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Dose dependent cataractogenesis and Maximum Tolerable Dose ($MTD_{2.3:16}$) for UVR 300 nm-induced cataract in C57BL/6J mice

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Abstract

The purpose of the present study was to investigate the in vivo dose response function for UVR 300 nm-induced cataract in the C57BL/6J mouse lens and to establish a cataract threshold estimate expressed as Maximum Tolerable Dose ($MTD_{2.3:16}$) for UVR 300 nm-induced cataract in the C57BL/6J mouse lens. Knowledge of the $MTD_{2.3:16}$ in the C57BL/6J mouse will permit quantitative in vivo comparison of UVR-B threshold sensitivity of knockout mice, e.g. animals deficient in key antioxidative enzymes or mice suffering from genetically predetermined eye disease, to wild type animals. Eighty C57BL/6J mice were divided into four dose groups. The animals were exposed unilaterally to 0, 2, 4, or 8 kJ/m^2 UVR 300 nm for 15 min ($n = 20$). The radiation output of the UVR-source had λ_{max} at 302.6 nm with 5 nm full width at half maximum. Two days after exposure cataract was quantified as forward lens light scattering intensity in the exposed and the contralateral non-exposed lens. Morphological lens changes were documented using grid and dark field illumination photography. $MTD_{2.3:16}$ was estimated from the forward light scattering measurements. Two days after exposure mainly anterior subcapsular but also cortical and nuclear cataract developed in lenses that had received 2, 4, and 8 kJ/m^2 UVR 300 nm. Forward light scattering intensity increased with increasing UVR 300 nm dose. $MTD_{2.3:16}$ for the mouse lens was estimated to 2.9 kJ/m^2 UVR 300 nm. Lens light scattering intensity in the C57BL/6J mouse lens increases with UVR 300 nm in vivo dose in the range 0–8 kJ/m^2. The $MTD_{2.3:16}$ of 2.9 kJ/m^2 in the C57BL/6J mouse lens determined here, is essential to quantify and compare in vivo the impact of genetic modulation on lens susceptibility to oxidative stress and plan dose-ranges in future investigations of UVR 300 nm-induced cataract pathogenesis.

Keywords: UVR-B; cataract; oxidative stress; dose-response relationship; C57BL/6J mouse; Maximum Tolerable Dose ($MTD_{2.3:16}$); light scattering

1. Introduction

The current paper addresses the dose-response function for UVR 300 nm-induced cataract, and defines a threshold estimate, Maximum Tolerable Dose ($MTD_{2.3:16}$), for UVR-B induced cataract in the C57BL/6J mouse lens.

Cataract is currently the number one cause of blindness in the world and there are no strategies to prevent the onset of the disease (McCarty and Taylor, 2002). Cataract surgery, the most common procedure performed by ophthalmologists in industrialized countries, accounts for 10% of the annual health care budget, $4.1 billion, in the United States alone (Busbee et al., 2003). The demographic development of the world population and the rising demand for independent high-quality living at high age generates a quickly growing demand for cataract surgery. As a result the financial load on national and international health care systems increases rapidly. Cataract therefore represents not only a significant medical concern but has also a growing socioeconomic impact.

Oxidative damage is currently held to be a major cause of age related nuclear cataract (Truscott, 2005). It is widely accepted that photo-oxidative stress induced cataract can be caused by continuous high-energy photon induced generation

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of reactive oxygen species (ROS) such as singlet oxygen, superoxide, hydroxyl radical, and hydrogen peroxide, in the lens. Hydrogen peroxide was proposed as the major oxidant contributing to cataract formation already in 1995 (Spector, 1995). UVR may be a source of exogenously induced ROS stress in the lens (Lou, 2003). Epidemiological and experimental evidence has consistently demonstrated that exposure to UVR-B induces cataract in humans and in animals (Taylor et al., 1988; Cruickshanks et al., 1992; Jose and Pitts, 1985; Zigman et al., 1991). Experimental evidence indicates a maximum lens sensitivity to UVR at wavelengths around 300 nm (Merriam et al., 2000; Pitts et al., 1977), and shows that UVR 300 nm penetrates a short distance into the lens (Dillon et al., 1999; Löfgren and Söderberg, 2001).

