Calorie restriction (CR) and CR mimetics for the prevention and treatment of age-related eye disorders

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ABSTRACT

The morbidity of ocular diseases, including macular degeneration, diabetic retinopathy, and dry eye disease, has been gradually increasing worldwide. Because these diseases develop from age-associated ocular dysfunctions, interventions against the aging process itself may be a promising strategy for their management. Among the several approaches to interrupt aging processes, calorie restriction (CR) has been shown to recover and/or slow age-related functional declines in various organs, including the eye. Here, we review interventions against the aging process as potential therapeutic approaches to age-related ocular diseases. The effects of CR and CR mimetics in animal models of age-related eye diseases are explored. Furthermore, we discuss the possibilities of expanding this research to prospective studies to elucidate the molecular mechanisms by which CR and/or CR mimetics preserve ocular functions.

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1. Introduction

Aging is thought to play an important role in many eye diseases, including cataracts, age-related macular degeneration (AMD), glaucoma, dry eye disease, pterygium, conjunctival chalasis, diabetic retinopathy, and retinal vein occlusion. These disorders account for more than 80% of all eye diseases, and their incidence has been gradually increasing worldwide because of aging populations and longer life expectancies.

Preventive measures for aging and early disease intervention are good strategies because the aging processes are closely related to various ocular conditions that result from diminished functions. Calorie restriction (CR) reverses or slows age-related functional declines in various organs (Bordone and Guarente, 2005; Fontana et al., 2008; Lin et al., 2004; Wolf, 2006), including the eye (Abe et al., 2001; Heilbronn et al., 2006; Kawashima et al., 2010; Li and Wolf, 1997; Nadakavukaren et al., 1987; Obin et al., 2000a, 2000b). Ocular diseases that have been studied include age-related macular degeneration, cataract, dry eye disease, and corneal endothelial cell loss. Although it remains controversial whether CR can prevent age-related eye diseases, most data suggest that CR is a useful intervention to control various ocular diseases. Here, we review the clinical evidence and animal model findings suggesting that CR and CR mimetics have therapeutic benefits in age-related ocular diseases. Furthermore, we suggest expansion of the research to prospective studies in order to further understand the molecular mechanisms influenced by CR and CR mimetics in the preservation of ocular function. Particular attention is given to the effects of CR on mitochondria, sirtuins, and levels of reactive oxygen species (ROS). We also briefly discuss some antioxidants that can have similar effects as CR mimetics, and their biochemical availability for disease prevention. Together, these discussions summarize the molecular mechanisms underlying the protection of tissue from age-related changes.

2. Impact of calorie restriction on ocular diseases

2.1. Dry eye disease

Dry eye disease is an important public health problem with a rapidly increasing prevalence in aging populations. The disorder causes ocular discomfort, fatigue, and visual disturbances that often interfere with daily activities. Lacrimal gland function gradually decreases with age, leading to reduced tear secretion and increased dry eye morbidity in elderly people (Lu et al., 2008; Schaumberg et al., 2002; Uchino et al., 2006).
Recently, CR was demonstrated to prevent age-related decline in lacrimal gland function and morphology in middle-aged rats (Kawashima et al., 2010). This was thought to result from reductions in oxidative stress status and inflammation. Aging occurs, in part, as a result of increasing levels of oxidative stress from accumulation of ROS that are continuously generated during normal metabolic processes. Mitochondria produce high amounts of ROS and are the main source of cellular organelle ROS. Kawashima et al. (2010) showed that compared with lacrimal glands of rats fed ad libitum, lacrimal glands of CR rats produced a higher volume of tears and had more intact mitochondrial structures. Because the lacrimal glands from CR rats also had lower amounts of 8-hydroxydeoxyguanosine (8-OhdG), an oxidized nucleoside of DNA, and 4-hydroxynonenal (HNE), the authors concluded that lacrimal gland preservation could be attributed to lower oxidative stress.

