Review

The promise of neuroprotection by dietary restriction in glaucoma

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Abstract

Glaucoma, a progressive age-related optic neuropathy characterized by the death of retinal ganglion cells, is the most common neurodegenerative cause of irreversible blindness worldwide. The therapeutic management of glaucoma, which is limited to lowering intraocular pressure, is still a challenge since visual loss progresses in a significant percentage of treated patients. Restricted dietary regimens have received considerable attention as adjuvant strategy for attenuating or delaying the progression of neurodegenerative diseases. Here we discuss the literature exploring the effects of modified eating patterns on retinal aging and resistance to stressor stimuli.

Key Words: aging; caloric restriction; fasting; glaucoma; neurodegeneration; retina; retinal ganglion cells

Introduction

Glaucoma is the most common neurodegerative cause of irreversible blindness worldwide.

The global prevalence for the disease is 3–5% for people aged 40–80 and it has been estimated that the number of affected people will reach about 111.8 million by 2040 (Tham et al 2014). Despite the currently available therapies, focusing on reducing intraocular pressure (IOP), the therapeutic management remains challenging since the disease may progress even when target IOP values are achieved. The partial inefficacy of IOP-lowering therapies, and the neurodegenerative nature of glaucoma have driven the research toward IOP-independent approaches focusing on neuroprotective strategies. Studies on dietary restriction (either as reduced calorie intake or intermittent fasting) support the notion that metabolic and energy balance are tightly linked with aging and neurodegeneration (Mattson et al., 2012; Pani, 2015). Indeed, the regulated limited access to food activates mechanisms (i.e. autophagy, mitochondrial biogenesis, neuronal plasticity, reduced oxidative stress and inflammation) that translate into protective adaptive responses improving neuronal health and survival (Lin et al., 2014; Bagherniya et al., 2018; Gabandé-Rodríguez et al., 2019; Popov et al., 2020).

Here we discuss the effects of caloric restricted regimens on retinal aging and neurodegeneration focusing on the available evidence from animal models of glaucoma.

Search Strategy and Seletion Criteria

Literature search for studies published up to 2020 was performed on PubMed, Web of Science and Google Scholar databases using the following keywords: glaucoma, retinal aging, retinal neurodegeneration, caloric restriction, fasting, restricted diet, dietary restriction, caloric restriction mimetic and combinations of the above terms.

Glaucoma: an Age-Related Neurodegenerative Disease

Glaucoma is an umbrella term used for a group of progressive optic neuropathies sharing common structural alterations of the optic nerve head and characterized by the progressive loss of retinal ganglion cells (RGCs) (Quigley, 2011). The neurodegenerative process is associated with typical pattern of visual field defects which are initially localized in the paracentral areas and become wider and more numerous as the disease progresses (Nucci et al., 2016). Primary open angle glaucoma, the form accounting for three-quarter of all glaucoma cases, is basically painless and asymptomatic and about 50% of the patients are diagnosed in an advanced stage, when significant and irreversible RGC loss has occurred (Kapetanakis et al., 2016).

The etiopathogenesis of the optic neuropathy is complex and includes genetic and environmental factors, which are only partially defined. Along with the presence of elevated or unstable intraocular pressure (IOP), age is the main risk factor and the prevalence of the disease exponentially increases with population aging (Tham et al., 2014). The therapeutic management of glaucoma, which relies on drugs or surgical procedures aiming at lowering IOP, is a therapeutic challenge. Indeed, despite the treatments, in approximately 10% of glaucoma patients vision loss progresses even when "target" IOP values are achieved (Cohen and Pasquale, 2014). Furthermore, not all patients with ocular hypertension develop the neuropathy and normal tension glaucoma, a subtype of the disease accounting for one-third of all open angle glaucomas, occurs in patients with IOP values falling in the physiological range (Mallick et al., 2016).

Although it is clear that additional, IOP-independent and still unidentified factors are involved in the pathogenesis of the disease, the apoptotic death of RGCs is the road end of a cascade of molecular events (i.e., excitotoxicity, alteration

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of neurotrophic support, hypoxic/ischemic events, oxidative stress, mitochondrial damage, chronic inflammation, autoimmunity, autophagy dysregulation, etc.) altering neuronal homeostasis and creating a hostile environment for neuronal survival (Zhang et al., 2016; Thomas et al., 2017; Russo et al., 2018). The mechanisms underlying the RGC degeneration are similar to those engaged by other neuronal subtypes vulnerable in neurodegenerative disorders, such as Parkinson's and Alzheimer's disease, and also recur in the process of cell senescence (Mirzaei et al., 2017; Matlach et al., 2018).

