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Maximum tolerable dose for avoidance of cataract induced by ultraviolet radiation-B for 18 to 60 week old rats

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Abstract

The purpose of the present study was to investigate the maximum tolerable dose for avoidance of UVR-B-induced cataract in rats in the age interval 18–60 weeks and establish the functional relationship between age and sensitivity to UVR-B. Four groups of 20 albino Sprague–Dawley rats each, aged 18, 26, 40 or 60 weeks, were included. Each age group was divided into five UVR dose sub-groups. The rats were unilaterally exposed to ultraviolet radiation ($\lambda_{max}=302{\cdot}6$ nm, $\lambda_{0{\cdot}5}=4{\cdot}5$ nm). The incident dose on the cornea varied between 0 and $9{\cdot}2$ kJ m^{-2}. One week after exposure, the rats were sacrificed and both lenses were extracted. The intensity of forward light scattering was measured and photographs were taken. The functional relationship between age and sensitivity to UVR-B was estimated as the maximum tolerable dose based on rats age from 3 to 60 weeks. The maximum tolerable dose for 18, 26, 40, and 60 weeks, respectively, was estimated to $5{\cdot}2$, $4{\cdot}9$, $4{\cdot}7$, and $5{\cdot}1$ kJ m^{-2}. The sensitivity to UVR-B for Sprague–Dawley rats increases with increasing age during the first third of the rat life span, and then stabilizes to a constant level during the remaining two-thirds.

Keywords: ultraviolet radiation; age; rat; lens; cataract; light scattering; dose–response function; maximum tolerable dose

1. Introduction

Age related cataract is the leading cause of blindness in the world today, with an estimated 17 million individuals bilaterally blind (de Gruijl, 2000). A delay in cataract onset of only 10 years may reduce the need for cataract surgery by as much as half (Congdon, 2001).

High solar UVR irradiances in the environment increase the risk for cataract (Hightower, 1994; Quinlan et al., 1999; Taylor, 1990; Taylor et al., 1988; West et al., 1998). The incidence of cataract will ultimately rise by $0{\cdot}5\%$ for every 1% decrease in ozone (Longstreth, 1998). A gradual downward trend in the amount of stratospheric ozone has been measured in temperate and polar climate zones over the last two decades (McKenzie, 1999). In view of the above, it is important to establish a reliable safety limit for avoidance of UVR-B-induced cataract.

The current safety limit for avoidance of cataract induced by UVR-B is primarily based on an experiment by Pitts et al. (1977). They based their estimation of threshold on a binary model with cataract/no cataract as the response to UVR exposure. Age was not considered. We have found that cataract induced by UVR-B follows a continuous dose–response function (Michael et al., 1998a). We have also found that age modifies the lens response to UVR-B (Dong et al., 2003; Löfgren et al., 2003). In addition, we demonstrated that the lens sensitivity to UVR-B decreases in rats in the age interval 3–18 weeks (Dong et al., 2003). Löfgren studied the effect of age on the intensity of forward light scattering induced after exposure to UVR-B (Löfgren et al., 2003). The study indicates that there is no change in the response induced, in ages over 18 weeks. But the sensitivity to UVR-B in ages older than 18 weeks has not been studied. Investigation of the impact of age on UVR-B sensitivity for the whole life span is important for derivation of correct safety limits for avoidance of cataract induced by UVR.

In the present experiment, a new concept, maximum tolerable dose (MTD) for estimation of the safety limit for

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avoidance of cataract induced by UVR-B, is adopted (Söderberg et al., 2002). MTD is based on quantitative measurement of the intensity of forward light scattering in the lens.

1.1. Maximum tolerable dose (MTD)

The low dose region of the dose response function for UVR-induced light scattering in the lens (Fig. 1) can be simplified to a second order polynomial, omitting the zero and the first order term (Eq. (1))

$$I_d = kH_e^2 + \varepsilon \quad (1)$$

Here, I_d is the difference of intensity of forward light scattering between exposed and contralateral lens, H_e is the dose of UVR and ε is a random error due to biological variation and measurement error.