Recently, our research group also obtained data that indicated a direct influence of mitochondrial ROS on lacrimal gland function in several different rodent models of oxidative stress, including Tet-mev-1 mice, superoxide dismutase 1 (SOD1) knockout mice, and smoking rats. Additionally, we demonstrated that corneal epithelial cell damage is mediated by oxidative stress (Nakamura et al., 2007, 2010; Higuchi et al., 2011; Kojima et al., 2012) and that oxidation of ocular surface protein, fat, and DNA is accelerated (Nakamura et al., 2007, 2010) in a blink-suppressed rat model of severe dry eye. Blink suppression itself can over-expose the ocular surface to ambient oxygen and induce direct oxidation of cellular components. Kojima et al. (2012) reported that mice with genetically disrupted SOD1, a key enzyme in-and induce direct oxidation of cellular components. Kojima et al. (2012) observed that elevated ROS levels, induced by mice with genetically disrupted SOD1, a key enzyme involved in superoxide anions (O2-) control, exhibited lacrimal gland dysfunction and a compromised ocular surface. Additionally, Uchino et al. (2012) found that the excessive mitochondrial electron transport chain ROS production in Tet-mev-1 mice induced lacrimal inflammation and corneal injury. Together, these studies suggest that mitochondrial oxidative stress, combined with the dysfunction of the electron transport chain, can influence the pathogenesis and progression of age-related lacrimal gland and corneal deficiencies, accelerating the aging of these tissues.

Higuchi et al. (2011) observed that elevated ROS levels, induced by smoking, reduced lacrimal gland function through an upregulation of poly-peptide cytochrome P450, family 1, subfamily A1 (CYP1A1) in the lacrimal gland ducts. The elevated CYP1A1 levels led to further increases in lacrimal ROS production. The exact molecular mechanism by which elevated levels of ROS affect the lacrimal gland and tear production are still unclear, and further experiments are required to clarify these mechanisms. However, these observations still shed light on the prevention of age-related decline in lacrimal gland function.

### 2.2. Cataracts

Senile cataracts of the eye lens are a major cause of blindness, particularly among the elderly. As summarized in Table 1, most animal studies indicate a positive effect of CR on cataracts. Senile cataract models, such as those in the Emory mouse and brown Norway rat, indicate that CR delays the onset, formation, and progression of cataracts (Taylor et al., 1989; Gong et al., 1997). CR may retard age-related degeneration of the lens by slowing aggregate formation, including those of gamma- and alpha-crystallins, which is associated with attenuation of oxidative stress in the lens (Mura et al., 1993; Wang et al., 2004). These studies clearly suggest that CR diets provide protection against cataract formation in pigmented animals, but not in albinos. This anomaly in albinorods may be related to their greater susceptibility to light-induced damage than that in normal, pigmented rodents.

### 2.3. Retinal diseases

AMD causes central vision loss and is the leading cause of blindness in developed countries. By 2020, over 7.5 million people aged >65 years are estimated to have vision loss resulting from AMD (Taylor and Keeffe, 2001). Because of these alarming statistics, research has focused on ways to delay disease progression and the resulting retinal damage.

Lipofuscin, resulting from phagocytosis of degraded photoreceptor cells, is an aggregate of complex materials that accumulates in the lysosomes of retinal pigment epithelial (RPE) cells. Age-related accumulation of lipofuscin may result in RPE dysfunction and accelerate aging processes within the retina, resulting in AMD (Sparrow et al., 2006). In Wistar rats, CR decreases lipofuscin accumulation in RPE cells (Katz et al., 1993). Additionally, in brown Norway rats, CR exhibits neuroprotective effects in aged retinas by reducing age-related photoreceptor cell death (Obin et al., 2000a, 2000b). This process was attenuated by reducing oxidative stress and/or by sustaining the pool of protective

### Table 1

| Eye diseases | Calorie restriction effect | Animal | References |
|-------------|---------------------------|--------|------------|
| Dry eye Cataract | Positive Tear secretion | Fischer 344 rats | Kawashima et al. (2010) |
| | Positive Delayed onset, formation, progression of cataract | Emory mice | Taylor et al. (1989), Mura et al. (1993) and Taylor et al. (1995a, 1995b) |
| | Positive Decline of proliferative capacity of lens epithelial cells (in vitro and in vivo) | C57BL/6 × DBA/2 mice | Li et al. (1997) |
| | Positive Attenuated age-related shortening of telomeres in lens epithelial cells/retarded age-related degeneration of lens by reducing oxidative stress in the lens/prevented age-related decline in glycolytic enzymes, molecular chaperones | Brown Norway rats | Wolf et al. (2000), Pendergrass et al. (2001) and Wang et al. (2004) |
| | Positive Delayed onset, formation, and progression of cataracts | (C57BL/6, C57BL/6 × DBA/2)Fl, (C57BL/6 × C3H)F1 mice | Wolf et al. (2000) |
| | Positive Improved alpha-crystallin chaperone activity, Lowered γ- and γ-crystallin aggregation | Wistar rats | Reddy et al. (2002) |
| Retinal diseases | Negative Decreased the accumulation of lipofuscin in retinal pigment epithelial cells | Fischer 344 rats | Wolf et al. (2000) |
| | Negative Deleterious effect of bright light was more pronounced in CR rats | Wistar rats | Katz et al. (1993) |
| | Negative Neuroprotective effects Reduced age-related photoreceptor cell death Reduced decline of thiols, glutathione, ascorbic acid, and tauine in the retina | Albino Fischer 344 rats | Obin et al. (2000a, 2000b) |
| | Positive Protected against the loss of retinal ganglion cells (RGCs) | Brown Norway rats | Obin et al. (2000a, 2000b), Li et al. (2003) and Li et al. (2004) |
| | Positive Attenuated loss of age-related RGCs | Albino Fischer rats, Albino Wistar rats, Albino BALB/cBy mice | Kawai et al. (2001) |
| | Positive Improved α-crystallin chaperone activity | Wistar rats | Reddy et al. (2002) |
factors such as retinal thiol, glutathione, ascorbic acid, and taurine (Li et al., 2003). However, in Fischer 344 rats, CR increased light-dependent photoreceptor cell loss in the neural retina (Obin et al., 2000a, 2000b). Retinal ganglion cells, which are neurons that transmit visual information from the retina to the brain, decrease in number with advancing age (Neufeld and Gachie, 2003); CR slows the age-related loss of these cells (Neufeld and Gachie, 2003). These studies suggest that CR protects against the loss of these cells, irrespective of the pigmentation of the animal.