The Effects of Dietary Restriction on Retinal Aging and Glaucoma-Related Neuronal Loss

Over the past few decades the research on calorie restriction has rapidly expanded and changing of caloric intake and meal timing has been identified as a reproducible environmental intervention to extend life-span and improve health in several species, from yeast to rodent and primates (Fontana and Partridge, 2015). In particular, the effects of two different eating patterns, caloric restriction and fasting, have been studied as possible strategies to sustain healthy aging and modify the risk and progression of age-related chronic diseases (Belsky et al., 2017; Das et al., 2017).

Caloric restriction is a dietary regimen based on the reduction (between 10 and 40%) of daily caloric consumption without affecting the intake of essential nutrients (i.e. vitamins and minerals). At variance, fasting imposes the ingestion of limited or no food and may or may not include caloric restriction during the non-fasting periods. Several regimens in terms of time, length and type can be applied for caloric restrictions, and fasting can be part of a caloric-restricted diet (Longo and Mattson, 2014).

Data from the literature also show that caloric restriction is the most effective non-pharmacological intervention able to increase resistance to stress and offering protection in pathological conditions like diabetes, cancer, cardiovascular and neurodegenerative diseases (Baumeier et al., 2015; Noyan et al., 2015; Ntsapi and Loos, 2016; Kopeina et al., 2017). Indeed, restricted caloric regimens prevents age-related neuronal loss and attenuates or delays neurodegeneration in animal models of Parkinson's and Alzheimer's diseases, as well as in acute neuronal injury induced by focal stroke or cervical spinal cord lesion (Plunet et al., 2008; Ran et al., 2015; Bayliss et al., 2016). Despite the amount of scientific reports supporting the beneficial results of caloric restricted regimens in pathological states affecting the nervous system (Gillette-Guyonnet et al., 2013), evidence regarding their effects on the onset and progression of retinal neurodegenerative diseases, and in particular glaucoma, are still limited. Nevertheless, data available in the literature suggest that, in animal models, modify the eating pattern could improve the resistance of RGCs to stressor stimuli, delay retinal aging and support retinal neurons' viability (Kawashima et al., 2013; Guo et al., 2016; Adornetto et al., 2020).

Aging is associated with a decline in retinal cell densities, a reduction of retinal layers thickness (Obin et al., 2000) and an age-dependent inherited loss of RGCs (Kawai et al., 2001). In mammals, a total loss of approximately 35–40% has been estimated over the lifetime (Harman et al., 2000). Obin et al. (2000) firstly observed that a reduction of caloric intake by 40% preserved retinal cell densities and thickness and modulated aging in the sensory neurons of 30-month-old rats. Similarly, an age-related decline in all three nuclear layers of the neural retina (outer nuclear layer, inner nuclear layer and ganglion cell layer) was reported in Brown Norway rats by Li et al. (2003). This was attenuated by a progressive restriction of dietary regimen initiated at 14 weeks of age and maintained throughout the animals' life (Li et al., 2003).

Kaway et al. (2001) analyzed the loss of peripheral RGCs following exposure to transient elevation of IOP in old (2-years old) versus young (2-month old) rats subjected to ad libidum access to food or caloric restriction regimen (achieved by providing food three days per week for three months) (Kawai et al., 2001). The study revealed that RGCs from old rats show an increased susceptibility to ischemia reperfusion injury as compared to young ones and caloric restriction protected animals from both ages against the loss of RGCs in the peripheral retina (Kawai et al., 2001).

A similar finding was reported by Kong and colleagues (2012) who demonstrated a clear age-related decline in the ability of optic nerve and retina to withstand an acute IOP stress (Kong et al., 2012). Indeed, following a transient elevation of IOP, 18 months old mice with ad libidum access to food showed increased retinal vulnerability, with greater functional loss and poorer recovery, as compared to 3-months old mice. This negative effects of aging on retinal function were significantly reduced in old mice subjected to a dietary restricted regimen (limited access to food for 24 hours every other day) between 12 and 18 months of age (Kong et al., 2012).