Considering the dose response function (Fig. 1), MTD is defined as the dose corresponding to the cross-over between the tolerance limit for normality (L_n) and an arbitrarily chosen limit (L_a) above the average dose–response function. At $MTD_{2\cdot3:16}$ there is a 16% probability to find a lens that expresses higher intensity of forward light scattering than is found in less than 2·3% of normal lenses (Fig. 1).

It is seen in Fig. 1 that $MTD_{2\cdot3:16}$ can be expressed as a function of the residual standard deviation, σ, and the increase rate, k (Eq. (2)).

$$2\sigma = k(MTD_{2\cdot3:16})^2 + \sigma \text{ or } MTD_{2\cdot3:16} = \sqrt{\frac{\sigma}{k}} \quad (2)$$

The residual standard deviation and the increase rate can readily be estimated in a small number experiment. The sensitivity to UVR-B for each age group can be expressed as the inverse of $MTD_{2\cdot3:16}$.

The aim of the current study was to establish the functional relationship between age and sensitivity to UVR-B in the lens, expressed as $MTD_{2\cdot3:16}$. The $MTD_{2\cdot3:16}$, was investigated in rats in the age interval 18–60 weeks.

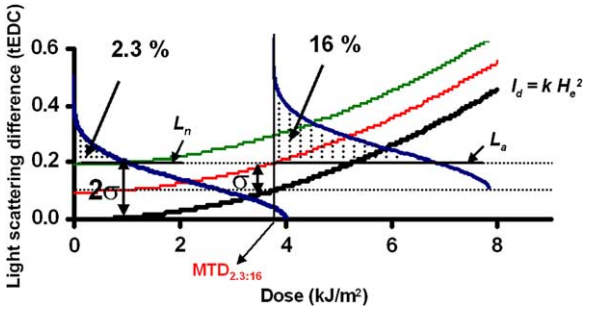

Fig. 1. Black line is UVR-B induced dose–response curve. Red line is 1 residual standard deviation (σ) above the dose–response function. Green line is 2 residual standard deviations (σ) above the dose–response function. L_n is limit for normality. L_a is an arbitrarily chosen limit above the average dose–response function.

2. Methods

2.1. Experimental animals

All animals were treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Ethical approval was obtained from the Northern Stockholm Animal Experiments Ethics Committee.

A total of 83 female outbred Sprague–Dawley (SD) rats were included in the experiment. All rats were purchased (M&B AB, Denmark) at the age of 12 weeks and thereafter kept in the local animal department until proper age. One 60 weeks-old rat was used for testing the photography setting. Two 60 weeks-old rats died during the anaesthesia and were replaced.

2.2. Devices

The radiation from a 300 W high-pressure mercury lamp (Oriel Instruments, Stratford, CT) was collimated, passed through a water filter, and then a double monochromator set at 300 nm (Söderberg, 1990). The resulting spectrum peaked at 302·6 nm and had a 9 nm full width at half maximum. Irradiance was measured with a thermopile (7101, Oriel Instruments, Stratford, CT) in the corneal plane. The thermopile had been calibrated to a NIST (National Institute of Standard) traceable source by the Swedish National Bureau of Standards.

The intensity of forward light scattering was measured with a Light Dissemination Meter developed by Söderberg et al. (1990). The readings were calibrated with a standard lipid emulsion of the drug diazepam (Stesolid Novum, Alpharma AB, Stockholm, Sweden) and the unit of intensity of forward light scattering was expressed as transformed Equivalent Diazepam Concentration (tEDC) (Söderberg et al., 1990).

2.3. Procedure

Ten minutes preceding the UVR-B exposure, the animals were anesthetized with a mixture of 95 mg kg^{-1} ketamine and 14 mg kg^{-1} xylazine, injected intraperitoneally. Five minutes after the injection, the mydriatic tropicamide was instilled in both eyes and both eyes were checked with a slit lamp microscope. After another 5 min, one eye of each animal was exposed to a narrow beam of UVR-B covering only the cornea and the eyelids.

One week after exposure, the animals were sacrificed by carbon dioxide asphyxiation. The eyes were enucleated and both lenses were extracted and placed in balanced salt solution. Remnants of the ciliary body were removed from the lens equator. Photographs were taken of each lens with incident illumination on a dark background with a white grid.

