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Editorial

Vitamin B3: More than meets the eye

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Glaucoma refers to a group of ocular conditions united by an intraocular pressure (IOP)-linked, clinically characteristic optic neuropathy, with associated degeneration of retinal ganglion cells (RGCs) and corresponding visual loss.[1] Although the pathogenesis of glaucoma remains poorly understood, there is considerable evidence that the primary site of insult is the optic nerve head and that impaired energy metabolism is a pathogenic component in at least some forms of glaucoma. This notion aligns with the vascular theory of glaucoma and evidence supporting an intrinsic mitochondrial disorder in RGCs. The RGCs are particularly vulnerable to compromised energy metabolism due to several anatomical factors: (1) For optical reasons the intraocular RGC axons are unmyelinated in the retinal nerve fibre bundle and require relatively more energy to maintain action potentials than the saltatory conduction in the myelinated portion outside the globe; (2) the retinal blood supply to the RGCs is limited for optical reasons due to the relatively poor light transmissibility of blood; (3) to retain predatory vision with forward-positioned eyes whilst accommodating our large forebrains, the RGC axons must extend approximately 11 cm from the soma to their first synapse in the lateral geniculate body. The possible role of impaired energy metabolism in the pathogenesis of glaucoma makes bioenergetic neuroprotective strategies attractive.

Metabolism refers to the total of all chemical processes occurring in a living entity and in some definitions, is considered a *sine qua non* for life. Energy metabolism is the component of metabolism required to do cellular work. A problem that the first life forms on Earth needed to overcome was how to transfer energy around gradually without a destructive burst. The solution was to use the energy transitions that accompany the movement of electrons in redox reactions. Arguably, the most important of the biological substrates in cellular redox reactions is nicotinamide adenine diphosphate (NAD), a molecule present in all living creatures.

In 2010, Gilley and Coleman, determined that nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2) was a critical survival factor for axons.[2] This short-half-life, cytosolic enzyme is expressed in RGCs and catalyses an essential step in NAD synthesis. In 2012, Lee et al. demonstrated Complex I dysfunction, which is driven by

NAD/NADH, in mitochondrial oxidative phosphorylation in people with primary open-angle glaucoma, further highlighting the potential importance of NAD in glaucoma.[3]

In human metabolism, NAD is synthesised via multiple pathways, including from niacin in limited capacity via the Preiss–Handler pathway.[4] However, NAD production is predominantly driven by the NAD salvage cycle, of which nicotinamide (NAM), the amide form of vitamin B_3, plays a crucial role, and is partly regulated by NMNAT2.[5] Though all vitamins (niacin, nicotinamide, nicotinamide riboside) drive NAD production, they do so at different efficiencies in different tissues, and nicotinamide and nicotinamide riboside do not have the lipid targeting effects that niacin has.

In 2017, Williams et al. showed that NAD levels were reduced in the retina with age and in the DBA/2J mouse, a genetic mouse model of glaucoma, but that it could be ameliorated by oral supplementation of high-dose NAM.[6] Subsequently, NAM supplementation conveyed protection to the retina in the glaucoma model – fewer RGCs were lost, mitochondria appeared healthier and RGC function was significantly improved compared to control mice. In 2020, Hui et al. then reported the first clinical trial of high-dose NAM supplementation in people diagnosed and treated for glaucoma.[7] The crossover trial design meant that participants took both NAM and placebo during the trial. After 3 months of NAM supplementation, RGC function, as measured using the photopic negative response of the electroretinogram, showed improvement in the NAM-treated group compared to placebo. This was subsequently supported by a similar clinical trial performed in the US using oral NAM and pyruvate, with improvement of visual field parameters in the treated group.[8] These results have motivated an international collaborative clinical trial in Australia, Sweden, Singapore (NCT05275738) and the UK (NCT05405868) investigating whether high-dose NAM supplementation can reduce the rate of visual field loss in individuals with glaucoma over a 2-year period.

In this issue, Charng et al. have investigated the relationship between dietary niacin and retinal nerve fibre layer (RNFL) thickness across various age groups in healthy individuals from three population-based cohort studies.[9] Dietary niacin intake was

estimated from food questionnaires. These studies can be useful when generating hypotheses about the physiological mechanisms that contribute to the anatomical characteristics of a population. Here, they have reported no substantial link between dietary niacin intake and RNFL thickness, concluding that normal daily consumption of niacin does not influence RNFL thickness as we age. This is not surprising, given only NAM and nicotinamide riboside have been identified in recent literature to have potential neuroprotective properties. Indeed, there has been considerable confusion in the medical literature in the past, where the umbrella term of 'vitamin B_3' has been used to represent niacin, nicotinamide and nicotinamide riboside. It is important to distinguish the three, as each have different potential in driving NAD production, via different mechanisms and efficiencies in various tissues. Whilst the study shows that dietary niacin intake is unrelated to RNFL thickness, it also highlights the need to study the effect of supplementation at doses that are higher than the average dietary intake. The current clinical trials investigating the longitudinal effect of high-dose NAM in glaucoma will be key in providing definitive evidence for the potential of NAM supplementation to attenuate visual field loss in individuals with chronic glaucoma.

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