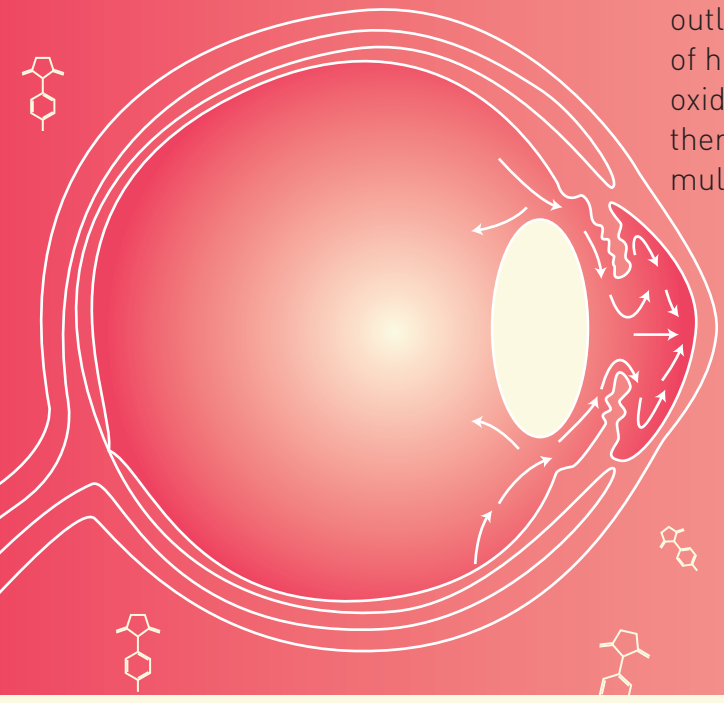
A vision of eye health

Professor Peter F Kador is investigating an alternative treatment to stem the progression of cataracts. He outlines the development of his research on reducing oxidative stress and the therapeutic potential of multifunctional antioxidants



How did you become interested in reducing oxidative damage?

I have had a lifelong interest in eye research, especially the development of age-related cataracts and how to prevent them. These cataracts are linked to oxidative stress, which has led me to research how to reduce oxidative damage.

Can you explain the ways in which multifunctional antioxidants (MFAOs) reduce oxidative damage?

MFAOs are compounds that reduce oxidative stress in tissues. They do this by quenching the excess reactive oxygen species, which are generated by mitochondria in cells or when light enters the eye. These MFAOs also prevent excess reactive oxygen species from reacting with transition metals such as iron or copper by binding these metals so that the damaging hydroxyl radicals cannot form.

Counteracting age-related changes in the eye

Researchers from the **University of Nebraska Medical Centre** and **Therapeutic Vision, Inc.** have developed compounds that show promising potential to halt the progression of age-related and neurodegenerative diseases

A CATARACT IS an age-related condition that causes vision to become more cloudy and blurred and which, if left untreated, can lead to complete blindness. There are many factors that increase the risk of cataract development, including a person's heredity, sun exposure and smoking. However, one factor that stands out as the reason behind many cases of this disease is ageing. This is because the defenses that protect against the damage caused by antioxidants get progressively weakened and less effective as a person gets older.

OXIDATIVE STRESS: HOW DOES IT WORK?

Oxidative stress is caused by the generation of free radicals, especially the production of hydroxyl radicals. These damaging radicals are produced when superoxide and hydrogen peroxide react with transition metals within mitochondria inside cells. They are also formed when UV light enters our eyes.

With age a person's natural defenses against these damaging radicals are weakened and the threat of oxidative stress increases. This can lead to irreparable damage to mitochondria and cell death, resulting in the increased progression of neurodegenerative and other age-related diseases, such as cataracts, age-related macular degeneration (AMD), glaucoma, or Alzheimer's disease (AD).

With an increasingly ageing population, cataracts are becoming a more prevalent global health issue. Currently, the only treatment is the surgical removal of the affected part of the lens and its replacement with a plastic lens. But this is a costly procedure that requires skilled professionals. Furthermore, there are no treatments that prevent AMD, AD or neurodegeneration in glaucoma.

Professor Peter F Kador and his team from the University of Nebraska Medical Centre and Therapeutic Vision, Inc. are therefore conducting research that ultimately aims to reduce the prevalence of these diseases and lift the financial burden on the healthcare system. The researchers have made great progress so far, having developed a new class of drugs called multifunctional antioxidants (MFAOs), which have demonstrated the ability to delay the onset of cataract formation, AMD and changes in AD and neurodegenerations.

SYNTHESISING SURPRISES

What initially led Kador to develop MFAOs was an experiment conducted in the 1990s. In this study, it was demonstrated that a compound that broke down into an inhibitor of sorbitol dehydrogenase actually delayed the last stages of cataracts induced by diabetes or galactosaemia.

Cataracts are first formed when glucose or galactose are converted to sorbitol or galactitol, collectively known as sugar alcohols. As these sugar alcohols accumulate in cells they induce biochemical changes in the lens, which causes cataracts to form. The sugar alcohol,

What were the most intriguing findings from your research on MFAOs?

