2

Oxidative Stress Induced Damage of the Human Retina: Overview of Mechanisms and Preventional Strategies

Katrin Engelmann[1,2,3],
Klio Ai Becker[1] and Richard Funk[2,3]
[1]*Augenklinik, Klinikum Chemnitz gGmbH,*
[2]*Institut für Anatomie, Medizinische Fakultät der TU Dresden,*
[3]*CRTD, Zentrum für Regenerative Therapien Dresden,*
DFG-Forschungszentrum und Exzellenzcluster, TU Dresden,
Germany

1. Introduction

A number of studies have shown that excessive visible light or a special wavelength (blue light) can induce damage to photoreceptor and retinal pigment epithelial cells of the retina, inducing apoptosis. Most of these studies were performed in experimental animal models. However, the mechanisms which lead to damage and subsequently to degenerative diseases like age related macular degeneration (ARMD) remain still unclear. Whether direct interaction of light with retinal cells or a secondary mechanism of transport or circulation of the retinal pigment epithelium or the choroid causes this retinal damage is currently under debate. Cellular mechanisms involved are lipid peroxidation, production of reactive oxygen species (ROS), apoptosis, DNA-damage and others. Clinical or epidemiological studies on this topic are rare and publications about light damage of retinal cells *in vivo* are difficult to achieve. Nevertheless, the clinical practise to implant yellow artificial lenses during cataract surgery is a common practise. These implants are expected to prevent blue light damage to the aging retina. We will address the fact that numerous basic scientific publications point to a rationale for this practice, although it is often difficult to derive clear-cut evidence from clinical epidemiological studies for the preventive use of yellow tinted artificial lenses. We refer to studies showing that the shortwave part of the visible spectrum of light can be harmful to the retina, especially to the macula and optic nerve. For this, we have screened the literature for the major sources of radical production and for the targets of oxidative stress after impingement of "blue light" on the retina. Furthermore, we can show that many studies in cell and molecular biology, animal experiments and first clinical trials point to a preferential use of yellow tinted lenses especially in the elderly and ARMD patients. As in several other fields, so too in this field does "cell biological knowledge" exceed clinical knowledge. Thus, prevention strategies and therapies are still missing. It is important that clinicians should become more aware of this topic so that more informed treatments decisions can be made.

2. Anatomical features of the macula and photoreceptors: Possible mechanism of blue light damage

During passage through the eye the spectrum of electromagnetic radiation (ultraviolet light (UV) UVA 280 - 315 nm and UVB 315 – 400 nm), visible light (400 – 780 nm) and infrared light (>780 nm)) undergoes different modifications: the cornea absorbs mostly short and longer wavelengths (UVA 280 - 315 nm and UVB 315 – 400 nm). Parts of UV light around 320 nm reach as far as into the lens, where they are finally absorbed. The visible part of the spectrum and only very few of the 320 nm fraction are transmitted through the vitreous body and reach the receptors of the retina. Only 1 % of the full spectrum of sunlight, or a comparable continuous spectrum, actually reaches the retina. The spectrum above 1400 nm is absorbed mainly by the water molecules (Barker & Brainard, 1991; Boettner & Wolter, 1962). With increasing age, the lens blocks more and more of the blue (short wave) fraction of light (Bron et al., 2000).

This is why some authors suggest adjusting the spectral transparency of artificial intraocular lenses to that of natural lenses of elderly persons. Indeed, some of the artificial lenses allow more passage of short wavelength light than it is found in lenses of newborn babies (van Norren & van de Kraats, 2007). The retina of elderly persons, however, is not comparable to that of a newborn.

The macula as the site of maximal retinal vision degenerates fastest because (a) it is located directly in the focus of an envisioned light source and (b) there are no other layers situated more centrally in the path of ray of lights. In the peripheral retina layers of nerve and glial cells normally filter out the short wavelengths with their cytochromes and other pigments (Algvere & Seregard 2002).

The discovery of antioxidative molecules within the macula gave a first hint that this direct impact of light onto the macula might cause oxidative damage. The antioxidative molecules are lutein (luteus, latin, means yellowish and gave the name lutea to the macula) and zeaxanthin respectively. These molecules filter out blue light due to their yellow colour. The fact that these radical scavengers are concentrated thousand-fold at this location compared with elsewhere in the retina is a real clue that too much blue light and also oxidative damages may be prevented. Indeed, many animal and cell culture experiments have shown that short wavelength light can enhance the fraction of free radicals and reactive oxygen species (Wu et al., 2006).