More recently our group has shown that 48 hours of fasting significantly reduced the RGC loss induced by acute ocular hypertension; the neuroprotection afforded by the restricted caloric regimen was associated with the suppression of mTOR activity and the activation of autophagy (Russo et al., 2018). Using EAAC1 (excitatory carrier 1)-deficient mice, an animal model of normal tension glaucoma, Guo and colleagues showed that seven weeks of every-other-day fasting suppressed RGC degeneration and ameliorated visual impairment by upregulating the expression of neurotrophic factors and reducing oxidative stress levels (Guo et al., 2016).

Beside supporting neuronal survival, caloric restriction may also contain the retinal glial cell activation in response to detrimental insults inhibiting the release of pro-inflammatory factors. Indeed the prevention of ischemia-induced retinal damage observed in old rats subjected to a caloric restriction regimen was associated with suppression of reactive gliosis (Kim et al., 2004).

While the data on the effects of caloric restricted dietary regimens seem promising in preclinical animal studies, to the best of our knowledge there are no reports regarding its effect on patients with glaucoma (**Figure 1**). However, it is worth noting that in a retrospective cohort study the risk of developing primary open angle glaucoma was reduced in diabetic patients taking the hypoglycemic drug metformin but not in patients assuming other diabetes medications

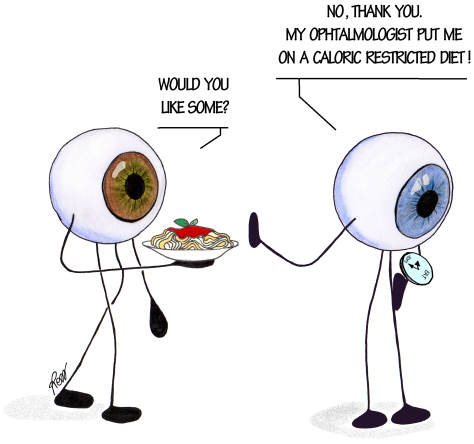

Figure 1 | **Will the knowledge of the beneficial effects of calorie restriction (mainly derived from animal studies) be applicable to patients affected by glaucoma?**

with similar efficacy on glycemic control. Since metformin is considered a drug mimicking the health promoting effects of caloric restriction it can be conceivable to hypothesize that the reduced risk of developing glaucoma may involve the activation of longevity pathways similar to those involved in the protective effects exerted by restricted caloric regimen (Lin et al., 2015).

The positive effects of calorie restriction may rely on several mechanisms including induction of autophagy, improvement of mitochondrial function, activation of sirtuins, reduced oxidative stress and anti-inflammatory effects (Madeo et al., 2019). Furthermore, some of the metabolic adaptations induced by these dietary regimens in neuronal tissues may not stem from local effects but can be mediated by circulating factors present in the sera (Amigo et al., 2017).

Conclusion

To date, the molecular basis of the dietary restriction-mediated effects in the aging retina and after exposure to detrimental insults remain elusive, although an overlapping with those observed in other tissues can be speculated.

In-depth studies aimed at identifying the genetic and physiological mediators of caloric restriction beneficial effects in the retina are fundamental for developing the research in this field. Indeed, the adherence to a long-term or early life starting caloric restriction regimen in humans is questionable and basically impractical and would not meet the compliance of patients. The alternative approach is represented by the search and identification of caloric restriction mimetics: substances/drugs that mimic, at the molecular level, the beneficial physiologic responses of caloric restriction without the need to reduce calorie intake (i.e., metformin, resveratrol, rapamycin) (Madeo et al., 2019).

Further studies are warranted to strengthen the hypothesis that modified dietary regimens or caloric restriction mimetics represent potential adjuvant approaches to be associated with the currently used therapies (**Figure 1**), for preventing or delaying glaucomatous neurodegeneration and other age-related ophthalmic disorders.

