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Oxidative stress: cataract enhancer

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Abstract

In many countries, cataract is the leading cause of blindness. This review article focuses on oxidative stress that leads to cataract formation. In cases of hyperglycaemia, superoxides of the mitochondria are elevated mainly by age, but also in cases of diabetes. There are different factors that leads to activation of free radicle and enhance the formation of cataract like oxidation imbalance, stress signalling, protein kinase pathway, lipid peroxidation, lens epithelial cell apoptosis. Additionally, this article includes synthetic and herbal anti-cataractous drugs that helps in preventing the formation of cataract.

Keywords

Cataract, Cataractogenesis, Oxidative stress, Oxidation, Glutathione, Aldose reductase

Introduction

Cataract is a multifaceted eye disease connected to oxidative stress, aberrant glucose metabolism, irradiation, and toxicity. The major reason of human blindness is cataract, which is caused by crystallin protein aggregation [1]. Although congenital and juvenile cataracts are far less prevalent than cataracts related to age, it is one of the main causes of blindness among children and young people. Cataractogenesis involves numerous risk factors, but not only ageing, gene mutations, ultraviolet – B or severe exposure of the light and systemic disorders. In the development of age-related cataract, oxidative damage was suggested among different risk factors [2]. Oxidation is a very early and initial event in a general sequence of cataract. Various factors involved in cataractogenesis start-up- Low defences against antioxidants, high peroxidation, increased non-enzymatic glycosylation and reduced alpha crystalline chaperone function and increased permeability of lens membranes [3]. Cataractogenesis can result from oxidative stress on two different fronts: directly through the reactive oxygen species (ROS) and indirectly through Lipid peroxidation (LPO) [4].

Oxidative stress

The lens' major component is protein, also known as crystalline, which is produced during embryogenesis by migrating fibre cells from the anterior cuboidal epithelia. Nuclei and mitochondria are lost during migration, leaving fibre cells vulnerable to injury due to the lack of a turnover process. Loss of mitochondrial repair systems, which helps in repairing oxidative damage using electron donors by glutathione (GSH), thioredoxin (Trx), NADPH, and FADH2 to restore oxidative damage and keep proteins in a stable redox state. Oxidation is widely considered to be a key element in the formation of cataracts. Crystalline lens structural damage and cataract formation may occur in free radicals as super-oxide anion radical (O_2), hydrogen peroxide (H_2O_2), and hydroxylic-free radicals (OH) [5]. Due to UV light and ionising exposure

to radiation, exogenous ROS are produced. Endogenous ROS is produced in different cell compartments as a result lipoxygenases metabolism, cytochrome P-450, NADPH and mitochondrial transport (mitochondria, peroxisomes, cytoplasm). If pro-oxidant amounts in the body are increased than antioxidant concentrations, then the oxidative stress should be controlled and, if uncontrolled, the mitochondrial damage and leads to overproduction of ROS. Antioxidant are used in systems whereas, proteins repair the systems to reduce the damage caused by ROS. The superoxide anion produced by the electron's transport chain transforms the Mn-SOD (SOD2) into a mitochondrial matrix of hydrogen peroxide [6]. On regulating the SOD2 level, and the cells of lens epithelial may recover from oxidative stress. Also, in intermembrane mitochondria space the effect of SOD1 is similar for the transformation of superoxide anion into the hydrogen peroxide. The lens is protected from damage caused by H_2O_2 with high SOD1 levels. The H_2O_2 is more stable ROS species with harmful effect. Some enzymes, such as GSH, peroxidase and peroxiredoxins, are reduced to cause damage. Most of the stable species of oxygen are found in water humours is H_2O_2 among ROS H_2O_2 can spread in the internal lens, and lenticular epithelial cells are capable of eliminating aqueous-derived H_2O_2 defences. Concentrations of H_2O_2 in the aqueous humour and lens are generally 25 – 30 μM.

The lens has a large amount of GSH, and synthesise it. The reduced GSH is a part of the GSH repair system, both with its oxidised shape. In the presence of NADPH and the creation of mixed disulphide, GSH is maintained in its reduced form rather than its oxidised shape by GSH reductase enzymes. The reduced GSH acts as a source electron to reduce H_2O_2 to H_2O and O_2 peroxidase. The amount of GSH oxidised increases dramatically as the cataract progresses. GSH deficiency is also a common observation in artificially induced cataract. Reduced GSH also reduces the intramolecular disulphide cross-linking of protein sulfhydryl groups, according to research [7]. As a result, GSH can inhibit high molecular weight protein aggregation in the lens, preventing light diffusion and cataract degeneration. As a result, GSH is thought to be an important element in the development of cataracts. GSH has a concentration-dependent protective effect. GSH production is efficiently inhibited by hydroxyl radical generation over 1 mM, whereas production is promoted by concentrations less than 1 mM.