Until today, the impact of genetic modulation on lens sensitivity to oxidative stress, from exposure to UVR, remains unexplored. We have previously reported $MTD_{2.3:16}$ for UVR 300 nm-induced cataract in the Sprague–Dawley rat (Söderberg et al., 2002; Mody et al., 2006) and demonstrated that lens sensitivity to UVR-B is age-dependant (Dong et al., 2005). Importantly, the C57BL/6 mouse, unlike other species, offers the possibility to study the effects of genetic modulation, on altered lens sensitivity to oxidative stress, using knockout- and transgenic animals. Recent data by Wolf et al. support the importance of ROS damage in the development of age related cataracts in different knockout mouse models (Wolf et al., 2005). We have characterized light scattering level and variability in the normal C57BL/6J mouse lens (Meyer et al., 2007) and studied the evolution of acute cataract development following single high-dose UVR-B exposure (Meyer et al., 2005).

The purpose of the present investigation was to determine the dose-response relationship and to define a cataract threshold estimate expressed as ($MTD_{2.3:16}$) for UVR-B induced cataract in the wild type C57BL/6J mouse lens. The Maximum Tolerable Dose ($MTD_{2.3:16}$) is a threshold dose concept for toxic agents expressing a continuous dose-response function (Michael et al., 1998; Söderberg et al., 2002; Dong et al., 2005), such as UVR-B induced cataractogenesis. The concept is an alternative to the No-Observed-Adverse-Effect Level (NOAEL) approach and the Benchmark Dose (BMD) method (Falk Filipsson et al., 2003). $MTD_{2.3:16}$ is here defined as the exposure dose at which there is a 16% probability that the difference of light scattering between exposed and contralateral lens is as high or higher than found in less than 2.3% lens pairs of non-exposed animals.

Knowledge of $MTD_{2.3:16}$ for the mouse lens is necessary to allow future investigations of the effect of genetic modulation on in vivo UVR-B sensitivity by comparing wild type C57BL/6J mice with genetically modified mice.

2. Materials and methods

Six weeks old C57BL/6J female mice obtained from Charles River Laboratories (Charles River Laboratories, Sulzfeld, Germany) were unilaterally exposed in vivo to UVR-B. All animals were maintained and treated according to the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research. Ethical approval was obtained from the Northern Stockholm Animal Experiments Ethics Committee Protocol Number 227/03.

2.1. Experimental devices

UVR-B in the 300 nm wavelength region (UVR 300 nm) was generated with a high-pressure mercury arc lamp. The emerging radiation was collimated, passed through a water filter and focused on the entrance slit of a double monochromator. The exciting beam had a $\lambda_{MAX} = 303$ nm with 5 nm full width at half maximum, and was finally projected on the cornea with a collimating lens (Michael, 2000). UVR intensity was measured as irradiance in the corneal plane with the beam exceeding the detector area, with a thermopile (model 7101; Oriel, Stratford, CT) calibrated to a National Institute of Standard (NIST) traceable source. Intensity was adjusted by varying the height of the entrance slit of the first monochromator.

Experimentally induced cataract was quantified as forward lens light scattering. Intensity of forward light scattering was measured with a light dissemination meter (Söderberg et al., 1990). This instrument uses the principle of dark field illumination. Light transilluminates a transparent object (e.g. a mouse lens) at 45 degrees against the horizontal plane. At this angle, the light cannot enter the objective aperture. If the object scatters light in the forward direction, a defined fraction of light reaches the objective and is measured by a photodiode.

A lipid emulsion of Diazepam (Stesolid Novum®, Dumex-Alphapharma, Denmark) was used as the scattering standard. Light scattering was therefore expressed as transformed equivalent Diazepam concentration [tEDC] (Söderberg et al., 1990).

2.2. Experimental procedure

Ten minutes preceding UVR-B exposure, the animal was anaesthetized with a mixture of 40 mg/kg ketamine and 5 mg/kg xylazine injected intramuscularly. Five minutes after the injection, 1% tropicamide was instilled into both eyes to induce mydriasis.

Prior to exposure, all animals were checked with a slit lamp to exclude pre-existing cataract. One eye of each mouse was exposed in vivo to UVR 300 nm for 15 min. The contralateral, non-exposed eye was shielded during exposure and kept as a control.

Each animal was kept for a latency period of 48 h from the start of the exposure to UVR, based on published data on the evolution of cataract after in vivo exposure to UVR 300 nm (Meyer et al., 2005). After the mouse was sacrificed, the eyes were enucleated and the lenses were extracted microsurgically. Remnants of the ciliary body were removed from the lens equator under a microscope, keeping the lens in balanced salt solution (BSS, Alcon, Sweden). Thereafter, the intensity of forward light scattering was quantitatively measured three times for each lens. Cataract morphology was visualized in

incident illumination against a grid and in light- and dark field illumination photography.