This is especially true for the photoreceptors. The photopigment rhodopsin is located in their outer segments, which can be induced by blue light to react in photochemical processes. This leads to intermediates, which produce radicals. That the visual cycle of the photopigments is involved in these reactions can be probed by depletion of the protein RPE65 (a protein involved in the regeneration of rhodopsin): after depletion of this protein blue light has no impact on the retina (Grimm et al., 2000a). Additionally the narcotic gas halothane can block the regeneration of rhodopsin and makes the retina insensitive to blue light impact (Keller et al., 2001). In contrast to green light, which can regenerate the bleached rhodopsin completely, blue light is only able to regenerate 30 % of it. That means that a large fraction of rhodopsin remains unbleached and is absorbing further photons and creating radical producing intermediates ("photoreversal" of rhodopsin) (Grimm et al., 2000b; Grimm et al., 2001, Organisciak et al., 1990; Wu et al., 1999a).

All-trans-retinal is a candidate of these intermediates because it is the most photosensitizing molecule (Delmelle, 1978). A triplet state can be created there by blue light, which releases free radicals (Rozanowskaet al., 1998). Thus, an excited electron can fall back into its ground state and the extra energy transfer into e.g. "reactive oxygen species" (ROS), superoxide radicals, hydrogenperoxide, hydroxyl radicals and other metabolites (Foote, 1968; Spikes & Macknight, 1972; Witting, 1965).

The radicals which originate in the rhodopsin cycle transform all-trans-retinal into di-retinoid-pyridinium-ethanolamine (A2E, see below). This metabolite then accumulates as most dangerous component of lipofuscin in the retinal pigment epithelium (RPE) (Katz et al., 1994; Katz & Gao, 1995; Katz et al., 1996; Wassel & Boulton, 1997).

Moreover, the highest concentration of polyunsaturated fatty acids within the human body is found within the outer segments of the photoreceptors. These lipids are oxidized along with the outer segments of the photoreceptors also by impinging blue light.

Furthermore, carboxyethylpyrrol-modified proteins (CEP, derivates of the non enzymatic oxidation of docosahexanoid acid) are in discussion as very harmful components (see below).

The regeneration of the outer segments by renewal and shedding of discs prevents the accumulation of too many products of oxidation in the outer segments. About 10 of the 100 disci in the outer segments shed per day. Then they are phagocytosed by the RPE – this means 3 billion times in the eyes of a 70 year old person over his or her lifetime (Birch et al., 1984; Marshall, 1987;Young, 1971).

3. Blood retinal barriers, retinal capillaries and choriocapillaries

It is a further peculiarity that the photoreceptors, as specialized nerve cells, reach out with the outer segment into a micro–milieu which is totally different from that of neural (inner, ellipsoid, perikaryon and neurite with the synapses) part of the cell: the neural part is supplied by a microcirculatory unit (the retinal capillaries) which is typical for the central nervous system. Here, capillaries with a small lumen and tight endothelium are characteristic of glial cells (Müller cells) in the immediate vicinity.

In contrast to this, the outer segments are embedded within the interphotoreceptor matrix. This contains special proteins and hyaluronic acid (Acharya et al., 2000; Hollyfield, 1999; Hollyfield et al., 2001) and the outer segments "bathe" in a sea of plasma, which is supplied by the sea of blood within the choriocapillaries (fenestrated capillaries) and choroid (Funk, 1997). The membrana limitans externa serves as watershed zone between both regions.

The choroid is regulated only minimally via the concentration of oxygen, thus, very high concentrations of oxygen can occur in the outer segments which are independent of the oxygen consumption, a fact which makes this system prone to oxidative stress (Wu et al., 2006). The mitochondria deliver the vast amount of energy which is needed for the steady synthesis of the outer segment disci. The photoreceptors consume via mitochondria 3-4 times more energy than all other retinal neurons or cells in the central nervous system. They are probably the cells with the highest oxygen consumption of all (Alder et al., 1990; Linsenmeier et al., 1998). Moreover, the mitochondria are the organelles which are preferentially susceptible to oxidative stress (Field et al., 2011): they harbour the enzymes of the respiratory chain which handle electrons. Under normal circumstances, this works with

only a small leakage of free radicals. However, if the mitochondria are under stress or if they are pre-damaged by multiple small genetic failures then radicals can spread out into the cell (Jang & Remmen, 2009). Therefore damage to mitochondrial DNA can occur with increasing frequency as age advances.

The effect of short wavelength light on the metabolism of mitochondria has been an important topic of experimental *in vitro and in vivo* studies. Indeed, the studies of King et al. (2004) could show that blue light impact leads to an enhanced production of radicals in mitochondria. Molecules of the respiratory chain like flavins and cytochromoxidases can absorb at wavelength of 440 – 450 nm and they can cause the production of ROS and oxidative stress (Lascaratos et al., 2007).