Photooxidative stress

Photooxidative stress and the production of ROS are caused by photosensitizing processes in the bio-molecules of the lens. UV radiation may cause specific damage to lens structures due to the fact that the cellular components directly absorb the incident light resulting in an excited state formation. Photosensitizing systems in which endogenous photosensitisers are absorbed by light and excited in their triple state; and photosensitizing systems in which endogenous photosensitisers are absorbed by light and stimulated in their triple state. The enthusiastic photosensitizer can damage free radicals or transmit power with O_2 using the electron transmission and abstraction processes of hydrogen for arousal, single oxygen reactive state. Reasons that lead to formation of Cataracts are by photochemical production of superoxide, hydroxylic and H_2O_2. Other researchers indicate that the genesis of cataracts associated with age involves the production of lens reactive species of oxygen and consequent damage of the tissue. The fact that cataracts are more exposed to the single population requires molecular oxygen to be converted from soil into highly reactive molecular oxygen (O_2, H_2O_2, HO, and other) [8]. Particular photo-induced damage to the tissue, is assumed in high concentration of

ascorbate, that needs to be filtered that prevents the of UV light to enter into the lens. The photosensitive material that absorbs certain light wavelengths can be activated and removed in the substratum by transforming it into free radicals. The energy in the presence of O_2 is transferred from the exciting material and produces the O_2 that causes lipid peroxidation. Many substances in the eyes may cause photodynamic reactions. These substances consist of riboflavin, hemo-derived substances, tryptophane and N-formyl urenin oxidant, lipofuscin and photosensitive substances of exogenic origin such as medicines, visible pigments (retinol). The production of disulphide bridges between molecules, and photooxidation in thiol groups on lens crystals leading to a protein aggregation or cataract aggregation, is a key link between photooxidation and cataract [9].

Non-enzymatic glycation

Sugar-reducing condensation between the amino groups is termed as non-enzymatic glycation. Another oxidative or no oxidant reaction can take the glycated product, called the first glycated product. In oxidative conditions, the early glycation product does not responses. But, the glycation product with many amino groups can react in non-oxidant conditions to create brown products. Whereas, the interlinked products are known as advanced glycation products. Increased intracellular glucose is assumed dur to the glycolytic pathway, resulting in aldose reductase activation. Lately, the cellular osmotic pressure increases and water flow to the cell membrane causes the lens to swell and opacification [10]. Partly glycation exposes the proteins of the lens and sulphur dioxide entered into disulphide formation and the high aggregation of the molecular weight. Moreover, cortical proteins are more sensitive than nuclear proteins to glycation. This mechanism can also lead to high molecular weight accumulation and eventual in solubilization of proteins. Glycation affects the lenticular membrane as well as the lens protein. Cross-linking of the membrane's intrinsic proteins affect membrane rigidity and permeability as well as membrane opacity [11].

Factor involved in development of Cataract

External risk factors that induce cataract development include smoking, which increases the chance of nuclear cataract, excessive UV exposure, and diabetes, all of which raise the risk of cataract. But additional factors like oxidative stress, removal of protein, lipid peroxide and protein kinase are factors for cataract development. As seen in **Fig.1**.

Oxidant/antioxidant imbalance

A major role in ageing is oxidant and antioxidant imbalances. The imbalance in oxidant/antioxidant systems has also been shown to have potential significance for eye tissues. Oxidative mechanisms, especially, age-related cataracts, seem to play an important role in the pathology and aetiology of cataract formation. In particular, lens proteins are subject to considerable oxidative changes. Among the protein alterations in oxidative stresses are mixed disulphides formed with glutathione, cysteine, methionine and tryptophan oxidation, Cataracts in in vitro models were shown to cause oxidative stress. Light exposure may lead by photo-sensitive mechanisms to the formation of reactive oxygen species [12]. Many tissues regenerate oxidisation slowly, increasing the risk of oxidising tissue components being damaged. This is based on previous findings that, in presence or absence of aromatic amino acids, lens proteins are exposed to ultraviolet light or even sunlight. These are insoluble, colourful and fluorescent

proteins. The lens fibre does not turn over crystalline and other proteins, and must be used by the person for the duration of his life. The lens is therefore even more dependent on oxidative damage than most tissues [13]. The lens, like other tissues, has a set of defence mechanisms that may protect it against oxidative damage. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are examples of these enzymes. Because protein turnover in the lens is limited, particularly in the nucleus, these protective processes are more important in preventing the accumulation of changed proteins.

