Cataractogenesis

Kataraktogeneza

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Izvleček

Kataraktogeneza je proces nastanka sive mrene. Katarakta, ki jo je mogoče opredeliti kot katero koli motnost leče, je prevladujoči vzrok odpravljive slepote po vsem svetu. Mehanizmi, ki sodelujejo v kataraktogenezi, še niso popolnoma znani. Namen tega članka je podati pregled sodobnih raziskav o kataraktogenezi. Več dejavnikov tveganja za nastanek katarakte je že opredeljenih, vključno s starostjo, gensko nagnjenostjo, oksidativnim stresom in izpostavljenostjo UV-svetlobi. Katarakte so lahko prirojene, povezane s starostjo ali sekundarne. Sekundarna katarakta je lahko povezano z očesnimi stanji, kot so pigmentna retinopatija ali uveitis, ali sistemskimi stanji, kot je v primeru sladkorne bolezni ali homocistinurije, ali jo pa lahko povzročajo zdravila, zlasti kortikosteroidi.

Abstract

Cataractogenesis is the process of cataract formation. Cataract, which can be defined as any opacity of the crystalline lens, is the leading cause of avoidable blindness worldwide. The mechanisms involved in cataractogenesis are not yet understood. The purpose of this review is to give an overview of contemporary research in cataractogenesis. Several risk factors for cataract formation have been identified, including increasing age, genetic predisposition, oxidative stress and exposure to UV light. Cataract can be congenital, age-related or secondary. Secondary cataract can be associated with ocular conditions such as retinitis pigmentosa or uveitis, or systemic conditions as in the case of diabetes or homocistinuria, or can be also drug-induced, mainly by steroids.

Introduction

Cataract is a significant problem throughout the world and is responsible for the majority of visual impairments in adult humans. As classified by predominant types, cataract can be congenital, age-related or secondary. Congenital or juvenile cataract may have serious visual consequences on visual maturation and development of amblyopia, and account for approximately 30 % of blindness in infants. Age-related cataract is responsible for nearly half of all blindness worldwide.[1]

Cataract types

1. Congenital cataract

Congenital cataract is rare and occurs in developed countries with a frequency of 30 per 100,000 births with a further 10 cases being diagnosed during childhood, mainly as dominant form.[2] Rates are likely to be higher in developing countries because of rubella infections and consanguinity, for the recessive forms.[3] The knowledge about the mechanisms of cataractogenesis has been derived mostly from the genetic analysis of affected families and from the spontaneous or induced mutations in the mouse.[4]

Affected family analysis showed that there are contributions from genes coding for

transcription factors and structural proteins such as crystallins or connexins. Cataract may be inherited either as an isolated ocular abnormality or as part of a syndrome,[5] with the nonsyndromic cataract representing a significant proportion of cases where many causative genetic mutations have been identified.[6] Congenital cataract (in industrialized countries) reflects mainly genetically caused developmental alterations in the lens. There is a broad genetic heterogeneity in that which clinicians usually simply refer to as a »cataract«. [2] The most frequent mutations in congenital cataract affect genes coding for γ-crystallins (gene symbol: Cryg). Some postnatal, progressive cataracts have been characterized by mutations in the β-crystallin encoding genes (Cryb). Mutations in genes coding for membrane proteins like major intrinsic protein of lens fiber (MIP) or connexins and for transcription factors such as FoxE3, Maf, Sox1 and Six5 may also cause cataracts.[7] There are also contributions from enzymes affecting sugar pathways, particularly the galactose pathway, and from axon guidance molecules such as ephrins and their receptors.[4]

The mouse cataract models contributed to the understanding of lens development rather than to the ageing process affecting the lens. Early events are influenced by genes coding for transcription factors. In maturing lens, mutations affecting the lens membranes (aquaporins/Mip, Lim-2 or connexins) or the structural proteins of the cytosol of the lens fiber cells (the crystallins) become more important.[2]

2. Age-related cataract

a. Epidemiology

Age-related cataract is the most frequent type of cataract. The lens is clear during infancy and remains clear until sometime after 45 years of age when progressive opacities begin to form[8] starting the process of cataractogenesis. The prevalence of the 3 main subtypes of age-related cataracts, nuclear, cortical or posterior subcapsular cataracts (PSCs), differs in different regions of the world and in different racial groups.[9] However, in all areas and populations, PSCs are least common. Whether these differences are related to differences in genetics, environment, diet or other factors is difficult to discern.

