EDITORIAL

Niacinamide and Neuroprotection: The Glaucoma Holy Grail

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Glaucoma—a degenerative optic neuropathy—is a leading cause of irreversible blindness. Experts estimate that this neurodegenerative disease will affect 112 million individuals worldwide.[1] To date, all available therapies (medical, laser, and surgical) aim at the reduction of intraocular pressure (IOP) and none of the medical therapies aiming at neuroprotection have found much credence. Therapies targeting the degenerating neuronal population have received considerable attention, in particular antioxidant vitamins, not only for glaucoma but also for other neurodegenerative diseases of the eyes. The most promising among these has been niacinamide, along with its precursors. Even though a more thorough assessment of structural and functional endpoints may improve our understanding of its efficacy, there is enough reason to evaluate the molecule further, in the hope of managing the risk of glaucoma, and tailoring treatment for the individual.

The Cellular Basis

A progressive compartmentalized neurodegeneration in the retinal ganglion cells (RGCs) results in glaucomatous optic neuropathy. The long RGC axons traverse the entire retinal surface conducting the visually evoked action potentials in a non-saltatory fashion. This puts RGCs at the proverbial metabolic precipice, making them vulnerable to any energy deficit, and mitochondrial dysfunction.[2]

The mitochondrial abnormalities that lead up to it have been identified in both animal models[3] and glaucoma patients.[4] The decrease in nicotinamide adenine dinucleotide (NAD), an essential reduction–oxidation cofactor and metabolite has been documented in the retina. This decline is age dependent and makes RGCs more susceptible to IOP-related stress.

In addition, decreased serum levels of nicotinamide (NAM), which is a precursor of NAD, has also been documented in glaucoma patients.[5] NAD decline has been demonstrated by two modalities: one, by dietary supplementation of NAM, which is the amide form of vitamin B3, and by nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1) overexpression mediated *via* intravitreal viral gene therapy. The latter is a terminal enzyme for NAD production. Both of these have been known to protect against RGC degeneration.

Moreover, there is evidence that NAD buffers RGC metabolism, thus decreasing metabolic stress and increasing oxidative phosphorylation. An increase in mitochondrial size and motility, in addition to a simultaneous dampening of the action potential firing frequency, has also been documented.[6] All of these are known to be neuroprotective and may limit glaucomatous visual dysfunction.

Evidence So Far

Since decreasing levels of NAD and mitochondrial dysfunction are a final common feature of senescence in various tissues and species, therapies to improve the latter have been tried by various researchers to decrease the susceptibility to glaucoma.[3,7–11] Taechameekietichai et al. evaluated data from the 2005 to 2008 National Health and Nutrition Examination Survey in 5,780 adults. They found that an increased level of daily niacin intake to the order of 21.01–28.22 mg/day, and greater than 28.22 mg/day, significantly decreased the crude odds (0.57) of both, self-reported glaucoma, and by fundus imaging in the US population. They also concluded that dietary niacin intake may decrease the risk of developing glaucoma.[12]

Williams et al. reported that at the lowest and the highest doses tested (equivalent to ~2.7 gm/day and ~9.8 gm/day for a 60 kg human), NAM was very effective in decreasing glaucomatous damage in animal models. A total of 70 and 93% of the eyes in the two groups were protected from glaucomatous neurodegeneration, respectively. At the lower dose, there was no change in IOP, and its effect was therefore attributed to neuroprotection alone. At the higher dose, there was a decrease in the level of IOP elevation as well, making its action two-pronged.[13] Both, dietary NAM which is a precursor of NAD+, and the overexpression of a NAD-producing enzyme NMNAT1, were both reported providing robust long-term neuroprotection for RGCs. A reversal of age-related transcriptomic changes and preservation of RGC function in the dilute brown non-agouti/2J inherited mouse model of glaucoma was also documented.[3]

