2015). MeCbl, which is attached to proteins in food, is cleaved in the stomach under gastric pH for absorption in the intestine using the intrinsic factor (IF).MeCbl-IF complex will be absorbed in the distal ileum and its half life is about six days. Absorption of this complex is mediated through either diffusion or specific receptors. Following their absorption to intestinal cells, distribution to each and every cell is achieved by binding to transcobalamin II (TC2), a B-globulin carrier protein.TC2 releases B12 as hydroxocobalamin until the B12-TC2 complex enters the cell, where it is needed, which is then converted to MeCbl or AdoCbl and utilized by their respective enzymes.B12 is also transported via transcobalamin II to the liver where it is stored as transcobalamin III. B12 excess is eliminated in the urine.

Role in various pathophysiological conditions

Neuroprotection

Methylcobalamin, present in brain and spinal fluid functions by aiding in the synthesis of myelin, a substance that shields and safeguards nerve fibres, helps in neuronal conduction, axonal transport, axonal regeneration and rejuvenating the injured neuron (Li et al., 2021). Without adequate MeCbl, the myelination does not take place properly, which damages nerve fibres and causes irreparable nerve damage in humans (Gupta and Sana, 2015). Li et al have shown the importance of MeCbl in ischaemic stroke/reperfusion injury through the activation of ERK1/2 pathway present in neurons of ischaemic brain which mediate neuroprotection via anti-apoptotic, anti-inflammatory and autophagy processes. MeCbl improved cell injury, inflammatory response, apoptosis, neurological deficits and also reduced the infarct area in MCAO (Middle Cerebral Artery Occlusion) rats via ERK1/2 pathway activation(Li et al., 2021).

MeCbl and B vitamins are effective in diabetic neuropathy. Patients on diabetic treatment

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with metformin have reported decreased levels of vitamin B12 and increased levels of MMA (Methyl Malonic acid), resulting in myelopathy and further autonomic and peripheral neuropathy. Hence MeCbl supplements can improve neuropathic conditions and also improve diabetes mellitus in general (Essa and Aladul, 2022). It can also be given as a supportive therapy along with neuropathic medications like gabapentin, pregabalin etc. to improve the neuropathic complications in type 2 diabetes patients (Jaya and Dwicandra, 2017). Mutiawati et al have shown the potential effects of MeCbl in reducing sprouting (development of new branches of axon, a part of axonal damage) and neuropathic pain through various mechanisms. Through the creation of protein and lysitine, which is the main component of myelin, methylcobalamin may encourage the healing of nerve cells DNA. In addition to this it can also help in the synthesis of nucleic acids and proteins in neurons, promote the myelination and lipid transport processes, where protein and lipid are crucial building blocks for axon regeneration.In neuropathic pain situations, MeCbl also suppressed the ectopic spontaneous discharges (which can result in allodynia, hyperalgesia, and spontaneous pain) from peripheral primary sensory neurons (Zhang et al., 2013). All these factors contribute in its effective neuroprotective function (Mutiawati).

Hyperhomocysteinemia

Homocysteine, an essential amino acid that is supplied through diet can be transformed into cysteine or recycled into methionine utilizing various B vitamins. Hyperhomocysteinemia is a condition in which the homocysteine levels exceed 15 micro mol/L. Homocysteine levels that are elevated have been linked to an increase in thromboembolic, cerebro-vascular, and cardiovascular disorders. Despite the fact that there is a direct link between homocysteine and cerebrovascular illness, there is still debate about its assessment and treatment since studies have produced contradictory findings regarding how well it reduces the risk of both cardiovascular and cerebrovascular disease. But there are evidences which suggest that decreasing the levels of homocysteine, decreases cardiovascular risk in patients suffering from homocystinuria (Autosomal recessive disorder that can cause atherosclerosis) and also retards brain atrophy. Hip fracture, cognitive decline, osteoporosis, chronic renal disease, hypothyroidism, Alzheimer disease, and schizophrenia are additional illnesses that are associated with increased homocysteine levels (Son and Lewis, 2021).