What does this mean for the retina as a whole? The photoreceptors are stuffed with mitochondria in their inner segment, especially in the ellipsoid. The disci of the outer segments probably get loaded with radicals by these mitochondria. In addition they are sources of radical production and indeed, vast amounts of radicals are produced if photoreceptors are loaded with blue light (Yang et al., 2003).

Not only the photoreceptors but also the retinal ganglion cells, which contain numerous mitochondria, are prone to blue light damage. Studies of Osborne et al. (2008) showed that blue light was ineffective regarding radical damage in cells which are depleted of mitochondria.

An important new aspect linking blue light damage and genesis of glaucoma should be noted (Osborne et al., 2006): The axons of the retinal ganglion cells possess no myelin sheath because lipid sheets would not allow the light to pass through the retina. So a myelin sheath is not built before the passage through the sclera via the lamina cribrosa. This is unique amongst the body's neurons because normally the neurons are only non–myelinated at the end of their processes. This causes a so-called “impendance mismatch“, which leads to an enormous additional energy consumption. This additional energy is delivered by small clusters of mitochondria located in bulges along the axons from the ganglion cells till the optic papilla.

4. Experimental studies regarding light-induced damage of the retina

Regarding the retina as a whole, experimental studies have revealed the layers which are damaged by intense light (Noell, 1965; Noell et al., 1966).

Wenzel et al. (2005) showed damage and apoptotic processes especially in the photoreceptors. This fact is believed to be the main cause of the light induced cell stress.

Several animal studies demonstrated that light exposure leads to lipid oxidation. So Wiegand et al. (1983) assumed that the peroxidation of polyunsaturated fatty acids due to light is a cause for light-induced retinal degeneration. Here, antioxidative substances could prevent this effect (Tanito, et al., 2006).

Both short intense exposure to light and longer continous low-light exposure (e.g. light bulb emissions for several weeks or months) have been shown to lead to retinal damages in rat retina (Kuwabara & Gom, 1968; O`Steen et al., 1972). Interestingly, the first damages took place in the outer segments of the photoreceptors thereafter the mitochondria in the inner

segment began to swell. Also in monkeys, similar photoreceptor damage occurs after irradiation with light emission bulbs (Sykes et al., 1981). Here again the central part of the retina, the macula, is affected.

It is noteworthy that after a very high but short (1000 sec) dose the retinal pigment epithelium (RPE) but not the photoreceptors is damaged following irradiation (Ham et al., 1978). The RPE has to digest daily about 1/10 of the photoreceptor mass – together with this all the oxidation products and damaged molecules (see above; "disc shedding") (Bok, 1993).

As previously noted, blue light may induce damage by induction of intermediate reactive species, which act in the outer segments of the photoreceptors. These intermediates produce oxidated photopigments, proteins and probably also products of the lipid oxidation, substances which than are phagocytosed by the RPE. For this purpose RPE–cells posses besides of lysosomes also microperoxisomes, delivering peroxides for intracellular digestion and have a function for detoxification and antioxidation (Bok, 1993). They also regenerate the visual pigments (Bok, 1990).

All these enumerated metabolic products together build up the age-related pigment lipofuscin. Lipofuscin accumulates during life time in the RPE especially in ARMD. It leads to many damaging effects, including generation of ROS (Boulton et al., 1993) and phototoxicity (Davies et al., 2001). One specific lipofuscin fraction is A2E. This orange-reflecting pyridinium bisretinoid is a metabolite of the retinoid cycle. Data implicates that lipofuscin is an agent that makes RPE cells more sensitive to photooxidative stress. The action curve of blue light damages, the so-called blue light hazard, has a peak around 440 nm. Here, it seems very probable that the impact at this wavelength light is dominated by the chromophor A2E (Sparrow & Cai, 2001). If A2E has absorbed a photon, especially of the wavelength 430 – 440, then free radicals are generated, mostly ROS as mentioned above (Boulton et al., 1993; Gaillard et al., 1995). So Wielgus et al. (2010) were able to show that if albino rats were exposed to blue light (450 nm, 3,1 mW cm $^{-2}$), especially the oxidized form of A2E increased. This seems to be especially responsible for the damaging process of retinal cells. Recently it has been shown that A2E generates toxic oxidative products after adsorption of blue light (for review, see (Holz et al., 2004)). This results in a damaging cascade of cell function and the expression of inflammatory and angiogenic substances (Wihlmark et al., 1997; Rezai et al., 2008; Schutt et al., 2000; Sparrow et al., 2000). So A2E inhibits important functions of the cell and is able to increase the apoptosis of the RPE.