Tribble et al. found that NAM protects RGCs from metabolic damage in animal models. The authors further added that the tissue NAD pool is integral to RGC survival since it provides critical coenzyme resources for maintaining cellular homeostasis and stress resistance. These cellular functions include adenosine triphosphate (ATP) production, management of oxidative stress, gene expression, and deoxyribonucleic acid repair, as well as protein deacetylase activity and calcium homeostasis. The authors also concluded that NAM, administered as early treatment or for prophylaxis, produces no deleterious effects on normal RGCs, buffering against metabolic stress and bioenergetic insufficiency. It could thus be a potent neuroprotective agent against glaucoma and other metabolic and ophthalmic diseases.[6]

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Hui et al. evaluated the effects of oral NAM (1.5 gm/day and then 3.0 gm/day for 6 weeks each) on inner retinal function, in 57 patients receiving concurrent glaucoma therapy. They found that both the photopic negative response (PhNR) parameters, saturated PhNR amplitude (Vmax), and the ratio of PhNR/b-wave amplitude (Vmax ratio) were better after NAM. The former showed an improvement of more than 95% coefficient of repeatability in 23%, and 9% in the NAM and placebo groups, respectively. The Vmax ratio improved by 12.6% in the NAM, and by 3.6% in the placebo group. Interestingly, the authors also reported that the visual field mean deviation improved by ≥1 dB on NAM in 27% of patients, with deterioration noted in only 4% of patients.[14]

De Moraes et al. reported that a combination of NAM (ascending oral doses of NAM (1000–3000 mg) and pyruvate (1500–3000 mg) resulted in significant short-term improvement in visual function. They found that the number of improving test locations was significantly higher in the treatment group as compared to the placebo group (15 vs 7), and the rate of change of pattern standard deviation was also better in the former (–0.06 vs 0.02 dB/week; vs 0.02–0.24). However, the authors did not report a significant change in mean deviation or visual field index. Like other researchers, they also concluded that nutritional supplementation with NAM in glaucoma holds promise, but long-term studies are required to establish their efficacy in slowing glaucoma progression.[15]

Safety Profile

Systemic Side Effects

The commonly used NAD precursors include nicotinic acid (NA), NAM, and nicotinamide riboside (NR). Of these, NA is the most notorious for side effects. Flushing of the skin and gastrointestinal irritation are both known to result in poor compliance with NA. That said, both NA and NAM have been used safely in humans, with minimal adverse effects. Even studies evaluating high doses of ~3–9 gm/day of NA/NAM, for as long as 5 years, have reported only three cases of hepatotoxicity among 6,000 patients.[16,17]

Ocular Side Effects

There is a case report of an increase in IOP in a single patient with the use of NA.[18] On the other hand, lowering of IOP with the use of niacin was reported in age-related macular degeneration patients,[19] aging mice,[3] and inherited mouse glaucoma.[20]

Cystoid macular edema, which was easily reversed on stopping NA supplementation, has been reported in 0.67% of patients receiving the vitamin for hyperlipidemia.[21]

Choosing Between the Precursors

The better safety and tolerability of NAM over NA and other NAD precursors is well documented. However, NR can be converted to NAD independently of NAM using which is the rate-limiting process. NRKs are not needed for the conversion of NAM to NAD. NR, however, is known to have a better bioavailability in both, human, and animal models,[22] and is more effective at increasing NAD levels for any prescribed dosage. For this reason, there is increasing interest in the relatively less well-known NAD precursor. NAM, however, provides a more sustained increase in NAD levels.[13] There is evidence that NAM is available to the RGCs intact, unlike the other NAD precursors, preventing RGC and optic nerve degeneration. NAM is also the natural precursor for NAD in mammals, and also an inhibitor of NAD catabolic enzymes including the cluster of differentiation 38, poly adenosine diphosphate-ribose polymerase, and sirtuins (SIRTs). While not enough is known about the impact of these pathways in glaucoma pathogenies, NAM may protect the RGCs from ATP depletion under stressful conditions. NAM also influences calcium channel mobilization and calcium signaling,[23,24] which are key processes in axonal degeneration. NAM is also known to be vasoprotective *via* improved endothelial function,[25] and can reverse endothelin-mediated vasoconstriction.[26] NR, unlike NAM, does not inhibit the activity of SIRTs, enzymes that deacetylate lysines on proteins, which regulate age-related mitochondrial reprogramming and NAD-mediated cellular protection.[27–29]

Therefore, NR may be a better choice in situations where frequent or continuous dosing is possible. On the contrary, since better compliance can be expected from a less frequent dosing schedule, and given its historical safety and tolerability data, NAM may be the preferred treatment.[13] A definite answer merits a head-to-head comparison of the two precursors.