Stress signalling

NF κB is a transcription factor that is activated by ROS. In cytoplasm, NF κB can usually be found in an inactive complex with a κ B (I κ B) inhibitor, but oxidative stress causes I κ B to be released, translocating NF κB to the nucleus, where it binds to control components and influences transcription of specific genes involved in the signalling of stress and in cell death. The presence of an NF κ B-mediated pathway in lens epithelial cells subjected to hydrogen peroxide and UV exposure has been revealed, indicating that it plays a role in in cataractogenesis [14].

Protein kinase

Protein kinase-C (PKC) is a family of serine/threonine kinases that operates by phosphorylation in the cell signalling process. Like MAPK, oxidation and calcium are used to activate PKCs. Depending on the cofactors required to be activated, PKC were sub divided into three different types i.e., PKC α, β and μ. The PKC α transfers into the plasma membrane and phosphorylates as receptors and lens-opacity proteins after activation targets [15].

Modification and removal of modified protein

The arrangement of lens proteins is a key factor to maintain transparency and modification in the lens by means of oxidation, carbonylation, phosphorylation, etc.

Oxidation: Xanthine oxidase (XOD) is an enzyme that is likely to be involved in injury of diabetic lens and senile cataract genesis (SC). In SC operated patients, the effect of diabetes on XOD activity and its relations to lens oxidant stress markers. The diabetic and non-diabetic patients were tested for serum and lens activities XOD, malondialdehyde (MDA), connected dienes, superoxide dismutase (SOD) and the glutathione peroxidase (GPx) levels. With patient age, the levels Lens XOD, SOD, GPx and GSH declined gradually. Rise in MDA, serum XOD level. The activity of lens XOD that indicates low ocular XOD expression may be related to lower oxidative stress intensity and delayed SC appearance. Serum XOD, lens XOD and conjugated dienes were substantially superior to non-diabetic diabetic for confusing factors. In comparison with non-diabetic, lens SOD and GPx were moderately increased while the diabetic MDA and GSH remained the same. This means that poor glycaemic control can upregulate systemic and ocular XOD activities, which can contribute to lens oxidative stress and cataract [16].

Carbonylation: Protein carbonation is a metal-accelerated change of protein in an amino acid side chain like lysine, arginine, proline or histidine is a indicator of severe oxidative damage to the protein irreversible damage. Diabetic lenses are weak in patients. In diabetic senile Cataract cases, protein glycation is the highest and in non-diabetic senile Cataract patients the lowest.

In mitochondrial epithelial cells of the powerful cigarette smokers, the protein carbonylication is extremely high [17]. Cataract growth in humans is based on the glycation and carbonylation of human lens proteins. Specific factors like high glucose and tobacco smoke can change lens structure and stimulate cataract development, such as cigarette smokers. lens structure. Carbonated proteins tend to form degradation-resistant high-molecular aggregates which accumulate as proteins damaged or unfolded, and the carbonyl lenses are reported in the cataract lenses. In the epithel lens fractions of lens in persons with mature cataracts, protein carbonylation and glycation were observed [18].

Phosphorylation: In the cell signal transduction process, protein tyrosine phosphorylation plays an important role. An important part of many cellular functions is the intracellular signal mediator Phosphatidyline - 3 kinase (PI-3K). We examined in this study the changes in lens protein tyrosine phosphorylation and its effects in the development of selenite Cataract on 3-kinase (PI-3K) phosphate cylinositol signalling [19].

Lipid peroxidation

Lipids are molecules with long hydrocarbon chains, and phospholipids, glycolipids, and cholesterol are found in human lens lipids. Most lipids are protein bound and thus restrict their movement and also ensures their role in the opacity of the lens. The composition of the lens lipid changes significantly in cataract. With increasing age, there is a significant degradation of phospholipids in cataract, which could be due to lipid oxidation. According to the study, increasing age may contribute to mortality by acting as markers for oxidative stress.

Lipid deposition has been linked to the development of cataracts in diabetic patients. Along with retinal damage, diabetes has a higher chance of cataract formation, with the reason being that MDA, one of the breakdown products of lipid peroxidation, attaches to the amino group of lens proteins, disrupting them and making them more prone to stress. In diabetic cataracts, there is a higher quantity of glutathione, a recognised antioxidant that protects against lipid peroxidation, than in non-diabetic cataracts [20].

Lens epithelial cell apoptosis

A single layer of epithelial lens is a metabolic homeostasis critical to the maintenance of transparency for the whole lens. The opacification of the lens causes cells to last a long time under normal conditions, which affects their viability by factors such as oxidative stress. Large studies confirm the role of lens epithelial cell death in the cycle of cataractogenesis as a key biological event [21].