It has been shown that a significantly higher rate of cell death occurs in lipofuscin or chromophor A2E loaded retinal pigmented epithelial cells *in vitro*, when these cells were exposed to blue light (430 ± 30 nm) than when they are exposed to white light (390 till 750 nm) (Sparrow et al., 2004). But Tanito et al. (2005) found that an intensified exposure to white light induced also protein modifications. This reaction is mediated by 4-HNE and 4-hydroxyhexanal. Both are reactive aldehydes, which are produced during enzymatic oxidation of n-6 und n-3 nonsaturated fatty acids. The protein modifications did not occur if radical scavengers like phenyl-N-*TERT*-butylnitrone (PBN) were used in this *in vitro* system. Additionally, apoptosis of photoreceptors did not occur (Tanito et al., 2005; Ranchon et al., 2003). Thus, it was speculated, that the 4-HNE–based protein modifications may function as an indicator for oxidative stress which could be detected also in hereditary diseases like Retinitis Pigmentosa (Shen et al., 2005). Another possible marker for oxidative stress is the

carboxyethylpyrrol (CEP)-modified protein, a derivate of the non–enzymatic oxidation of the docosahexanoid acid. This protein modification could also be demonstrated in an ARMD eye (Crabb et al., 2002; Gu et al., 2003). A CEP – modification could also be identified after irradiation with blue light of shorter and longer wavelengths (Dunaief et al., 2002).

So we can summarize that chemical reaction of lipids and proteins induced by radical actions can be induced by oxidation as well as "blue light". This may lead to products (adducts) like "advanced lipid end products" (ALEs). This reaction is analogue to the reaction which induces a cross linking of proteins and carbohydrates (advanced glycation end products, AGEs, processed in the so-called "Maillard" reaction). These AGEs accumulate together with lipid oxidation products in extra cellular space (e.g. the Bruch Membrane) as well as within cells e.g. within the RPE (Glenn et al., 2009; Howes et al., 2004). Protein-sugar products or the protein – lipid oxidation products (e.g. CEP) can accumulate also in the intra cellular space and build up an important component of lipofuscin (see also (Schmidt et al., 2008).

The experimental data regarding "blue light damage" to photoreceptors shows that the recycling of the visual pigments in the retinoid cycle can be stressed by bright blue light. In doing so reactive intermediate are formed, which can generate radicals by themselves (Grimm et al., 2000a). Furthermore, the high concentration of polyunsaturated fatty acids favours the oxidation of lipids. In addition, advanced glycation end products enhance the formation of radicals.

Pigmented epithelial cells suffer from the overload of oxidized discs e.g. A2E in the outer segments because RPE cells have to phagocytise these products of oxidation (Wu et al., 1999a; Wu et al., 1999b).

Both radical sources the photoreceptor outer segment with their lipid membranes and the mitochondria can potentiate mutually: e.g. A2E can block the transfer of cytochrome C to complex IV in the respiratory chain; by this a deviation of electrons and cytochrome C takes place. The latter can induce apoptosis via typical signalling cascades (Shaban & Richter, 2002).

5. Light intensity and animal studies

Young primates were used to investigate the mechanisms of damage by specific parts of the spectrum (violet and blue-green) (Ham et al., 1976; Ham et al., 1979). It was found that light with damaging wavelengths does not correlate with light adsorption lines of the photo pigments like rhodopsin. That is why this group assumes other mechanisms of electron excitation and followed radical damage (Ham et al., 1976). On the other hand, other authors demonstrate that also low dosages of light can induce significant amounts of radicals (Lawwill et al., 1977). A cumulative damage occurs in the retina during this kind of irradiation. Here, fractionated doses of light are acting with higher intensity then comparable - although continuous – actions. This effect does not occur if the retina is allowed to regenerate in a longer dark period (Noell et al., 1966; Ham et al., 1979; Lawwill et al., 1977; Tsò et al., 1972).

When considering translation of these observations into a better understanding of human eyes, the following factors are important: the light dose, the duration and the time points of actions (also during day – night cycle).

6. Quality of light and adaptation

Sunlight possesses a continuous spectrum also in the long wavelength range (with a few dips due to water absorption, see below). Neon-strip lamps and energy saving bulbs have discontinuous spectra (only several peaks in the short- and middle wavelength part). This artificial light often is not very bright; however, the eye perceives this in a relative way. The eye adjusts its sensitivity over the whole spectral range as an integral over many wavelengths. If there are too few peaks e.g. due to the absence of some wavelengths, then the sensitivity of the eye increases. The retina produces more photopigment and a mydriasis occurs. So damaging wavelengths can be more harmful than under bright sunlight. Many experimental studies proof the capability of the photoreceptors to adapt by the mechanism mentioned above. Rats which were reared in darkness have an enhanced amount of rhodopsin (Noell, 1979). This can lead to an increased loss of photoreceptors after light exposure compared to animals reared under a normal day-night cycle (Battelle & LaVail, 1978; Organisciak & Noell, 1977; Organisciak et al., 1985; Penn & Anderson, 1987; Penn et al., 1987). Furthermore, the retinal cells can adapt in the antioxidative capacity, too.