Even age-related cataract, generally thought to be due to multiple insults accumulated over many years, may have a genetic component, making certain individuals more vulnerable to the environmental insults.[8]

b. Clinical types

i. Cortical cataract

The first human mutations associated with age-related cortical cataract were recently identified in EPH2A, a gene encoding a transmembrane tyrosine kinase.[10,11]

Epithelial changes are associated with the cortical cataract. Epidemiological information supports an association between exposure to UV radiation from sunlight and the development of cortical cataract in humans.[12] The opaque shades of cortical cataract represent cohorts of locally affected fibres segregated from unaffected neighbouring fibres.[13-15]

The lens epithelium is especially vulnerable to oxidative stress. Being the anteriormost portion of the lens, it is the first site for the interaction with the UV radiation. In vivo studies of the UV radiation effects showed that decreased cell density of lens epithelial cells was observed in all three epithelial zones along with a decrease in the levels of soluble sulfhydryls (S-SH), glutathione reductase, superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT).[16] After UV radiation exposure, p53 and caspase-3 expression increased in lens epithelial cells. Apoptosis induced by UV radiation may be associated with increased p53 expression.[17] Oxidative stress or UV radiation have also been reported to induce an aberrant in situ transglutaminase (TG) activation in human lens epithelial cells.[18] Transglutaminase 2 (TG2) is a multifunctional calcium-dependent enzyme that catalyzes the post-translational protein crosslinking. The up-regulation and activation of TG2 have been reported in cataractogenesis.[19]

Another mechanism of premature lens senescence phenotype that triggers human

cataractogenesis in human lens epithelial cells is believed to be erosion and shortening of telomeres and the lack of telomerase activity. The rate of telomere shortening is modulated by oxidative stress and by changed antioxidative defense capacity.[20] Lipid peroxidation (LPO) may also be associated with cataractogenesis, initiated by enhanced promotion of oxygen free radicals in the eye fluids and tissues and impaired enzymatic and non-enzymatic antioxidant defenses of the crystalline lens. The increased concentrations of primary molecular LPO products were detected in the lipid moieties of the aqueous humor samples obtained from patients with senile and complicated cataracts.[20]

All these mechanisms may possible cause cortical cataract.

ii. Nuclear cataract

In nuclear cataract the nucleus is substantially harder, more opaque and usually more brown than in persons of comparable age who did not develop cataract. Clinicians describe it as »nuclear sclerotic cataract« as an indication of the increased hardness of the cataractous nucleus. With increasing age, many types of modifications occur in the abundant crystallin proteins of the lens nucleus. When an internal barrier to the movement of small molecules, such as antioxidants, develops in the normal lens at middle age, the long-lived proteins in the lens centre become susceptible both to covalent attachment of reactive molecules and to oxidation. These processes of protein modification may, over time, lead to lens opacification and cataract[21] where effects of UV radiation and oxidative stress also play a role. These include protein truncation, cross-linking, denaturation, amino acid racemization, deamidation, glycation and oxidation. The exposure to increased levels of molecular oxygen and UV exposure accelerates the opacification of the lens nucleus, leading to nuclear cataract.[1,22-24]

Factors in the eye that maintain low oxygen partial pressure around the lens are, therefore, important in protecting the lens.[1] The key factor in preventing oxidation seems to be the concentration of nuclear glutathione.[22]

Loss of protein sulfhydryl groups and the oxidation of methionine residues are progressive and increase as the cataract worsens until > 90 % of cysteine and half the methionine residues are oxidised in the most advanced form.[22] Studies of the morphological structure and biophysical changes of the lens in human senile cataract have demonstrated the disappearance of normal fiber structure in the opaque region of the lens and the disintegration of the lens fiber plasma membrane in the lens tissue.[13] Modified with oxygen, phospholipid molecules, accumulating in the lipid bilayer, change its geometry and impair lipid-lipid and protein-lipid interactions in lenticular fiber membranes. Human lenses at various stages of age-related cataract studied by electron microscopy show that these disruptions are globules, vacuoles, multilamellar membranes, and clusters of highly undulating membranes. In the mature cataract nucleus, other potential scattering centers include variations in staining density between adjacent cells, enlarged extracellular spaces between undulating membrane pairs, and protein-like deposits in the extracellular space.[13]