2.3. $MTD_{2.3:16}$ estimation

The $MTD_{2.3:16}$ strategy is a concept designed for in vivo safety limit estimation for continuous dose-response relationships and was described in detail elsewhere (Söderberg et al., 2002; Dong et al., 2005).

2.4. Experimental design

The experimental design is given in Fig. 1.

A total of 80 C57BL/6J mice were subdivided into four dose groups of 20 animals each. Depending on the dose group, the mice unilaterally were exposed to 0, 2, 4 or 8 kJ/m^2 UVR 300 nm for 15 min. Mice in the 0 dose group received identical treatment as animals in dose groups 2, 4, and 8 but no UVR 300 nm exposure.

2.5. Statistical parameters

The light scattering data were analyzed with parametric statistics since it has been shown previously that these measurements are normally distributed (Meyer et al., 2007). Considering sample size, the significance level was set to 0.05 and the confidence coefficient to 0.95.

3. Results

Three lenses were damaged during the dissection and were therefore excluded from data analysis together with their corresponding contralateral lenses. Additionally, three out of 80 animals featured eye abnormalities such as microphthalmus with deformed lenses. In three animals, pre-existing cataract was present unilaterally or bilaterally. One mouse suffered from unilateral endophthalmitis in the non-exposed eye. Data from all above-mentioned animals, seven in total, were not considered in the data analysis.

3.1. Macroscopic appearance

The majority of exposed lenses developed anterior subcapsular cataract after exposure to 2–8 kJ/m^2 UVR 300 nm (Figs.2 and 3).

After a low dose, 2 kJ/m^2, small flake like opacities were observed subcapsularly on the anterior lens surface (Fig. 2).

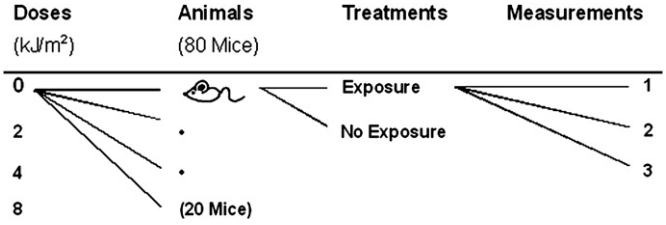

Fig. 1. Experimental design.