Drug therapy for cataract

Aldose-Reductase Inhibitors

Inhibition of aldose reductase is one of the most effective ways to prevent diabetes' polyol pathway and its consequences. The pathway's first product, sorbitol, is broken down further to fructose, which produces free radicals on its own. Sorbitol can accumulate within lens cells, causing osmotic stress. As a result, it's obvious that the production of sorbitol and fructose could cause a breakdown in normal lens physiology, leading to cataract formation [22].

Antioxidant Treatments of Diabetic Cataracts

Oxidative stress is commonly known to play important role in the development of cataracts. Antioxidant enzymes that prevent cataract from occurring are: catalase, superoxide dismutase, and glutathione peroxidase. Antioxidants are an important preventative measure in the fight against oxidation-related cataracts. The role of dietary antioxidant supplements in the occurrence of cataract has been studied in a wide number of epidemiological and interventional research. Carotenoids are fat-soluble antioxidants that occur naturally in the body. Cataract risk is reduced in people who consume a lot of carotenes.

It has also established the effect of curcumin on cataracts. Curcumin prevented galactose- and streptozotocin-induced diabetic cataracts from forming and maturing. Curcumin also protected against cataracts caused by oxidative stress [23].

Non-steroidal anti-inflammatory drugs

Studies on aspirin use in individuals with rheumatoid arthritis and diabetes provided the first hint that NSAIDs could be used as prophylactic anticataract medicines. Following that, it was discovered that a variety of NSAIDs with different chemical structures could postpone the effect in experimental animals. Aspirin, paracetamol, ibuprofen, naproxen, sulindac, and bendazec are among the NSAIDs that have been thoroughly investigated. The anticataract activity of these medications can be explained by their impact on several metabolic pathways. Acetylation, suppression of glycosylation, and carbamylation of lens proteins are among the mechanisms linked to NSAID protection. Aspirin, sulindac, and naproxen eye drops were also examined for their anticataract efficacy, and they were found to delay the start and progression of cataract in various models of cataractogenesis, with no significant side effects even after long-term use. Aspirin's potential as an anticataract agent was proven in subsequent investigations. Bendazac inhibits the denaturation of lens and serum proteins. Bendazac, a radical scavenger and anticataract agent with a structure similar to indomethacin, was discovered [24].

Herbal Drugs

Antioxidant effects have been documented in a variety of medicinal plants and their preparations, as well as protection from cataracts. Medicinal plants that have long been utilised in traditional medicine are now being investigated as potential raw materials for significant medications used in modern medicine.

Alternanthera sessilis is a prostrate weed that grows as an annual or perennial in the hottest portions of India. Green *A. sessilis* stems and leaves are said to provide a variety of health benefits, hence they are commonly consumed as a leafy vegetable by Indians, particularly in South India. Hazy vision, night blindness, malaria, blood vomiting, and infertility are some of the problems treated with this plant extract (mostly leaves). Phytochemical composition, antioxidant, antibacterial, and anti-cataract properties of Alternanthera sessilis, a frequently consumed leafy vegetable in several parts of India, were examined using standard methodologies.[25]

Pterocarpus marsupium and *Trigonella foenum-graceum*, aqueous extracts of herbal antidiabetic medicines, have a positive anticataract effect. Grape seed proanthocyanidin extract successfully inhibited cataract formation in rats, according to a recent study. *Emilia sonchifolia*

flavonoids reduce selenite-induced cataract lens opacification and oxidative stress. *Dregea volubilis* is a medicinal plant that has long been used to treat a variety of eye diseases; now, its potential anticataract activity has been demonstrated. *Vaccinium myritillus*, popularly known as bilberry, has a long history of use for a variety of eye ailments.

The antioxidative potential is the main mechanism for prevention of cataractogenesis. The anti-catarsis activity of green tea (Camellia sinensis) has now been extensively studied. Green and black tea have recently been shown to slow the progression of diabetic cataracts due to their hypoglycaemic properties. E. officinalis, often known as amla, is beneficial in preventing diabetic cataract advancement, according to a recent study [26].

Conclusion

This review shows that cataract pathology is caused by oxidative stress. Many epidemic studies have studied the connection between cataract formation and nutrition. Nutritional intakes of high vitamins E, C and ß-carotene combined with lower risk of formation of cataracts. The lens is considerably higher than the plasma, and vitamin C is the most efficient way of reducing cataract incidences. Present finding of molecules are used to prevent or treat cataracts that can be more effective, in addition to the increase of endogenous antioxidants such as vitamins.

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Conflict of interest statement

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