3. Calorie restriction mimetics

Although CR may have beneficial effects in humans, it is very difficult to implement and maintain. Therefore, vigorous efforts have been made to find alternative ways to induce the benefits of CR, without imposing the strict guidelines required by CR. With the knowledge of the molecular mechanisms involved in the benefits of CR, suitable chemical compounds or natural products may be found to mimic the effects of CR. Candidate compounds include several polyphenols, lactoferrin, astaxanthin, lipidic acid (α-lipoic acid or ALA), and deoxy-D-glucose (or 2-DG), in addition to currently used drugs such as metformin, rimonabant, and rapamycin. In particular, metformin is already clinically approved to treat diabetes, and has been used for this indication for the past 40 years. It is considered to be a receptor sensitiz-er, because it enhances the sensitivity of insulin receptors on the surface of muscle and fat cells. Metformin activates genes that reduce the production of glucose and reduces the gene expression for enzymes that increase oxidation of fatty acids, which correspond to the same actions of CR genetic effects.

Studies strongly suggest that in a manner similar to CR, these compounds modulate numerous inflammatory pathways throughout the human body, including in the eyes. Several CR mimetics have been tested on various age-related eye diseases, and several compounds have shown promise in delaying the onset of age-related eye diseases. Polyphenols (including resveratrol, quercetin, anthocyanin, and curcumin) and other candidate CR mimetics (such as lactoferrin, lactin, and eicosapentaenoic acid) have been the most frequently studied in eye diseases. Therefore, this review focuses on these possible phytochemical CR mimetics, including how they may be beneficial in managing or preventing age-related eye diseases.

3.1. Polyphenols

A small molecule that safely mimics the ability of CR to delay age-related diseases in laboratory animals is highly sought after. Resveratrol is a type of polyphenol found in the skin of red grapes and other fruit. It is a popular CR mimetic and has been shown to suppress age-related pathological conditions (Timmers et al., 2011). Recent animal studies have shown that independent of change in body weight, a steady and sufficient resveratrol intake reverses the lower survival rate that is induced by a high-fat, high-calorie diet. This effect involves an increase in insulin sensitivity and in mitochondrial numbers, both of which are negatively affected by excessive oxidative stress. Autophagy is also associated with both CR and resveratrol intake. The involvement of the pathway through which sirtuin 1 (SIRT1) and/or its upstream AMP-activated protein kinase (AMPK) acts is a well-known mechanism underlying CR benefits. A recent study demonstrated that daily resveratrol intake in obese humans improved their general condition and beneficially increased SIRT1 gene expression (Timmers et al., 2011). However, another recent study reported that resveratrol supplementation does not improve metabolic function in non-obese women with normal glucose tolerance (Yoshino et al., 2012).