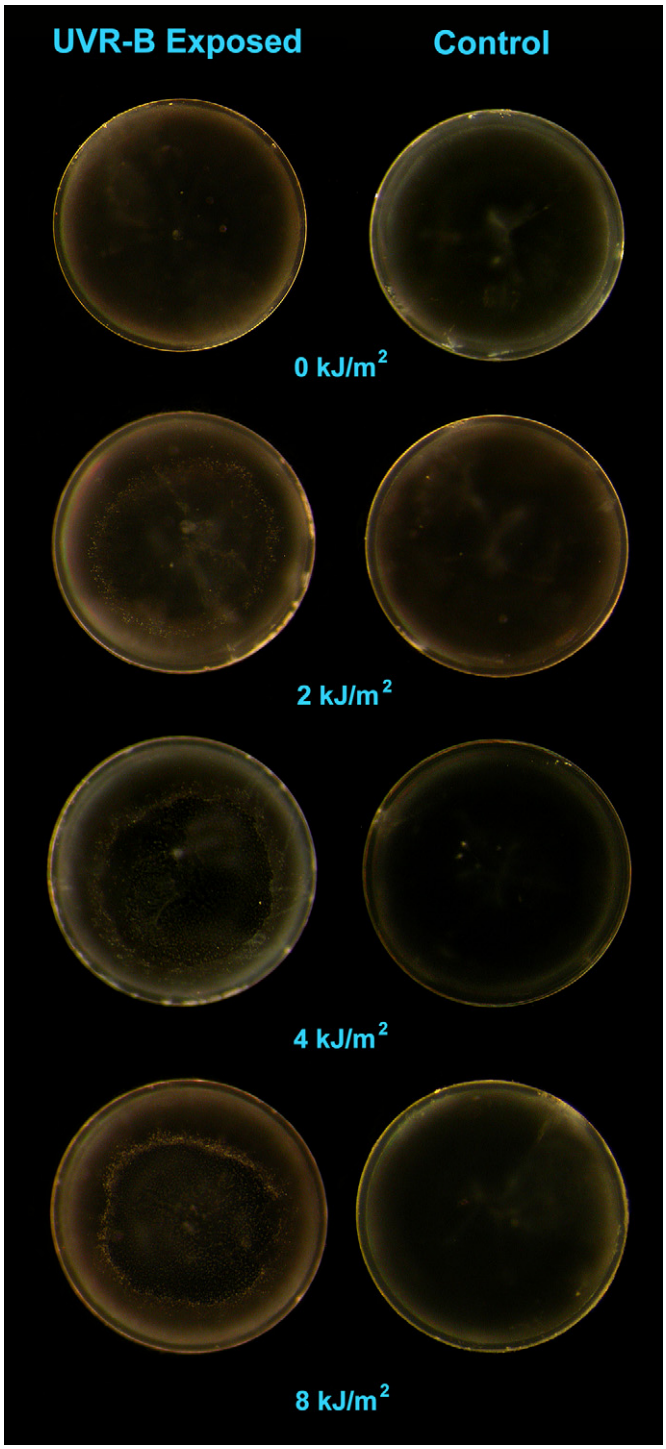

Fig. 2. Lenses with anterior subcapsular cataract 48 h after 0–8 kJ/m^2 in vivo exposure to UVR 300 nm and contralateral control lenses (anterior view).

Opacities induced were situated in an annulus starting pre-equatorially and extending towards the lens sutures (Fig. 3).

With higher dose, anterior subcapsular opacities intensified. A distinct line of demarcation separated the opacities from transparent lens tissue adjacent to the equator. In addition to anterior subcapsular cataract, approximately 12% of all animals developed cortical and/or nuclear cataract in the exposed eye (Fig. 4).

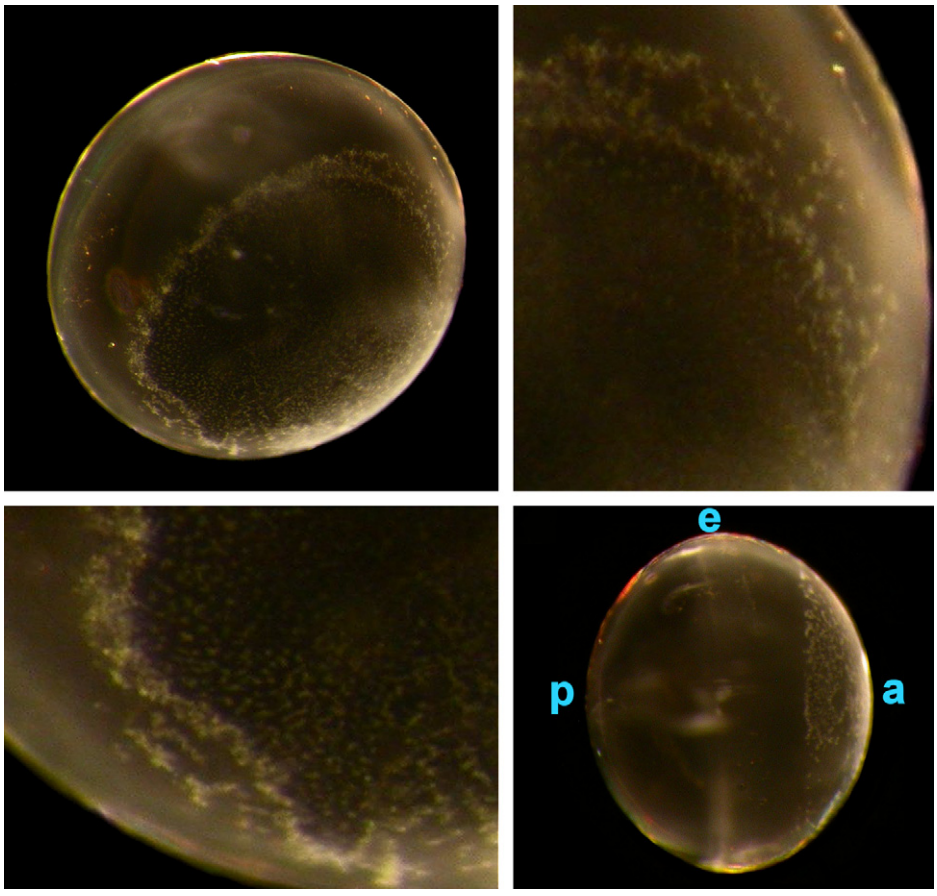

Fig. 3. Anterior subcapsular cataract in mouse lens 48 h post exposure to 8 kJ/m^2 UVR 300 nm, imaged in dark-field illumination. Upper left: Lens seen slightly tilted from the anterior side with the two areas indicated enlarged. Lower right: The same lens seen imaged from the side (a) anterior pole, (e) equator, (p) posterior pole.