6.1 Time of exposure

Nowadays we spend most of our time under relatively bright artificial light, especially at night times e.g. in shift working. In prior centuries people were working under dim candle or incandescent lamp at night time.

The human body is much more vulnerable to environmental stress in times of activation of the parasympathetic tone and in times of regeneration. More melatonin is released in the night than in times under the sympathetic tone due to activity.

Finally, an important factor cannot be mimicked correctly in cell- and animal experiments: the absolute duration of light impact and of other additional stressors, which can last for years and decades in a human lifetime.

7. Protective role of defined parts of the light spectrum

Opposite to the action of blue light, red or infrared light can have positive effects – a fact which is described in more and more recent studies (Eells et al., 2004; Wong-Riley et al., 2005; Albarracin et al., 2011)

These parts of the light spectrum are present in all continuous spectra of natural light sources like sun or fire but also in incandescent or halogen lamps. Only in recent years have studies shown the positive effects of red or infrared light for regeneration processes in the retina. Here also, the mitochondrium seems to play a major role (Liang et al., 2008).

8. Pathogenesis of ARMD – The role of short wave light

The age related macular degeneration (ARMD) has become a leading cause for blindness in elderly persons (> 60 years) in the industrial world (Klein et al., 1992). ARMD is a degenerative disease caused by multiple factors. It seems that the kind of light to which a person`s eyes has been exposed may play a role. Over the last decades industrialisation makes a night a day. So the intensity and life-long duration of high light dosages increased

(Mainster et al., 1983; Margrain et al., 2004). This interferes with the sensitivity of the macula to light damage as explained above by the anatomical and cell-biological considerations. Another important factor for degenerative diseases is the increasing lifespan of people (Schrader, 2006).

The late form of ARMD – wet or exsudative ARMD – is mainly caused by angiogenesis. Fortunately anti-angiogenetic therapies became available for such patients during the last years (Holz et al., 2004). But therapeutic strategies for the early stages of ARMD are missing up to now. One reason is the poor understanding of key mechanism which results in degeneration of the different cell types of the macula. Also, specific pathologies of ARMD like detachment of the pigment epithelium or geographic atrophy are still poorly understood, although models based on cellular mechanisms are beginning to be discussed. It has been shown that in the case of geographic atrophy degeneration started in all cell types, the RPE, the photoreceptors and in the choroidea. Previously it was assumed that the degeneration started in the RPE (Grebe et al., 2009).

During the last years a genetic predisposition for ARMD came into focus. Two gene loci were identified which are related to ARMD and which can be both used to explain the above mentioned pathogenetic concept. These loci are the complement factor H (CFH) and C3 which normally down-regulate inflammatory processes. Other candidates are the high temperature requirement factor A1 (HTRA1) and LOC387715/ARMS2 (Age-related maculopathy susceptibility 2) and additionally a locus that is responsible for the synthesis of the mitochondrial membranes. Furthermore two mutations of the locus ABCA4 were found. ABCA4 regulates the ATP – binding cassette reporter in the discs of the photoreceptor outer segments. This reporter replaces worn out molecules of the visual pigment and impedes an accumulation of toxic metabolites (Scholl et al., 2007; Swaroop et al., 2007).

It is interesting that Gu et al. (2009) found out that modifications (CEP adducts) and antibodies against CEP-proteins were found in higher concentration in the blood plasma of AMD patients. Patients with the ARMS2 and HTRA1 allele, which leads to a higher AMD risk, showed especially elevated CEP-markers.

There are some hints and observations that in the living human eye radicals may be produced also in mitochondria. Mitochondrial DNA deletions and deficiencies of cytochrome c oxidase (complex IV of the respiratory chain) were detected preferentially in the cones of the fovea centralis of aging retina (Barron et al., 2001).

9. Experimental studies on blue light action and on the use of tinted intraocular lenses

If the hypothesis is true that an increase in the overall amount of irradiation dose and especially a higher percentage of blue light may trigger the ARMD process towards higher stages after removal of the natural lens, it seems logical to examine light effects on the known pathomechanisms for early and late ARMD. Only few valid data from epidemiological studies can currently be generated. In contrast multiple cell-based and animal studies were performed to investigate the effect of yellow tinted intraocular lenses:

In cell cultures of retinal pigmented epithelial cells toxicity tests were performed (Rezai et al., 2008). It could be shown for fetal RPE cells that exposure to blue light (430 - 450 nm) up

to 10 days was accompanied by an increasing rate of apoptosis (up to 85 % cell death). If the cell culture dishes were covered with yellow tinted artificial lenses (Acryl-Soft-Natural-Filter) the apoptosis rate could be reduced to 37% (Rezai et al., 2008).