c. Mechanisms of cataractogenesis of age-related cataracts

i. Oxidative stress

A common environmental factor in most age-related cataracts is believed to be oxidative stress.[22,25] Cataract formation occurs when the rate of reactive oxygen species (ROS) production exceeds the rate of their removal.[26] During environmental stress (e.g. UV or heat exposure), ROS levels can increase dramatically. In vitro and in vivo studies suggest that light penetration into the eye is a significant contributory factor in the cataractogenesis, with the major effect being through photochemical generation of ROS and consequent oxidative stress to the tissue.[27] This may result in significant damage to cell structures such as damage of DNA, RNA, and proteins. Low levels of antioxidants, such as glutathione and vitamin C or inhibition of the antioxidant enzymes, such as catalase (CAT), superoxide dismutase (SOD) and various peroxidases, cause oxidative stress and may damage or kill cells. [28]

ii. Calcium

Calcium, Ca^{2+}, has an important role in the development of human age-related cataract. The Ca^{2+} level controls homeostasis of entire lens. Alteration in Ca^{2+} homeostasis is associated with various types of human and experimental cataracts. The raised levels of Ca^{2+} in human lenses with cortical cataract play a major role in the opacification process.[29-31] The very large increases in Ca^{2+} recorded in cortical cataract indicate that intracellular Ca^{2+} homeostasis breaks down and influx exceeds the ability of lens cells to remove Ca^{2+} from the cytosol.[29] The epithelial cell breakdown in cortical cataract causes dysfunction of active transport of electrolytes, causing passive inward movement of water.[32] Intracellular overload with Ca^{2+} in the epithelial cells triggers activation of Ca^{2+} dependent enzymes, irreversible breakdown of important structural proteins and cell death.[33] Nuclear cataract does not involve major Ca^{2+} alteration in the lens.[34,35]

The role of calcium in cataractogenesis was reviewed previously.[36] The lens epithelium is a subject of numerous studies because of its importance for functioning of the lens and its accessibility. A significant part of epithelial cell research is oriented towards the role of the altered Ca^{2+} signalling in lens epithelial cells and the effects this may have in cataract formation.[37-39] The role of lens epithelial cells in controlling the lenticular Ca^{2+} is interesting since other components of lens do not possess intracellular Ca^{2+}-store such as endoplasmic reticulum and mitochondria. In order for Ca^{2+} to act as a signalling molecule and to prevent the toxic effects of Ca^{2+} overload, intracellular Ca^{2+} is tightly regulated and the concentration of Ca^{2+} in the cytoplasm is kept low.

In our previous studies, we have used the human anterior lens capsule preparation consisting of the monolayer of anterior lens epithelial cells lying on the basal lamina, obtained during routine cataract surgeries. We have shown that the human anterior lens capsule preparation is an adequate source for investigating cellular Ca^{2+} dynamics of lens epithelial cells in different forms of cataract.[40] To investigate cellular Ca^{2+} dynamics, we used Ca^{2+} indicator dyes that allow the tracking of changes in $[Ca^{2+}]_i$ in real time. The lens epithelial cells respond to the bath application of acetylcholine (ACh) with a rise in intracellular calcium concentration, $[Ca^{2+}]_i$.[41-43] In human anterior lens epithelial cell ACh binds to M_1 muscarinic receptors and induces a rise in $[Ca^{2+}]_i$.[29,43,44] We have recently described fast contractions of lens epithelial cells[45] (Fig.1.) and found that these occur as a nonspecific response to ACh, water jet or mechanical contact. We have also found that $[Ca^{2+}]_i$ may not be directly involved in the changes of the shape of epithelial cells described, and therefore, some other mechanisms, such as activation of transient receptor potential channels (TRP channels),[46-49] may be involved in this process. During contraction, the cells stay conected to each other at several points, presumably representing regions containing desmosomes and/ or gap junctions. The gaps forming between the epithelial cells would very likely cause influx of water and seriously impair the normal function of the lens epithelium *in situ*. Water influx through these gaps may be linked to cataractogenesis, for example in injury or phakic intraocular lenses that are in contact with the cristalline lens. As contractions may be a new mechanism associated with cataractogenesis, there is a need for their further studies to assess the underlying physiological mechanisms and eventual therapeutic or prophylactic possibilities.