3.2. Dose response function for forward light scattering and $MTD_{2.3:16}$

There was a significant difference between exposed and contralateral not exposed lenses as expressed by a 95% confidence interval for the mean difference (0.09 ± 0.04, d.f. $= 72$) (Fig. 5).

The variances in the four dose groups were found to vary significantly as tested with Bartlett's test (test statistic $= 23.27$, $\chi^2_{3;0.05} = 7.81$). Therefore, the contrasts among the dose levels were analyzed with orthogonal *t*-tests. If variances for dose levels tested with orthogonal tests were found to be different as indicated by an *F*-test, the contrast was examined with approximate *t*-tests. The orthogonal *t*-tests demonstrated an incrementing dose response relationship (4 vs. 8: test statistic $=$ 0.58; $t_{0.975;36} = 2.03$, 2 vs. 2 and 8: test statistic $= 2.41$; $t_{0.975;55} =$ 2.00, 0 vs. 2, 4 and 8: test statistic $= 3.95$; $t_{0.975;71} = 1.99$).

Since there was an increase of light scattering as a function of unilateral UVR-dose received, the MTD concept (Söderberg et al., 2002; Dong et al., 2005) was applied. $MTD_{2.3:16}$ for the C57BL/6J mouse lens was estimated to 2.9 kJ/m^2 UVR 300 nm.

In some irradiated but not in non-irradiated animals, we observed a light scattering increase also in the contralateral non-exposed lens (Fig. 7) morphologically corresponding to cortical cataract. In these eyes, signs of intraocular inflammation such as posterior synechia and neovascularisation were observed. The recorded intensities of forward lens light scattering were compared to previously published intensity of forward light scattering in healthy non-exposed C57BL/6J mouse lenses (Meyer et al., 2007) (Fig. 7).

The presently estimated confidence intervals for the mean intensity of light scattering for contralateral non-exposed lenses were compared to the 95% confidence limit ($n = 17$) for the level below which 95% of means of intensity averaged over 17 lenses are expected based on the population mean and standard deviation for individual healthy non-exposed lenses as estimated by Meyer et al. (2007), using the strategy described by Beyer (1966). For this, the population standard deviation for means of 17 lenses was generated as the estimated standard deviation for individual lenses divided by the square root of *n*. This limit is below referred to as the *mean normality limit*.

The estimated 95% confidence intervals for mean intensity of light scattering in contralateral non-exposed lenses included the *mean normality limit* in the 0.2 and 4 kJ/m^2 dose groups but were above the *mean normality limit* in the 8 kJ/m^2 dose group (Fig. 7). No clear increase of light scattering was found in the contralateral non-exposed lenses as a function of UVR-dose (Fig. 7).

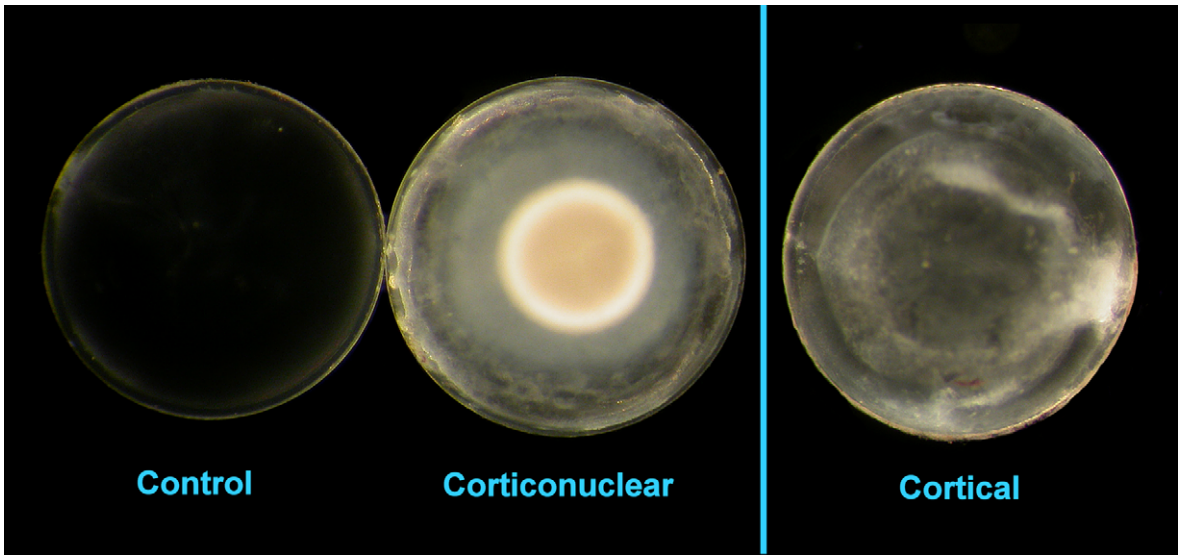

Fig. 4. Cortical and nuclear cataract after exposure to UVR-B 300 nm (anterior view) compared to non-exposed control lens.