Nilsson et al. (1989) investigated the reaction of Xenon light exposure over 3.5 hours to rabbit eyes. Untinted or yellow tinted lenses were used to protect the eyes. In the eyes treated with clear lenses a reduction of the b- and c waves in the electroretinogram (ERG) became visible in contrast to the tinted lenses. This experiment was one of the first that gave hints to a possible light damage of retinal tissue.

Tanito et al. (2006) demonstrated the damaging effect of blue light (both short and longer waves) using rats. The animals were exposed for 7 days to blue light with and without yellow light filter. Especially in case of short wavelengths of the blue light a reduction in the cell count of the outer nuclear cell layer (ONL) was found. In addition the a- and b-waves in the ERG were reduced in these rats. Postmortally the retinal tissue of the irradiated eyes was examined with respect to the protein modification 4-HNE and CEP. Western blot and enzymometric analysis showed a stronger reaction in the eyes which were not protected with yellow lenses. The relatively short exposure time to blue light was a disadvantage of the here described animal experiments. Another fact is that the experiments were performed on "healthy" retinas. Therefore it can be suggested that the elderly human eye would have shown much more oxidative damage due to extremely long exposure time respectively years compared to the experimental situation.

10. Evidence of light damage in epidemiological studies

Severe sclerosis of the lens nucleus seems to protect people against acquiring degenerative diseases of the macula (Sperduto et al., 1981; West et al., 1989). On the other hand few studies showed that ARMD is significantly increased in pseudophakic or aphakic eyes (Mitchell et al., 1995; Mitchell et al., 2002; van Newkirk et al., 2000; Wang et al., 2003, Wang et al., 1999). Other authors could not find a significant difference (Wang et al., 1999). In pseudophakic eyes with clear artificial lenses, blue sensitive cones are the first photoreceptors, which decrease in number – due to specific light damage (Werner et al., 1989). Moreover, in histopathological sections of ARMD eyes a higher incidence of severe stages of ARMD was observed (van der Schaft et al., 1994).

One of the first who speculated about a higher incidence of wet ARMD after cataract extraction was Pollak et al. (1996). The retrospective character of the study, the small number of patients and the short follow-up time were criticized. Up to now only non-multicenter studies were initiated and therefore only small studies can be found regarding the question: Can blue light induce wet ARMD or induce a progress of dry ARMD? Some of these studies are discussed here: Photodynamic treatment (PDT) needed for subfoveal chorioretinal neovascularisations (CNVs) after cataract surgery in comparison to a control group was investigated (Kaiserman et al., 2007). In this study data of 5913 patients after lens extraction were evaluated and compared to 29565 matched controls. Follow-up time was about four years (1/2001 to 5/2005). The average patient age was comparable in both groups at 74 years. After cataract extraction PDT was significantly higher in pseudophacic eyes of patients compared to phacic eyes during the first 6 months and 1 to 1.5 years after

cataract surgery (p=0.004 and p=0.001). However, no differences were observed between both groups prior to surgery. On the other hand PDT 12 month after cataract extraction was comparable in both groups. This study showed an increased risk to develop exsudative ARMD during a "vulnerable" phase directly after cataract extraction. This might be due to a sudden drop down of the protection of the patient-own, aged, and yellow tinted natural lens. The authors also discussed that the higher treatment rate might be caused by better prerequisites for ophthalmoscopic examination after removal of an opacified lens. This argument of a better view on the retina also animated other authors to look at retrospective data of cataract patients. Baatz et al. (2008) did not find a difference between the control and treatment group. A disadvantage of this study is the relatively short follow up time and the heterogeneity between the number of patients in which a fluorescein angiography was performed (177 prior to surgery, 225 after surgery and 97 in the control group). An angiogram was only performed if the clinical examination gave a clue for ARMD.

Blue Mountain Eye Study und Beaver Dam Eye Study indicated a higher incidence of ARMD after cataract extraction (Cugati et al., 2006; Wang et al., 2003).

The Australian Prospective Study of Cataract Surgery and Age-Related Macular Degeneration Study (Cugati et al., 2007) evaluated data from 2000 patients over a follow-up time of five years and at the time of publication about 1600 patients were included. If the preoperative fundus photography was not analysable due to dense cataract the 1-month post-operative retinal photographs were set as a preoperative status. This was based on the fact that a primary documentation of the macular was missing in all prior non-comparable studies. It is assumed that this study will be a sufficient basis for further discussion. Sufficient data are not available yet.