Rapid Lab-to-clinic Transition

Nicotinamide (NAM), Vitamin B3, has a well-established safety profile, with documented tolerance at high doses.[16] It is a familiar molecule and is extremely affordable and accessible. Its oral route of administration, and the fact that it is a "familiar vitamin" mean it is equally acceptable to clinicians and patients.

Caveat

However, the results of large-scale clinical trials are still awaited, before NAD can be considered an accepted therapeutic modality for glaucoma. Glaucomatous damage to the optic nerve is almost always heterogeneous, the RGCs are in various states of physiological stress: some are normal, others dead, while some are combating neurodegeneration.[2] The most important caveat to the use of NAD in glaucoma prophylaxis and treatment, therefore, is its differential impact on normal and diseased RGCs. Given that NAD does not exclusively target the latter, its impact on the physiology of non-diseased RGCs also must be documented before widespread clinical use.

Trials to Watch Out For

The Glaucoma Nicotinamide Trial is a prospective, randomized, placebo-controlled double-masked clinical trial that started in May 2022, with a projected end date of December 2026. It has two arms: the Swedish Glaucoma Nicotinamide Trial and the vitamin B3 in glaucoma study. Primary open angle glaucoma (POAG) patients will be randomized to two groups: receiving NAM (1500 mg for 6 weeks and then 3000 mg) or the placebo. The primary outcome measure is the change in visual field progression over 2 years.[30]

The NR as a Neuroprotective Therapy for Glaucoma Trial is also a prospective, randomized, placebo-controlled study in open angle glaucoma patients. These patients will receive oral NR 300 mg/day or placebo until 24 months. The trial finished recruitment in March 2021. The primary outcome measures include rates of progressive retinal nerve fiber layer thinning and change in visual field sensitivity.[31]

The Nicotinamide in Glaucoma Trial, a randomized, placebo-controlled, multi-centric trial, aims to evaluate the impact of NAM on mitochondrial capacity in peripheral blood lymphocytes to produce ATP, protecting newly diagnosed glaucoma patients from progressive vision loss. The participants will receive either a placebo or NAM (1.5 gm/day for the first 6 weeks, then the dose

increase to 3.0 gm/day for 21 weeks). The primary outcome measure is the change of visual field mean deviation at 27 months. The trial is scheduled to start recruitment in March 2023, with an estimated end date of November 2026.[32]

The targeting metabolic insufficiency in glaucoma trial is yet to start recruiting but aims to investigate the effect of vitamin B3 in older patients (>60 years of age) with moderate to severe POAG.

It is important to note that in all the study protocols, the subjects will continue to receive their IOP-lowering glaucoma medications as concomitant medications.

The Verdict

Robert Solow, Nobel Prize winning growth economist, had famously said in 1987 (when computers had become widely prevalent in the American workplace) "we can see the computer revolution everywhere but in productivity statistics"—it came through but a few years later as technology advanced further. Given the results with niacinamide and its precursors, a much more widespread adoption is called for so that glaucoma management statistics across the patient population start reflecting the true value of this adjunct to conventional therapy.

For now, NAM may be considered a potentially attractive adjunct to conventional glaucoma therapy. This may be of special importance in normal tension glaucoma patients and those refractory to conventional IOP-lowering medications. If indeed NAM can prevent glaucomatous neurodegeneration, it will dramatically change not just glaucoma therapy in the years ahead, but also the treatment of various other age-related and neurodegenerative diseases.

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