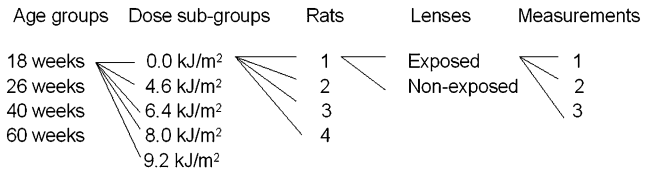

Fig. 2. Experimental design.

2.4. Experimental design

The experimental design is given in Fig. 2.

The rats were divided into four age groups with 20 rats. Each group was subdivided into five dose subgroups of four rats. The subgroups were assigned to receive doses according to Eq. (3).

$$H_{e:g} = \sqrt{(g-1)\frac{[E(\mathrm{MTD})]^2}{2}} \quad (3)$$

Here, $H_{e:g}$, is an individual subgroup dose, for the g:th subgroup ($g = 1,\ldots,5$) and E(MTD), the expected MTD. The expected MTD was set to $6{\cdot}5$ kJ m^{-2} based on a previous experiment (Dong et al., 2003). Thus, the subgroup doses were 0, $4{\cdot}6$, $6{\cdot}4$, 8, and $9{\cdot}2$ kJ m^{-2}. One eye in each rat was exposed while the contralateral eye was kept non-exposed. The intensity of forward light scattering was measured three times for each lens.

2.5. Statistical parameters

The significance levels were set to be $0{\cdot}05$ considering the small sample size.

3. Results

3.1. Intensity of forward light scattering and $MTD_{2\cdot3:16}$

In all four age groups, an increase in light scattering developed with increasing UVR-B dose (Fig. 3).

Regression coefficients of different age groups were compared with orthogonal t-tests according to the strategy; 60 vs 40 weeks; [60 and 40 weeks] vs 26 weeks; [60, 40 and 26 weeks] vs 18 weeks. For this, subgroups were pooled together for regression analysis.

There was no difference between regression coefficients among any of the orthogonal comparisons (Table 1).

The $MTD_{2\cdot3:16}$ for 18, 26, 40, and 60 weeks, respectively, was estimated to $5{\cdot}2$, $4{\cdot}9$, $4{\cdot}7$, and $5{\cdot}1$ kJ m^{-2} (Fig. 4).

It is seen that in the age interval 18–60 weeks there is little change of the threshold for damage.

3.2. Macroscopic appearance

All rats were devoid of cataract under slit lamp examination before UVR-B exposure.

One week after exposure to $4{\cdot}6$ kJ m^{-2} UVR-B, limited anterior subcapsular opacities developed in some lenses in all four age groups. With the highest dose ($9{\cdot}2$ kJ m^{-2}), all groups developed either anterior subcapsular cataract or equatorial cataract, but no nuclear cataract was seen. Anterior subcapsular cataract also developed after exposure to 8 kJ m^{-2} UVR-B and there was no apparent difference among the groups (Fig. 5).