3. Secondary cataracts

a. Secondary cataracts in systemic disorders

i. Diabetes

Diabetes is potential cause of cataract development in affected individuals,[50,51] with cataract in diabetic patients being a major cause of blindness in developed and developing countries.[52] Aldose reductase is involved in secondary diabetic complications including cataractogenesis. It is a key enzyme of polyol pathway that catalyzes coensyme NADPH-dependent reduction of glucose to sorbitol (sorbitol pathway) and lipid aldehydes to lipid alcohols. An excessive accumulation of intracellular sorbitol found in various tissues of diabetic animals and in

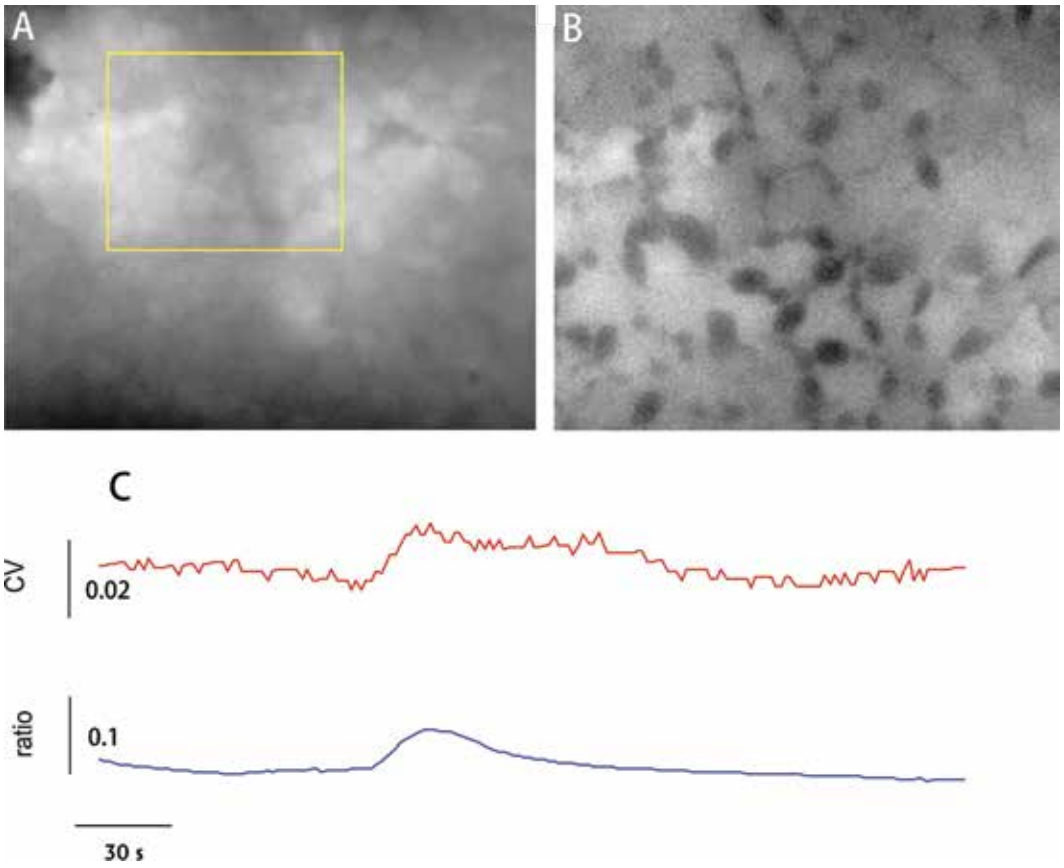

Figure 1: The contraction of the lens epithelial cells. A. Lens epithelial cells in non-contracted state, before stimulation. B. Enlarged image of the selected region of interest (yellow, A) showing the contraction of the lens epithelial cells upon ACh stimulation. C. The time courses of the coefficient of variation, indicating the changes in morphology, are shown in red and the time courses of the 360/380 ratio, proportional to $[Ca^{2+}]_i$, are shown in blue. In this case, the change in morphology starts synchronously with the Ca-response.

cells cultured under high glucose conditions has been proposed to be an important factor for the pathogenesis of diabetic complications.[53]

The intracellular accumulation of sorbitol results in hyperosmotic effects that can induce cellular swelling that initiates a cascade of biochemical steps that result in lens opacification. Among these steps is the osmotic induction of endoplasmic reticular stress [54,55] which then can initiate an unfolded protein response that generates ROS and apoptotic signaling. As sorbitol accumulates primarily in the epithelium and superficial lens fibers of the diabetic lens, free radical production is increased and natural antioxidant defenses are compromised. This results in increased oxidative stress [56-59] and apoptotic signaling.[60] This generation of ROS has been reported by many investigators.[56,57]