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References

Adornetto A, Morrone LA, Satriano A, Lagana ML, Licastro E, Nucci C, Corasaniti MT, Tonin P, Bagetta G, Russo R (2020) Effects of caloric restriction on retinal aging and neurodegeneration. Prog Brain Res 256:189-207.
Bagherniya M, Butler AE, Barreto GE, Sahebkar A (2018) The effect of fasting or calorie restriction on autophagy induction: a review of the literature. Ageing Res Rev 47:183-197.
Baumeier C, Kaiser D, Heeren J, Scheja L, John C, Weise C, Eravci M, Lagerpusch M, Schulze G, Joost HG, Schwenk RW, Schurmann A (2015) Caloric restriction and intermittent fasting alter hepatic lipid droplet proteome and diacylglycerol species and prevent diabetes in NZO mice. Biochim Biophys Acta 1851:566-576.
Bayliss JA, Lemus MB, Stark R, Santos VV, Thompson A, Rees DJ, Galic S, Elsworth JD, Kemp BE, Davies JS, Andrews ZB (2016) Ghrelin-AMPK signaling mediates the neuroprotective effects of calorie restriction in Parkinson's disease. J Neurosci 36:3049-3063.
Belsky DW, Huffman KM, Pieper CF, Shalev I, Kraus WE (2017) Change in the rate of biological aging in response to caloric restriction: CALERIE Biobank Analysis. J Gerontol A Biol Sci Med Sci 73:4-10.
Cohen LP, Pasquale LR (2014) Clinical characteristics and current treatment of glaucoma. Cold Spring Harb Perspect Med 4:a017236.
Das SK, Balasubramanian P, Weerasekara YK (2017) Nutrition modulation of human aging: The calorie restriction paradigm. Mol Cell Endocrinol 455:148-157.
Fontana L, Partridge L (2015) Promoting health and longevity through diet: from model organisms to humans. Cell 161:106-118.
Gabandé-Rodríguez E, Gómez de Las Heras MM, Mittelbrunn M (2019) Control of inflammation by calorie restriction mimetics: on the crossroad of autophagy and mitochondria. Cells 9:82.
Gillette-Guyonnet S, Secher M, Vellas B (2013) Nutrition and neurodegeneration: epidemiological evidence and challenges for future research. Br J Clin Pharmacol 75:738-755.
Guo X, Kimura A, Azuchi Y, Akiyama G, Noro T, Harada C, Namekata K, Harada T (2016) Caloric restriction promotes cell survival in a mouse model of normal tension glaucoma. Sci Rep 6:33950.
Harman A, Abrahams B, Moore S, Hoskins R (2000) Neuronal density in the human retinal ganglion cell layer from 16-77 years. Anat Rec 260:124-131.
Kapetanakis VV, Chan MP, Foster PJ, Cook DG, Owen CG, Rudnicka AR (2016) Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. Br J Ophthalmol 100:86-93.
Kawai SI, Vora S, Das S, Gachie E, Becker B, Neufeld AH (2001) Modeling of risk factors for the degeneration of retinal ganglion cells after ischemia/reperfusion in rats: effects of age, caloric restriction, diabetes, pigmentation, and glaucoma. FASEB J 15:1285-1287.
Kawashima M, Ozawa Y, Shinmura K, Inaba T, Nakamura S, Kawakita T, Watanabe M, Tsubota K (2013) Calorie restriction (CR) and CR mimetics for the prevention and treatment of age-related eye disorders. Exp Gerontol 48:1096-1100.
Kim KY, Ju WK, Neufeld AH (2004) Neuronal susceptibility to damage: comparison of the retinas of young, old and old/caloric restricted rats before and after transient ischemia. Neurobiol Aging 25:491-500.
Kong YX, van Bergen N, Bui BV, Chrysostomou V, Vingrys AJ, Trounce IA, Crowston JG (2012) Impact of aging and diet restriction on retinal function during and after acute intraocular pressure injury. Neurobiol Aging 33:1126 e1115-1125.
Kopeina GS, Senichkin VV, Zhivotovsky B (2017) Caloric restriction- A promising anti-cancer approach: From molecular mechanisms to clinical trials. Biochim Biophys Acta Rev Cancer 1867:29-41.
Li D, Sun F, Wang K (2003) Caloric restriction retards age-related changes in rat retina. Biochem Biophys Res Commun 309:457-463.