4. Discussion

This study determined the dose-response relationship for cataractogenesis in the C57BL/6J mouse lens following in vivo exposure to UVR 300 nm. Further, we established a cataract threshold estimate for in vivo UVR 300 nm-induced cataract in the mouse lens expressed as $MTD_{2.3:16}$ (Söderberg et al., 2002; Dong et al., 2005). Knowledge of the Maximum Tolerable Dose in the C57BL/6J mouse permits not only qualitative but also quantitative comparison of UVR-B sensitivity of knockout mice, e.g. animals deficient in key antioxidative enzymes or mice suffering from genetically predetermined eye disease, to wild type animals.

4.1. Macroscopic appearance

The finding that mice exposed to UVR 300 nm primarily developed anterior subcapsular cataract (Figs. 2 and 3) and occasionally cortical and/or nuclear cataract (Fig. 4) is in concordance with earlier studies and is discussed elsewhere (Meyer et al., 2005). Anterior subcapsular cataract seen here is consistent with our current understanding of shallow UVR-B penetration depth into the lens, rendering epithelial cells and anterior cortex lens fibers to be the major site for UVR-B induced photooxidative damage. The current study does not provide information on the primary or secondary chemical alteration due to photooxidative damage. Membranes, as well as functional or structural proteins, including crystallins, and nucleic acids are potential targets for photooxidation. UVR-B exposure was found to be a risk factor for posterior subcapsular cataract (PSC) in humans (Bochow et al., 1989), a lesion not found in the current study. Jose demonstrated that PSC in mice occurs 5–6 months following chronic low dose exposure to UVR-B but not UVR-A (Jose, 1986). The anterior subcapsular lens opacities observed 48 h post exposure to UVR 300 nm in the current study (Fig. 2) do not exclude the occurrence of PSC at longer latencies post-exposure. On the contrary, Jose argues that posterior subcapsular opacities are a plausible long term effect of lens epithelial damage (Jose, 1986). Pathophysiological mechanisms underlying the occasional nuclear opacification observed in the current study remain unclear and call for further investigation.

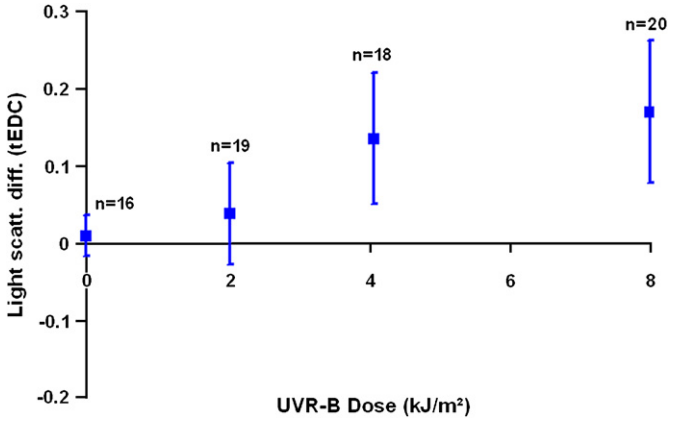

Fig. 5. Light scattering difference between UVR 300 nm exposed and contralateral lenses at doses 0–8 kJ/m^2. N = number of animals. Bar is 95% confidence interval for the mean.

4.2. Light scattering and $MTD_{2.3:16}$

We determined light scattering 48 h after exposure to UVR 300 nm since we previously showed that lens light scattering tends to peak two days post exposure to UVR 300 nm (Meyer et al., 2005) The demonstrated increase of light scattering as a function of UVR dose (Fig. 6) is consistent with the assumption that light scattering difference between the exposed and the contralateral non-exposed lens increases as a function of the squared UVR-B dose in the dose range studied (Söderberg et al., 2002).