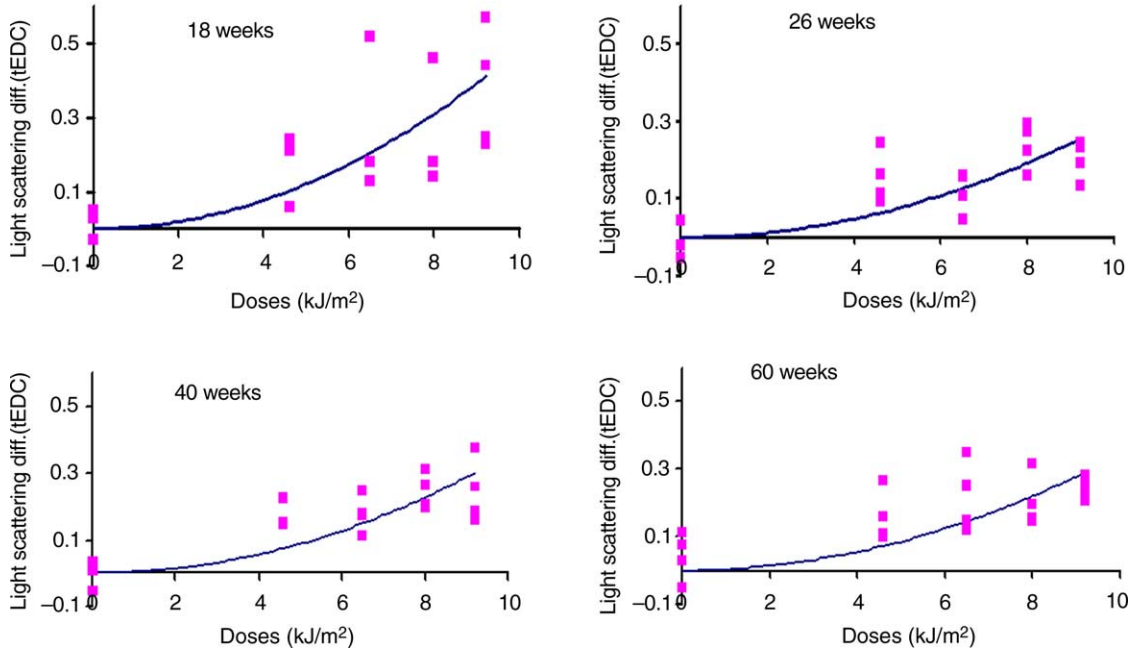

Fig. 3. Dose–response curves for the four age groups. ($R^2 \geq 0{\cdot}80$ for all groups).

Table 1
Orthogonal comparisons of regression coefficients for age groups 18–60 weeks

Comparison	Degrees of freedom	Test statistic	Significance limit ($P<0{\cdot}05$)
60 vs 40	38	−0·01	2·02
60 and 40 vs 26 weeks	54	0·02	2·00
60, 40, and 26 vs 18 weeks	72	−0·02	1·99

4. Discussion

In the present paper, the influence of age on sensitivity of the lens to exposures to UVR-B in the 300 nm wavelength region was determined for the age interval 18–60 weeks. The findings were compared to earlier findings for younger age groups.

In a previous experiment, we studied the lens sensitivity to UVR-B for younger age groups (Dong et al., 2003). In the present study, we investigated ages above those that had been previously studied. In order to cover the SD rat life span, an appropriate upper age limit had to be defined. The mean life span for SD rats is approximately 106 weeks. However, the 2-year survival rate is less than 50%, with cancer being the most common cause of death (Hubert, 2000; Keenan, 1997). The survival in SD rats is directly related to the amount of food consumed. The 2-year survival rate for female SD rats fed ad libitum is only 37%, but can be much higher if the rats are on a restricted diet (Hubert, 2000). Since the rats in our previous experiment were fed ad libitum, the same conditions were maintained in the present study. The oldest age group was 60 weeks in order to include rats as old and healthy as possible. A 3-week-old rat is weanling, while a 6-week-old rat is post-weanling but still pre-pubertal. An 18-week-old rat is a fertile young adult, a 26-week-old rat is adult, and a 1 year old rat is elderly.

Current safety limits for avoidance of UVR-induced cataract are based on animal experiments. As cataract is irreversible, human experiments would be unethical. Rats were used as experimental animals since they are readily available in uniform size in lager numbers. The aim of the current experiment was to reveal the relationship between UVR-B sensitivity and age. Several differences exist between the rat and the human eye. The intensity of UVR-B used in the present experiment was 10–100 times higher than the expected irradiance of the human cornea in sunlight (Dong et al., 2003).

We have transformed the previously published threshold data for younger age groups (Dong et al., 2003) to

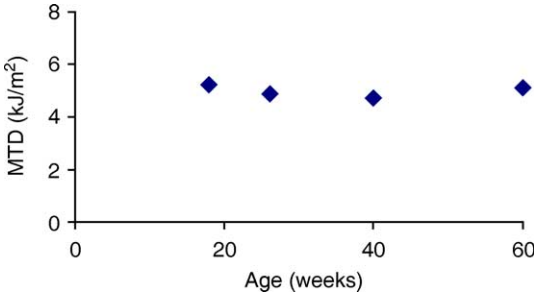

Fig. 4. Influence of age on $MTD_{2\cdot3:16}$ at high age.