Hyperhomocysteinemia occurs as a result of imbalance in remethylation pathway in renal failure patients. MeCbl acts a cofactor in folate dependent remethylation where homocysteine can be transformed to methionine and tetrahydrofolate utilizing methionine synthase enzyme and via the substrate 5 - methyltetrahydrofolate. Hence vitamin B12 alone or in combination with folic acid can alleviate atherosclerosis and cardiovascular diseases in renal failure patients undergoing hemodialysis (Koyama et al., 2002).According to studies by Obersby and colleagues, vegetarians who are vitamin B12 deficient are at an increased risk of having elevated total homocysteine (tHcy).It has been proposed that increased plasma tHcy is a risk factor in 82.8% of the CVD diseases investigated using epidemiologic and clinical data. These investigations revealed that plasma tHcy levels can be used as a biomarker for the likelihood of getting CVD in 71.4% of the reported cases.The only vitamin B12 form that has the direct ability to lower tHcy levels is MeCbl. Hence consumption of vitamin B12 as supplement can reduce the elevated levels of tHcy at a dose of $\geq$ 6 microgram/day that seems adequate to maintain a steady-state level of serum vitamin B12 (Obersby et al., 2015).

Also, there are reports where vegetarians who are B12 deficient are prone to hyperhomocysteinemia which is a secondary factor for the progression of cerebral venous thrombosis (Kapur et al., 2019). Since elevated plasma levels of homocysteine damage the vascular endothelium, hyperhomocysteinemia is associated with TMA (thrombotic microangiopathies) related clinical symptoms like apparent thrombosis, microangiopathic hemolytic anemia (MAHA), and different types of end-organ damage brought on by microvascular thrombosis (Yamanishi et al., 2021).

Others

- **Autism**

Autism, commonly known as autism-spectrum disorder, is a widespread developmental illness that affects social skills and psychological status. These issues may prohibit an individual from integrating into society normally and result in significant family suffering.Methylcobalamin's therapeutic potential in autistic patients has been associated with its power to affect methionine metabolism and enhance cellular methylation capacity,

mitochondrial malfunction, and oxidative stress.Numerous neurobehavioral problems, including autism, have been linked to oxidative stress, which is clinically defined by a decline in the GSH (Glutathione)/GSSG (oxidized glutathione) ratio. Numerous studies, including this study by Corejova, et al found that patients with autism had lower GSH levels and a lower GSH/GSSG ratio than healthy controls, while these levels improved upon methylcobalamin administration. Thus, they concluded that supplementation of MeCbl syrup reduced clinical and psychological status of autistic patients (Čorejová et al., 2022).

- **Pernicious anemia**

The death of stomach parietal cells and subsequent reduction of intrinsic factor production to bind the consumed vitamin B12 cause pernicious anaemia. The autoimmune death of parietal cells, which secrete IF, or the development of auto-antibodies directed against IF itself, both contribute to impaired IF production in pernicious anaemia. Gastrectomy and a rare congenital autosomal recessive illness that shows with IF deficit without gastric atrophy are two additional conditions that might limit IF production (https://emedicine.medscape.com/article/204930-overview). Pernicious anaemia is frequently linked to other autoimmune conditions, including thyroid issues, diabetes, and vitiligo. Chan and colleagues from their research concluded that for individuals with pernicious anaemia, oral vitamin B12 replacement at 1000 micro g per day was sufficient to restore vitamin B12 levels and is a much better substitute for vitamin B12 IM injections. After a thorough explanation of the benefits and drawbacks of both treatment methods, patients should be given this option (Chan et al., 2016).

- **Sleep disorders**

Sleep issues are a frequent concern among young kids and teenagers, and they occur more frequently in those with autism spectrum condition.Numerous studies have hypothesised that apparent vitamin B12 deficiency may play a part in people who have trouble sleeping. Even yet, the method is not clearly explained. Disordered sleep is linked to melatonin insufficiency, and studies have demonstrated that melatonin therapy can improve sleep patterns.The generation of melatonin and functional vitamin B12 levels are crucially related biochemically. One of the approximately 200 methylation reactions in the body that are critically dependent upon the methylation cycle, in which MethylCo (III) B12 plays an essential role, is the methylation of the melatonin precursor N-Acetyl-serotonin by the S-Adenosyl-methionine-dependent enzyme, Hydroxy-indole-O-methyl-transferase (HIOMT). Therefore, the rate of methylation decreases in either an absolute or functional vitamin B12 deficit, which would be predicted to result in less melatonin being produced. But this mechanism still remains unclear and studies are on its way as in this study upon retrospective analysis of urinary organic acids in young children, despite the higher serum B12, various signs of functional vitamin B12 insufficiency were found. As a result, the kids might have paradoxical B12, where their serum vitamin B12 levels were normal or high but they had elevated levels of functional vitamin B12 deficient markers. This appears to be a functional vitamin B2 deficit-related vitamin B12 deficiency which needs to be further investigated (Jones, 2022).