The threshold estimation for UVR 300 nm-induced cataract expressed as $MTD_{2.3:16}$ for the six week old C57BL/6J mouse

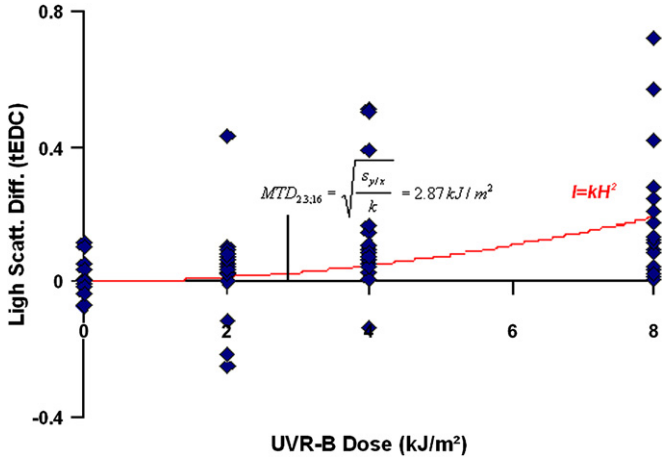

Fig. 6. Dose response function for UVR 300 nm-induced forward light scattering in the C57BL/6J mouse lens in vivo. Straight line is least square fit to the indicated model. I = difference of intensity of forward light scattering, k = the sensitivity (regression coefficient), $s_{y/x}$ = residual standard deviation, H = dose.

reported here, 2.9 kJ/m^2, is close to the $MTD_{2.3:16}$ in the Sprague–Dawley rat, 3.65 kJ/m^2 and indicates a comparable lens sensitivity to UVR-B in these two species. $MTD_{2.3:16}$ in the mouse was until now unknown and provides essential information for the use of this animal as a model for in vivo UVR-cataract research. Furthermore, the $MTD_{2.3:16}$ for the mouse estimated here, 2.9 kJ/m^2, provides a reference level for the dose 5 kJ/m^2 that was previously used to estimate evolution of UVR-cataract in the mouse (Meyer et al., 2005). When the evolution study was designed, the dose was chosen as a supra-threshold dose for single-exposure UVR 300 nm based on rabbit (Pitts et al., 1977) and rat data (Söderberg et al., 2002).

Our finding that in some animals intensity of light scattering in contralateral non-exposed lenses tended to be higher than the *mean normality limit* (Fig. 7) is consistent with previous in vivo observations (Pitts et al., 1983; Söderberg, 1990; Meyer et al., 2005) and cannot be explained by reported cataractogenous effects of anesthesia (Kufoy et al., 1989). Systematic measurement errors are most improbable since all measurements were calibrated to the same standard system and the same experimentalist did the dissections. The fact that the 95% confidence intervals for the estimated mean light scattering for the 0.2, and the 4 kJ/m^2 dose groups contain the *mean normality limit* (Fig. 7) implies that the tendency for higher light scattering intensity in contralateral non-exposed lenses could be due to a random experimental error. More importantly though, it is possible that unilateral exposure to UVR-B triggers a systemic response affecting also the contralateral non-exposed eye. Since a systemic and sympathetic response might be a crucial factor involved in cataract pathogenesis our findings demand further investigation. If confirmed, this finding might be of high clinical relevance and it could open up completely new approaches in cataract research. However, to quantitatively prove a contralateral sympathetic effect, an experiment addressing this particular aspect needs to be designed.

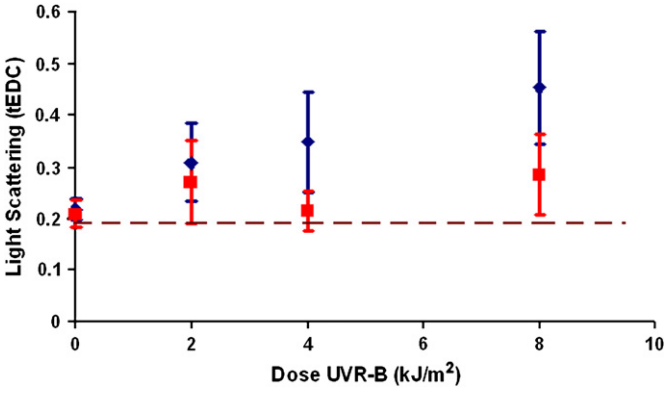

Fig. 7. Intensity of forward light scattering in exposed ◆, and contralateral non-exposed, ■, lenses 48 h after in vivo exposure to UVR 300 nm. Bar is 95% confidence interval for the mean. Dashed line (0.19 tEDC) is the estimated 95% confidence limit (*mean normality limit*) for the level below which 95% of means of intensity of forward light scattering in healthy C57BL/6J mouse lenses are expected as based on Meyer et al. (2007).