It can be assumed that the results of the published data may lead surgeons to restrict cataract extraction in ARMD patients. However, Armbrecht et al. (2000) and Shuttleworth and Galloway (1999) demonstrated that quality of life of ARMD patients increased after cataract surgery. The data were evaluated using standardized "Quality of Life" questionnaires. Especially, the specific and differentiated visual functions improved in patients with moderate cataract and ARMD (Armbrecht et al., 2000). In a pseudophakic group, which was examined by Shuttleworth et al. (1998), 10.1% of the patients showed a progression of ARMD, in 2% a CNV developed. Nevertheless, most of these studies included too few patients and were not randomized. On the other hand no disadvantages due to the use of yellow tinted artificial lenses have yet been described. So other authors support their use for preventive purposes (Falkner-Radler et al., 2008).

All published data coming from of larger or small retro- or prospective studies as well as of epidemiological studies used different criteria for the development of ARMD. Therefore, it is not possible to draw firm conclusions from current data. Is this reason enough to choose to implant yellow tinted lenses? Efforts should be made in clinical and basic preventive research to minimize the socioeconomic costs of this widespread disease ARMD. We hypothesise that other questions should be raised independent of clinical trials: What happens during cataract extraction that could lead to a progress of ARMD? And is the use of yellow tinted lenses in cataract patients still justified?

An interesting hypothesis was raised by Wegner and Khoramnia (2011). He claimed that the age-related cataract is not a single disease, but is induced by a retinal messenger of unknown character. So beside the protection of the eye from oxidative stress through e.g. high levels of vitamin C in the anterior and posterior fluids of the eye, the yellow pigments and isomers of a hydroycarotenoid, lutein and zeaxanthin are effective in protection of the macula. Both are powerful anti-oxidants and function as a filter for short wavelength blue light, thus limiting oxidative damage and stress to the retinal cells and inhibiting apoptosis (Snodderly, 1995). The macular pigment functions as a natural filter or "protector" that commonly decreases in density throughout the years in elderly persons (Beatty et al., 2001; Hammond & Caruso-Avery, 2000). Based on these facts Wegner hypothesised that with decreasing levels of protection by the macular pigment a retinal messenger is generated. This triggers cataract-formation as a self-defence reaction. Therefore, both cataract formation and ARMD development may depend on each other (Wegner A et al., 2011). Based on this hypothesis the implantation of blue filtering artificial lenses may be justified as a substitute for the "protective" elderly natural tinted yellow lens.

11. Oxidative stress and phako emulsification

It can be assumed that only a few surgeons know about the fact that during phaco emulsification oxidative stress is induced. In the past, the focus was set to mechanical damage through ultra sonic or the rinsing process during cataract extraction (for review, see Takahashi 2005). There are many reports about the induction of free radicals by ultra sound energy. This process is described as "acoustic cavitation" (Riesz & Kondo, 1992). Water molecules are disintegrated with potential formation of hydroxyl radicals that are most effective in their biological action. This phenomenon is called sonolysis. The specification of the different species of free radicals is complicate and guides the chosen test method and handling of the probes. Free radicals were described first at the beginning of the 1950s (Heimberg et al. 1953, Beauchamp & Fridovich 1970). The influence of such free radicals as damaging agent for the corneal endothelium, the most sensitive cell layer of the cornea was evaluated first. To protect the corneal endothelium from free radical damage during phaco emulsification high viscoelastic substances supplemented with natrium hyalurate as a radical scavenger were developed. Only few are known: Has the decreasing level of vitamin C in the anterior chamber a negative role? This ascorbic acid is highly concentrated in the anterior chamber compared to the blood-levels (anterior chamber 4.3 mg/dl blood plasma 0.8 mg/dl) and it plays an important role as a radical scavenger (Miratshi et al 2005). Therefore, it is not surprising that Rubowitz et al (Nemet et al., 2007; Rubowitz 2003) demonstrated a protective effect of ascorbic acid to prevent endothelial damage. Also other molecules, which act as antioxidants are relevant. Augustin and Dick (2004) found an elevated lipid peroxide level after phakoemulsification in 130 patients. The level correlated positively with the time of ultrasonic exposure during surgery. Even if this oxidative stress can be minimized using viscoelastic substances during surgery, we do not know what happens after the removal of these substances at the end of phacoemulsification. The aqueous humour is exchanged with a salt solution which does not represent the natural liquid environment, e.g by a reduced level of natural antioxidants. In an animal model it needs more than 15 days to build up a normal ascorbic acid level in the anterior chamber after experimental surgery (De Biaggi et al., 2006) On the other hand the overall protein amount in the anterior chamber increased as a sign of stress (De Biaggi et al., 2006). It is

supposed that this reconstitution is induced by ROS, which are also known to act as damaging agents (Cameron et al., 2001). Oxidative stress induced by "acoustic cavitation" should not be ignored especially if the retina or macula is impaired also. It is reported that cataract formation may be enhanced in patients with a generally reduced "antioxidative status" (Dherani et al., 2009), even if such data are difficult to evaluate with respect to different population and diseases. Nevertheless, the addition of several factors can potentiate the perioperative stress factors in real patient situations, and it is also conceivable that degeneration in the macula may be stimulated (Yagihashi et al., 2007). Even if it is a multifactorial, and therefore difficult, research field, it seems to be important to look deeper into the epidemiological field especially in times of aging populations.