REFERENCES

1. CHAN, C. Q. H., LOW, L. L. & LEE, K. H. 2016. Oral vitamin B12 replacement for the treatment of pernicious anemia. *Frontiers in medicine,* 3, 38.
2. ČOREJOVÁ, A., FAZEKAŠ, T., JÁNOŠÍKOVÁ, D., REPISKÝ, J., POSPÍŠILOVÁ, V., MIKOVÁ, M., RAUOVÁ, D., OSTATNÍKOVÁ, D., KYSELOVIČ, J. & HRABOVSKÁ, A. 2022. Improvement of the Clinical and Psychological Profile of Patients with Autism after Methylcobalamin Syrup Administration. *Nutrients,* 14, 2035.
3. ESSA, N. S. & ALADUL, M. I. 2022. Role of Neurotropic B Vitamins in the Treatment of Diabetic Neuropathy: Narrative Review. *Iraqi Journal of Pharmacy,* 19, 98-111.
4. GUPTA, J. & SANA, Q. S. 2015. Potential benefits of methylcobalamin: A review. *Austin J Pharmacol Ther,* 3, 1076.
5. HTTPS://EMEDICINE.MEDSCAPE.COM/ARTICLE/204930-OVERVIEW.
6. JAYA, M. & DWICANDRA, N. 2017. Effectivity analysis of neuroprotector (vitamin B complex and mecobalamin) as neuropathic pain supportive therapy in elderly with type 2 diabetes mellitus. *Asian J Pharm Clin Res,* 10, 320.
7. JONES, G. R. 2022. Functional Vitamin B12 Deficiency in Sleep Disorders in Children. *Int J Psychiatry,* 7, 159-163.
8. KAPUR, V., D'CRUZ, S. & KAUR, R. 2019. An uncommon presentation of hyperhomocysteinemia and vitamin B12 deficiency: A case report. *Journal of medical case reports,* 13, 1-5.
8. KOYAMA, K., USAMI, T., TAKEUCHI, O., MOROZUMI, K. & KIMURA, G. 2002. Efficacy of methylcobalamin on lowering total homocysteine plasma concentrations in haemodialysis patients receiving high-dose folic acid supplementation. *Nephrology Dialysis Transplantation,* 17, 916-922.
9. LI, Y., ZHENG, J., ZHU, Y., QU, Y., SUO, R. & ZHU, Y. 2021. Neuroprotective effects of methylcobalamin in cerebral ischemia/reperfusion injury through activation of the ERK1/2 signaling pathway. *International Immunopharmacology,* 99, 108040.
10. MUTIAWATI, E. A preliminary study on the effect of methylcobalamin application on reducing neuropathic pain.
11. OBERSBY, D., CHAPPELL, D., TSIAMI, A. & DUNNETT, A. 2015. Efficacy of methylcobalamin to normalise elevated homocysteine of vitamin B12 deficient vegetarians: A double blind placebo control study. *Current Research in Nutrition and Food Science,* 3, 187-196.
12. SON, P. & LEWIS, L. 2021. Hyperhomocysteinemia. *StatPearls [Internet].* StatPearls Publishing.
13. YADAV, R. K., MISHRA, S. & JAIN, D. 2021. Methylcobalamine (Vitamin B12): Water Soluble Vitamin with Various Pharmacological Aspect. *Journal of Drug Delivery and Therapeutics,* 11, 130-137.
14. YAMANISHI, M., TAMURA, A., MIYOSHI, T. & IMASHUKU, S. 2021. Hyperhomocysteinemia-related lung disease and hemolytic anemia with bone marrow features masquerading as myelodysplasia. *American Journal of Blood Research,* 11, 266.
15. ZHANG, M., HAN, W., HU, S. & XU, H. 2013. Methylcobalamin: a potential vitamin of pain killer. *Neural plasticity,* 2013.
16. ZHANG, Y.-F. & NING, G. 2008. Mecobalamin. *Expert opinion on investigational drugs,* 17, 953-964.