It should be pointed out that the presently recorded measurements of forward light scattering intensity, regardless of origin, do not affect the current $MTD_{2.3:16}$ estimation since $MTD_{2.3:16}$ is a measure of individual light scattering variability due to biological and measurement variability related to the increase of light scattering per dose increase (Söderberg et al., 2002) and is thus independent of calibration of light scattering measurements between experiments.

4.3. The C57BL/6J mouse as a cataract model

The current phacoemulsification technique used for cataract surgery makes it increasingly difficult to obtain human lenses for experimental in vitro cataract research. Further, an in vitro approach always lacks the in vivo influence of ocular tissues surrounding the lens, thus neglecting potentially important pathophysiological pathways. In the current study for instance, there was an indication that inflammatory response of the uvea may modulate the direct effect of UVR on the lens. This is consistent with the findings of Andley et al. who demonstrated that increased prostaglandin synthesis is associated with UVR-B induced cataract formation in rabbit eyes (Andley et al., 1996). Therefore an analysis of a possible inflammatory response following UVR-B exposure is needed.

Anatomical differences between the human and the mouse eye cause different exposures. The human cornea and aqueous (standardized to 3 mm anterior chamber depth), respectively, transmits at 300 nm on the order of 9 and 18%, respectively (Boettner and Wolter, 1962), resulting in a total transmittance for cornea and aqueous of 1.6%. The transmittance of the adult albino mouse cornea at 300 nm was in a previous study estimated to 40% (Dillon et al., 1999), the difference from the human primarily being due to a thinner cornea in the mouse. Considering an equivalent linear attenuation coefficient for human and mouse aqueous, the mouse aqueous transmittance was, based on an anterior chamber depth of 0.4 mm (Schmucker and Schaeffel, 2004), calculated to 80%. Thus,

the total transmittance for mouse cornea and aqueous at 300 nm can be approximated to 32%. Therefore, the mouse lens is exposed to a 20 fold higher dose of UVR in vivo compared to in the human, for an equivalent on the cornea dose.

Oxidative damage is currently held to be the most common cause of age-related cataract. Truscott pointed out, that the guinea pig is probably the best non-primate model currently available for studying oxygen and UVR-A exposure in relation to cataract development because guinea pigs can be made scorbutic, and their lenses contain a UVR filter that mimics the human UVR filter (Truscott, 2005). To our best knowledge, there is currently no data on lens pigments in the mouse but in our experience mouse lenses do not become yellow with increasing age.

In studies of experimentally induced in vivo cataract, the effect of a single dose of UVR is usually studied. The results of such studies can be directly compared to the effect of short onset cataract after one high dose as is done in current guidelines for safe exposure to UVR (Sliney et al., 2004).

However, such information should cautiously be interpreted for the understanding of the pathophysiology of age related opacification of the human lens since most human exposure is daily chronic low dose exposure to UVR and potential damage accumulates over the whole individual life span (Hockwin et al., 1999).

Despite these deficiencies, the mouse currently is the only option for the investigation of the effect of genetic modulation on the sensitivity for in vivo UVR induced cataract, since the mouse is the only animal for which genetically modified strains are easily available. Furthermore, the mouse genome is the most thoroughly studied of all non-human genomes and the mouse and the human genomes are extensively mapped and compared. High-level homology between mouse and human genomes implies that similar disease manifestations often are identified in mice and in humans (Smith et al., 1997). The current understanding of the similarities and differences between the human and the mouse genomes permits researchers to apply data from human gene mapping and use the DNA sequence for analysis of inherited susceptibilities long before similar comparisons can be conducted with a second non-human mammalian species (Carver and Stubbs, 1997) such as e.g. the guinea pig. Therefore, the C57BL/6J mouse currently offers unique opportunities to study the impact of genetic modulation of lens sensitivity to oxidative stress as caused by exposure to UVR-B.

4.4. Final remarks

The currently established dose response function for UVR 300 nm-induced cataract in the C57BL/6J mouse lens and $MTD_{2.3:16}$, a cataract threshold estimate, serve as important reference information for the use of this most common laboratory mouse strain as an in vivo cataract model (Schmucker and Schaeffel, 2004). We have recently characterized light scattering in the normal C57BL/6J mouse lens and studied the evolution of UVR-B induced cataract in the C57BL/6J mouse lens following single supra-threshold exposure (Meyer et al., 2005, 2007). The information provided by all three studies now makes it possible to study the effects of mutations, and lack of genes in knockout mice, on in vivo UVR-B lens sensitivity. It is anticipated that the C57BL/6J mouse characterized as an in vivo cataract model could be an important tool to increase the etiopathological understanding of UVR induced cataract in humans.

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