B Vitamins: Small molecules, big effects

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The B vitamins comprise a group of eight water soluble vitamins (thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folate (B_9) and cobalamin (B_{12})) with a myriad of cofactor roles in human metabolism. These B vitamins perform essential, closely inter-related roles in cellular functioning, acting as co-enzymes in a vast array of catabolic and anabolic enzymatic reactions. Their collective effects are particularly important for numerous aspects of brain function, including energy production, DNA and RNA synthesis and repair, genomic and non-genomic methylation, and the synthesis of numerous neurochemicals and signalling molecules. Given the importance of B vitamins in neurodevelopment and neurological functioning, it is not surprising that B vitamin deficiency is a leading cause of neurological impairment and disability throughout the world. In nutritional B vitamin deficiency, administration of relatively small amounts of the relevant vitamin generally results in rapid resolution of the symptoms of deficiency, although the effects of secondary tissue damage may persist.

Inborn errors of B vitamins may arise because of mutations in transporters leading to impaired absorption or intracellular trafficking of the vitamin, or as a result of mutations affecting the normal metabolic processing of a B vitamin within the cell to its active cofactor form(s), or because of mutations in protein(s) that affect the utilization or binding of the vitamin cofactor. Genome-wide next generation sequencing initiatives (including whole exome and whole genome sequencing) have led to the identification of a rapidly growing number of known inborn errors of B vitamin transport and metabolism in recent years. Clinical presentation of these B vitamin inborn errors can occur at any time from the antenatal period until late adult life and may affect virtually any organ system, ranging from severe megaloblastic anaemia, pancytopaenia and combined immune deficiency to cardiac arrhythmias, dermatitis, sensorineural hearing loss, optic neuropathy and complex neurological disorders. In contrast to nutritional B vitamin deficiency, treatment of disease caused by inborn errors of B vitamin transport and metabolism usually requires very large (supra-physiological) doses of the relevant cofactor. Encouragingly, such pharmacological

therapy often results in correction of the metabolic defect and (partial) reversal of the signs of disease. Thus, the B vitamin disorders represent some of the most treatable inborn errors of metabolism, and warrant prompt recognition and early intervention.

In this themed issue of the *Journal of Inherited Metabolic Disease*, we review the roles of six of the B vitamins in human disease, focussing on treatable inborn errors of metabolism. The special issue starts with a review of thiamine metabolism (Marce-Grau et al., 2019). A comprehensive review of the riboflavin transporter disorders emphasises the role of mitochondrial dysfunction in the pathophysiology of these neuronopathic syndromes (O'Callaghan et al., 2019), whilst a companion article focusses on disorders of riboflavin metabolism, in particular the recently discovered flavin adenine dinucleotide (FAD) synthase deficiency, and the rapidly growing list of riboflavin-responsive disorders associated with mutations in the human flavoproteome, i.e. the >90 human proteins that use FAD or flavin mononucleotide (FMN) as cofactors (Balasubramaniam et al., 2019). Two reviews focus on B6 dependent seizures. The first provides new insights into human lysine degradation pathways relevant for pyridoxine-dependent epilepsy caused by antiquitin deficiency (Crowther et al., 2019), whilst the second reviews all the known causes of B6-dependent seizures, including the recently discovered disorder of an intracellular PLP-binding protein (PLPBP deficiency) (Wilson et al., 2019). The roles of biotin in metabolism, gene expression and human disease are examined (Leon-Del-Rio, 2019). Analytical methods for detecting cerebral folate deficiency are reviewed, and the differential diagnosis of this condition is discussed, including disorders of folate transport and metabolism, secondary deficiencies related to other inborn errors and acquired causes (Pope et al., 2019). Finally, there is a comprehensive review of vitamin B12, folate and the methionine remethylation cycle, focussing on biochemical pathways and regulation (Froese et al., 2018), accompanied by a clinical review of the cobalamin-related disorders (Huemer and Baumgartner, 2018).

In conclusion, we anticipate that improved understanding of the complex relationships between the different biochemical pathways regulated in the brain by these vitamins will facilitate more prompt diagnosis and improved treatment of inborn errors and acquired B vitamin deficiencies in the future.

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