Lin AL, Coman D, Jiang L, Rothman DL, Hyder F (2014) Caloric restriction impedes age-related decline of mitochondrial function and neuronal activity. J Cereb Blood Flow Metab 34:1440-1443.
Lin HC, Stein JD, Nan B, Childers D, Newman-Casey PA, Thompson DA, Richards JE (2015) Association of geroprotective effects of metformin and risk of open-angle glaucoma in persons with diabetes mellitus. JAMA Ophthalmol 133:915-923.
Longo VD, Mattson MP (2014) Fasting: molecular mechanisms and clinical applications. Cell Metab 19:181-192.
Maalouf M, Rho JM, Mattson MP (2009) The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res Rev 59:293-315.
Madeo F, Carmona-Gutierrez D, Hofer SJ, Kroemer G (2019) Caloric restriction mimetics against age-associated disease: targets, mechanisms, and therapeutic potential. Cell Metab 29:592-610.
Mallick J, Devi L, Malik PK, Mallick J (2016) Update on Normal Tension Glaucoma. J Ophthalmic Vis Res 11:204-208.
Matlach J, Wagner M, Malzahn U, Schmidtmann I, Steigerwald F, Musacchio T, Volkmann J, Grehn F, Gobel W, Klebe S (2018) Retinal changes in Parkinson's disease and glaucoma. Parkinsonism Relat Disord 56:41-46.
Mattson MP (2012) Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab 16:706-772.
Mirzaei M, Gupta VB, Chick JM, Greco TM, Wu Y, Chitranshi N, Wall RV, Hone E, Deng L, Dheer Y, Abbasi M, Rezaeian M, Braidy N, You Y, Salekdeh GH, Haynes PA, Molloy MP, Martins R, Cristea IM, Gygi SP, et al. (2017) Age-related neurodegenerative disease associated pathways identified in retinal and vitreous proteome from human glaucoma eyes. Sci Rep 7:12685.
Noyan H, El-Mounayri O, Isserlin R, Arab S, Momen A, Cheng HS, Wu J, Afroze T, Li RK, Fish JE, Bader GD, Husain M (2015) Cardioprotective signature of short-term caloric restriction. PloS One 10:e0130658.
Ntsapi C, Loos B (2016) Caloric restriction and the precision-control of autophagy: a strategy for delaying neurodegenerative disease progression. Exp Gerontol 83:97-111.
Nucci C, Russo R, Martucci A, Giannini C, Garaci F, Floris R, Bagetta G, Morrone LA (2016) New strategies for neuroprotection in glaucoma, a disease that affects the central nervous system. Eur J Pharmacol 787:119-126.
Obin M, Pike A, Halbleib M, Lipman R, Taylor A, Bronson R (2000) Calorie restriction modulates age-dependent changes in the retinas of Brown Norway rats. Mech Ageing Dev 114:133-147.
Pani G (2015) Neuroprotective effects of dietary restriction: evidence and mechanisms. Semin Cell Dev Biol 40:106-114.
Plunet WT, Streijger F, Lam CK, Lee JH, Liu J, Tetzlaff W (2008) Dietary restriction started after spinal cord injury improves functional recovery. Exp Neurol 213:28-35.
Quigley HA (2011) Glaucoma. Lancet 377:1367-1377.
Ran M, Li Z, Yang L, Tong L, Zhang L, Dong H (2015) Calorie restriction attenuates cerebral ischemic injury via increasing SIRT1 synthesis in the rat. Brain Res 1610:61-68.
Russo R, Varano GP, Adornetto A, Nazio F, Tettamanti G, Girardello R, Cianfanelli V, Cavaliere F, Morrone LA, Corasaniti MT, Cecconi F, Bagetta G, Nucci C (2018) Rapamycin and fasting sustain autophagy response activated by ischemia/reperfusion injury and promote retinal ganglion cell survival. Cell Death Dis 9:981.
Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY (2014) Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 121:2081-2090.
Thomas CN, Berry M, Logan A, Blanch RJ, Ahmed Z (2017) Caspases in retinal ganglion cell death and axon regeneration. Cell Death Discov 3:17032.
Zhang SH, Gao FJ, Sun ZM, Xu P, Chen JY, Sun XH, Wu JH (2016) High pressure-induced mtDNA alterations in retinal ganglion cells and subsequent apoptosis. Front Cell Neurosci 10:254.

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