12. Conclusion

Evidence-based medicine unquestionably improves the quality of the practice of medicine. However, it can often be difficult to generate sufficient evidence for the best treatment of degenerative, multi-factorial, chronic diseases like ARMD from clinical and epidemiological data alone. The implantation of artificial lenses that filter blue light is such an example, and the discussion on this topic is vigorous. There are good arguments for their use, and a few against, but strong clinical evidence is difficult to find. In the end, arguments for or against protection from blue light may be too focused: Does this discussion really matter in the treatment of a degenerative disease like ARMD? In our opinion, it is desirable that the preventive or protective aspects of treating degenerative diseases like ARMD should become an increasing focus of medical and scientific research, especially as the population ages. However, practical considerations suggest that the development of preventive and protective strategies should not be excluded in the absence of rigorous clinical studies. It is simply not possible to design and execute studies for such a complex, multifactorial disease. The state of research into the protective effects of supplements, e.g. antioxidants such as the macula pigments lutein and zeaxanthin, presents similar questions over which different clinical specialties (e.g. ophthalmologists vs. nutrition specialists) may argue. This is in contrast to the often clear results of cell-biological experiments. These reveal strong arguments for a protection against too much blue light or regarding to a deficiency of preventional factors inside the eye. We may find ourselves at the beginning of the development of preventive strategies, which must be developed from various points of view especially for such a multi-factorial disease as ARMD. However, we must also be prepared to accept a perpetual discrepancy between the rigorous scientific data obtainable from cell biology experiments and the difficulty of interpreting these data into meaningful therapeutic strategies.

There will certainly be many things to consider. For example, take the argument that blue light is important for the daily light balance for the body (sleeping-waking rhythms), while one should also be mindful of a potential blue light "overdose" due to night-time light intensity and unnaturally high blue-light rays from energy saving light bulbs, LEDs, televisions (LCD, plasma, or cathode ray), and long hours in front of the computer. These lifestyle-induced changes in people's light balance are difficult to account for and separate in current arguments. It is known that blue light (e.g. from LED diodes) reduces melatonin production and increases activity in younger people (which have relatively high levels compared to the markedly reduced levels of melatonin in elderly persons) (West et al. 1989).

Does this suggest similar activity (and also no yellow lenses) for older people? Do the elderly not already get too little sleep for proper regeneration? We already know that melatonin production is reduced in older people. Before we speculate too much on the role of the sleep-wake cycle, we should increase age-related research.

However, perhaps these considerations could help us to reflect better on our lifestyles. What external factors influence our physical and psychological conditions? If we are aware of the possible consequences of lifestyle choices, then we may pay closer attention to these influences. We may come to find potentially protective options in other fields, as tinted artificial lenses may offer in cataract surgery. In conclusion, although traditional clinical studies cannot answer such complex, multifactorial questions completely, the other experimental results discussed here may nonetheless be useful in devising new therapeutic strategies.

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14. References

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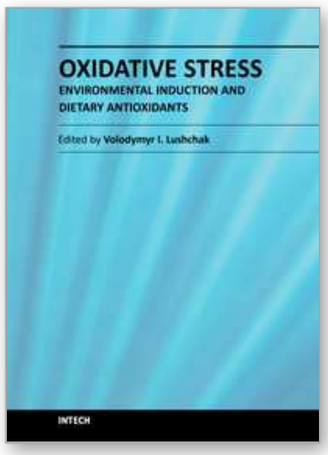

Oxidative Stress - Environmental Induction and Dietary Antioxidants

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This book focuses on the numerous applications of oxidative stress theory in effects of environmental factors on biological systems. The topics reviewed cover induction of oxidative stress by physical, chemical, and biological factors in humans, animals, plants and fungi. The physical factors include temperature, light and exercise. Chemical induction is related to metal ions and pesticides, whereas the biological one highlights host-pathogen interaction and stress effects on secretory systems. Antioxidants, represented by a large range of individual compounds and their mixtures of natural origin and those chemically synthesized to prevent or fix negative effects of reactive species are also described in the book. This volume will be a useful source of information on induction and effects of oxidative stress on living organisms for graduate and postgraduate students, researchers, physicians, and environmentalists.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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