In the eye, resveratrol suppresses vascular lesions associated with diabetic retinopathy (Kubota et al., 2011) and decreases the innate retinal inflammation in endotoxin-induced uveitis (Kubota et al., 2009). In diabetic retinopathy, AMPK activation is the known mechanism for vascular lesion suppression, and the effects of resveratrol have been reproduced with the AMPK activator 5-aminimidazole-4-carboxamide ribonucleoside (AICAR) (Kubota et al., 2011). Resveratrol also has a neuroprotective effect in light-induced retinopathy (Kubota et al., 2010). Pearson et al. (2008) found that resveratrol induces gene expression patterns in multiple tissues; these patterns parallel those induced by CR and every-other-day feeding in mice. Moreover, resveratrol-fed elderly mice showed a marked reduction in signs of aging, including reduced cataract formation (Pearson et al., 2008). Doganay et al. (2006) reported that resveratrol suppressed selenite-induced oxidative stress and cataract formation in rats; these findings were supported by higher Glutathione and lower malondialdehyde in lenses and erythrocytes. The presence of oxidative stress in development of selenite cataract and its prevention by resveratrol suggest that consumption of foods with high levels of natural resveratrol may help prevent the formation of senile cataracts in humans (Doganay et al., 2006).

Among other polyphenols, a flavonoid phytopigment (anthocyanin) may have health benefits, including obesity control, diabetes control, prevention of cardiovascular disease, and improvement of visual functions (Tsuda, 2012). Anthocyanins can suppress retinal neurodegeneration caused by innate retinal inflammation (Miyake et al., 2012). Another polyphenol, quercetin, has shown effectiveness against cataract formation (Stefek and Karasu, 2011).

3.2. Other CRM compounds with proven beneficial effects on eye diseases

3.2.1. Lutein

Lutein, a carotenoid belonging to the xanthophylls group, is concentrated in the macula (center of the retina) and is referred to as a macular pigment in humans. Based on the results of small-scale clinical studies, lutein is thought to prevent AMD development and progression and is now being studied as part of a very large, prospective trial, the Age-Related Eye Disease Study 2 (AREDS2).

The biological effects of lutein have been elucidated through several animal studies (Ozawa et al., 2011, 2012). The carotenoid can suppress retinal neuronal degeneration in diabetic retinopathy (Sasaki et al., 2010), innate retinal inflammation in endotoxin-induced uveitis (Sasaki et al., 2009), and neurodegeneration in light-induced retinopathy (Sasaki et al., 2011). This protective effect against excessive light exposure is consistent with the belief that lutein is physiologically present to absorb excess light and to prevent or minimize light-induced retinal damage. In the 3 reports described above, the induced pathological oxidative stress was successfully suppressed by lutein administration.

3.2.2. Eicosapentaenoic acid

Eicosapentaenoic acid (EPA) is an omega-3 polysaturated fatty acid (PUFA), abundantly present in fish, and is also being studied in AREDS2. Daily dietary supplementation with EPA suppressed the development of laser-induced choroidal neovascularization in a mouse model of AMD (Koto et al., 2007). Interestingly, EPA dietary supplementation also affects the systemic ratio of omega-3 to omega-6 PUFAs; omega-3 PUFA levels increase not only in blood cells but throughout the body. EPA also suppresses innate retinal inflammation in mice with endotoxin-induced uveitis (Suzuki et al., 2010). Additionally, EPA/docosahexaenoic acid consumption is negatively related to the incidence of dry eye (Schraumberg et al., 2003; Miljanovic et al., 2005), and EPA administration may be helpful in treating the condition.

3.2.3. Lactoferrin

Lactoferrin is an antioxidant and an important component in tears. Animal and human data have demonstrated that oral lactoferrin intake may increase tear volume and ameliorate the symptoms of dry eye (Dogru et al., 2007; Kawashima et al., 2012). Although lactoferrin alleviates symptoms of dry eye disease in both animals and humans,
the mechanisms of its absorption in the body after oral intake and its stabilization of tear film are still unclear.

4. Future directions

Animal model studies have shown that CR slows age-related declines in ocular functions by attenuating oxidative stress. These types of CR interventions may be effective in humans as well, although the practicality of such an approach in humans makes clinical studies difficult; this approach has not been broadly studied in the clinical setting. Now that CR mimetics are known to control ROS in a similar way as CR, clinical studies with dietary supplements can be contemplated. Improvement of mitochondrial function with CR mimetics may have a great potential for managing, slowing, or even preventing age-related disorders.

Although we have not commented on the benefits of exercise in this review (Mares et al., 2011; Yip et al., 2011), we believe that proper exercise regimens and adequate CR and/or CR mimetic therapy may be synergistic and important interventions against various age-related eye disorders. Investigations into the effects of CR on eye disease will continue, with the goal of elucidating the molecular mechanisms underlying its beneficial effects on age-related and inflammatory ocular disorders. CR mechanism-based compounds, including siroptin activators and AMPK upregulators, are expected to be developed to enable the broad application of the benefits of CR in the clinical setting.

Conflict of interest
The authors declare no conflicts of interest.

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