It was exciting to discover that these compounds were able to prevent degeneration and retinal oxidation in dark-adapted rats. These rats are a model species for a certain age-related macular degeneration disease, for which there are currently no treatments.

We also found that the MFAOs prevented amyloid-ß plaque formation that develops in the lens, retina and brain in Alzheimer's transgenic mice. Amyloid-ß binds zinc to form neurotoxic plaque; we observed that our MFAOs are able to remove the zinc so that the remaining amyloid-ß plaque can then be removed.

With an increasingly ageing population, it is now more important than ever to develop effective ways to tackle age-related diseases. In what ways do you think your research is helping to overcome this global challenge?

It is becoming evident that a number of age-related diseases in the eye, such as cataracts, glaucoma and age-related macular degeneration, share biochemical similarities to other neurodegenerative diseases that are initiated by traumatic injury. These diseases are linked to the generation of reactive oxygen species and metal dyshomeostasis, which is also associated with mitochondrial dysfunction. By reducing reactive oxygen species and modulating metals, MFAOs appear to provide a general treatment that reduces and delays a number of the age-related diseases that are causing an increasing worldwide economic burden to our ageing populations.

Where do you see your research heading in the future?

We are focusing on the development of these agents for neuroprotection and mitochondrial dysfunction. Moreover, there are a number of diseases of iron and copper overload that are partially being controlled by select chelation agents. To date these chelators have limited oral availability and are generally quite toxic because they can also remove excess beneficial metals; therefore, there is a need for new, orally available chelators of low toxicity. We feel that MFAOs may also have a significant future role in the treatment of these metal overload diseases.

sorbitol, is further broken down into fructose by sorbitol dehydrogenase. So the inhibition of sorbitol dehydrogenase would stop this from happening and increase the levels of sorbitol, therefore speeding up cataract formation. "That is why the delay in the end stage was of interest – as it appeared independent of sorbitol dehydrogenase inhibition. Rather, it appeared to be associated with the delayed protein conformation changes," explains Kador.

This research led the team to separate the protein chaperone activity of this compound from its ability to inhibit sorbitol dehydrogenase and still retain its ability to delay cataract formation. Kador further recognised that if he made more alterations to the chemical structure of his synthesised compound he could introduce a strong free radical scavenging antioxidant activity. Further developments led him to work on introducing functional groups that were able to bind transition state metals.

These changes resulted in the production of the MFAO compound, which was able to reduce cataract formation through two independent means – by both reducing hydroxyl radicals and binding transition metals that catalyse the formation of these free radicals.

PROOF IN THE PUDDING

Kador has tested MFAO's in animal models and had successful results so far. "It was exciting to find that MFAOs were able to protect the animal's lenses from damaging the reactive oxygen species we targeted towards them," he highlights. "What was even more exciting was preventing complete retinal degeneration in an animal model of dry AMD, as well as reducing the formation of neurotoxic amyloid-ß zinc complex in transgenic AD mice."

Another great finding was that while MFAOs are able to bind metals, they do not alter them within the mitochondria and can even beneficially redistribute metals within the cell. The team also found that MFAOs are orally active, have low toxicity and have an effect not only within the lens, but also the retina, brain and neural tissues of the ears.

With these positive findings, MFAOs certainly look like promising therapeutic agents for neuroprotection of the eye and brain as well as the prevention of age-related ocular diseases. In the future, Kador and his team see the potential in developing this compound to treat diseases of iron and copper overload, as current treatments have limited effect and high toxicity.

MULTIFUNCTIONAL ANTIOXIDANTS

OBJECTIVES

- To research how oxidative stress and metal dyshomeostasis contribute to the development of age-related diseases in the eye and neurodegenerations
- To investigate the effectiveness of multifunctional antioxidants to delay the onset of cataract formation, age-related macular degeneration prevention, neuroprotection in glaucoma, and retinal and hearing protection against blast damage

KEY COLLABORATORS

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PETER F KADOR received a PhD in Medicinal Chemistry from the Ohio State University and, after a 25-year career at NIH, retired as the Chief of the Laboratory of Ocular Therapeutics from the National Eye Institute. For the past 14 years, he has served as a professor at the College of Pharmacy and adjunct professor in the Departments of Ophthalmology and Veterinary Sciences at the University of Nebraska Medical Center. He founded Therapeutic Vision, Inc. and under a US Food and Drug Administration (FDA) minor use/minor species designation is developing the topical Kinostat®. His work on diabetes and age-related eye diseases has been recognised with numerous national and international awards. He is a fellow of the American Association of Pharmaceutical Scientists and the Association for Research in Vision and Ophthalmology. He serves as the Executive Vice-President for the National Foundation for Eye Research and has served as President, Trustee and currently Treasurer of the Association for Ocular Pharmacology and Therapeutics. He has organised or co-organised over 28 national and international workshops and conferences and has over 240 publications and patents.