The rat lenses obtained from Aldose reductase knockdown rats were resistant to high glucose-induced lens opacification as compared to wild-type rat lenses. These experiments indicate a physiological role of aldose reductase in the pathophysiology of hyperglycemic cataract and the use of aldose reductase inhibitors in the prevention of cataractogenesis.[61]

ii. Homocystinuria

Cataract is frequently associated with homocystinuria. Homocystinuria is an inherited disorder in which the body is unable to process certain amino acids properly. There are multiple forms of homocystinuria, which are distinguished by their signs and symptoms and genetic cause. Homocystinuria is inherited in families as an autosomal recessive trait. Mutations in the genes for cystathionine beta synthase (CBS), methylenetetrahydrofolate reductase (MTHFR), 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR), and methylmalonic aciduria (cobalamin deficiency) cblD type, with homocystinuria (MMADHC), cause homocystinuria. Mutations in the CBS gene cause the most common form of homocystinuria.[62,63] The CBS gene provides instructions for producing enzyme cystathionine

beta-synthase that is responsible for converting the amino acid homocysteine to a molecule called cystathionine. As a result of this pathway, other amino acids, including methionine, are produced. Mutations in the CBS gene disrupt the function of cystathionine beta-synthase, preventing homocysteine from being used properly. Rarely, homocystinuria can be caused by mutations in several other genes. The enzymes made by the MTHFR, MTR, MTRR, and MMADHC genes play roles in converting homocysteine to methionine. Mutations in any of these genes prevent the enzymes from functioning properly, which leads to a buildup of homocysteine in the body.

The screening of patients for homocystinuria with and without cataract was done and analysed for homocystine and methionine.[64] Out of 29 homocystinuric patients, 24 had cataract. Only one had appreciable amounts of methionine in his serum. He also had mental retardation associated with Type I. The other types (II, III or IV) did not have methionine but had only homocystine. There was no mental retardation or ectopia lentis. As there is excess methionine in Type I, with low cysteine, cataract may be due to deficiency of cysteine and reduced glutathione and might be averted by suitable therapy, i.e., high–cysteine–low-methionine diet with B6. In other types with low methionine, cataract may be due to decreased availability of amino acids for the synthesis of lens proteins; the treatment of choice should be B12, and folate with methionine.[64]

b. Secondary cataracts in other eye diseases and conditions

i. Retinitis pigmentosa

Cataract is often also associated with the inherited retinal degenerations. Retinitis pigmentosa (RP) is a type of progressive retinal dystrophy, clinically and genetically heterogeneous group of inherited retinal disorders in which abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium of the retina lead to progressive visual loss and eventually incurable blindness. The mode of inheritance can be X-linked (xl), autosomal dominant (ad), or autosomal recessive (ar) and all of these can develop cataract.[65]

Patients with RP typically develop a combined posterior cortical and posterior subcapsular cataract which, when combined with a restricted central visual field, may cause significant additional visual disability even when the opacity appears to be relatively minor.[66] Cataract associated with retinitis pigmentosa may not occur until second or third decade.[8,66-69]

Based on a study of the Royal College of Surgeons (RCS) on rat model of retinal degeneration, posterior subcapsular cataract likely results from abnormal posterior lens fiber growth and suture formation development. Posterior subcapsular cataract develops presumably in response to toxic lipid peroxides formed by degenerating rod outer segments.[70]

ii. Uveitis

Cataract formation is one of the major complications of different forms of uveitis. Cataract development in uveitis results from chronic inflammation and as a consequence of long-term corticosteroid treatment.[71]

The etiologic cause and type of uveitis can influence not only disease course, but also the treatment response and rate of associated complications, such as cataract.[72] For example, a diagnosis of juvenile idiopathic arthritis (JIA)-associated uveitis is conected with an increased rate of cataract development and often more complicated post--extraction course in comparison to patients with other idiopathic diseases.[73,74] Risk factors for cataract include posterior synechiae and longstanding ocular inflammation.[75]

Cataract extraction with intraocular lens implantation with the control of inflammation can optimize visual outcome in adults and children with uveitis.[71] However, cataract surgery in uveitic patients is challenging.

The unpredictable behavior of some uveitic cataract capsules during capsulorhexis may occur due to changes in the capsule's ultrastructure. In white uveitic cataracts, extensive epithelial and capsular-epithelial border changes and epithelial-mesenchymal transition in some fibrotic capsules were fo-

und. Uveitic capsules showed more extensive and different ultrastructural changes that probably occurred because of inflammation in the eye than capsules of nuclear non-uveitic cataracts.[76] Intraocular inflammation causes high levels of pro-inflammatory cytokines such as TGF-b, within the aqueous humor and vitreous. These can pass across the lens capsule and induce mesenchymal transition of the anterior lens epithelium.[77]

c. Drug toxicity and cataract

Drugs can produce adverse reactions with the toxic effects of systemic and topically applied drugs manifested as cloudiness of the lens.[78]

i. Corticosteroids

Corticosteroids have long been associated with cataract, regardless of how they are administered, but the direct injection into the eye of triamcinolone, often to treat macular edema, frequently leads to a cataract.[79] Long-term use of glucocorticoids produces a characteristic posterior subcapsular cataract (PSC) and, although the opacities may remain stationary or progress, they rarely regress upon drug withdrawal.[78] Steroid-induced posterior subcapsular cataract exhibits three main distinctive characteristics: association only with steroids possessing glucocorticoid activity, involvement of aberrant migrating lens epithelial cells, and a central posterior location.[80] The evaluation of posterior capsule opacification (PCO) development after cataract surgery in eyes with or without a history of steroid use showed that steroid-induced posterior subcapsular cataract was associated with a higher risk for PCO after cataract surgery at the 1-year follow-up. [81]

The mechanisms responsible for the opacification are unknown. One proposed mechanism is that steroids do not directly act on the lens but rather affect the balance of ocular cytokines and growth factors.[82]

On the other hand, the finding of a classical, specific, functional lens glucocorticoid receptor suggests that glucocorticoids target lens epithelial cells directly, specifically, and similar to what has been observed in other cell types. The distinct changes in lens epithelial cell signaling pathways, mitogenactivated protein kinases (MAPKs) and phosphotidyl inositol-3-kinase/AKT (PI3K/AKT) regulators, suggest that glucocorticoids modulate several cellular functions.[83] The chronic glucocorticoids treatment possibly leads to prolonged modulation of these pathways and steroid-induced cataract.[84]

Glucocorticoid receptors (GR) have been shown to take part in the apoptotic process of human lens epithelial cells, but the GR antagonist RU486 does not rescue the cells fully.[85]

Dexamethasone, a steroid which has been used as a medical agent for a long time, increased expression of glucocorticoid receptors, GRE-luciferase, the GR-α gene and GR-protein and, in contrast, decreased the viability of human lens epithelial cells. The nuclear morphology of human lens epithelial cells showed an obvious apoptotic phenomenon under greater concentrations of Dexamethasone.[85,86]

ii. Sex hormones

The female sex hormone estrogen may modify rates of cataractogenesis. Ovarian hormones enhance radiation-induced cataract formation.

However, estrogen both enhances and attenuates the rate of cataractogenesis, depending on the time of hormone administration relative to the cataractogenic insult, as found with the use of a rat model of radiation-induced cataract.[87,88] The major endogenous estrogen, 17β-estradiol, has a mitogenic and anti-oxidative effects at physiologic concentrations, whereas pharmacological levels induce oxidative stress and act pro-apoptotic in cultured lens cells.[89] Hormone supplementation experiments indicate that estrogen is responsible for cataract formation.[90]

iii. Other drugs and cataract

Cataractous changes can result from antipsychotics. Systemic administration of antipsychotics phenothiazines or the anti-cancer drug busulfan induce cataractous changes in the anterior or posterior cortex, respectively.[78] Antipsychotics chlorpromazine or thioridazine, when used at high do-

sages and for prolonged periods, frequently cause lenticular opacifications.[91]

Conclusions

Cataract is responsible for the majority of visual impairments in adult humans. No clinically used non-surgical intervention exist that can prevent or treat age-related cataract. Several major risk factors for cataract formation have been identified, including increasing age, genetic predisposition, oxidative stress, exposure to UV light and other toxic agents, such as corticosteroids, and disease conditions. Understanding the process of cataract formation is of great importance. The mechanisms involved in cataractogenesis are heterogenous and not yet understood. However, there is a better understanding of the complexity of this multifactorial condition. There is a significant research work done and in progress by different groups in order to understand the cataractogenesis. Our work is also oriented in that direction. As we can conclude from this review, contemporary research is giving a significant new insights into the mechanisms of cataractogenesis, but the mechanisms do not seem to have a common denominator that would envisage possibilities of pharmacological treatment soon.

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