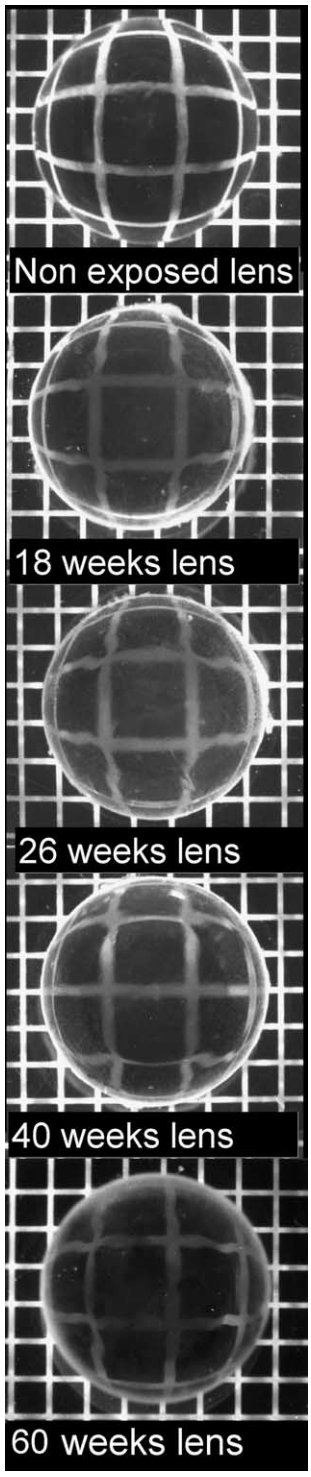

Fig. 5. Macroscopical appearance of isolated rat lenses from four age-groups. Non-exposed lens was from the 26 weeks old group. 18, 26, 40, and 60 weeks lenses were 1 week after in vivo exposure to 8 kJ m^{-2} UVR-B. The distance between the white wires is 0·79 mm.

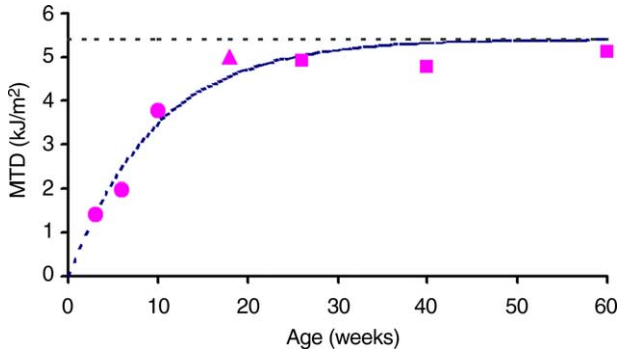

Fig. 6. Effect of age on threshold for cataract induced by in vivo exposure to UVR in the 300 nm wavelength region (●). Data from earlier experiment (Dong et al., 2003). (▲) Pooled data from both experiments. (■) Data from present experiment.

$MTD_{2\cdot3:16}$ and present those together with the currently generated data in Fig. 6.

The complete data set has been fitted to a non-linear regression model (Eq. (4)).

$$MTD = MTD_{max}(1 - e^{-\alpha\ Age}) + \varepsilon \quad (4)$$

Here, MTD_{max} is maximum MTD, α (yrs^{-1}) is the increase rate and ε is a random error expressing biological variability and measurement error.

The finding that $MTD_{2\cdot3:16}$ increases with age (Fig. 6) implies that the sensitivity to UVR-B in the lens is higher at a younger age. This is to our knowledge the first time that the influence of age on threshold for UVR-induced damage in the lens has been elucidated. We believe that until specific data for various species have been acquired, the present data should be applied generally for considering safety limit estimation for avoidance of cataract from UVR-B.

The dependence of MTD on age (Eq. (4)) demonstrates that sensitivity to UVR-B decreases with increasing age during the first third of the rat life span and remains stable during the remaining two-thirds. The finding that younger individuals are more susceptible to UVR for cataract induction is important information for programs for prevention of UVR-induced cataract.

Excessive exposure to UVR in childhood has been recognized as a risk factor for the development of skin cancer later in life (Moise, 1999; Parisi, 2000). A high incidence of age related cataract related to exposure to ionizing radiation in infancy has also been reported (Hall, 1999). Further, it has been shown that focal lens defects related to exposure to gamma radiation are more significant in age groups younger than 20 years old (Chen, 2001). Based on experimental studies, we know that ionizing radiation induces epithelial cell apoptosis and intracellular DNA modifications in the bovine lens (Belkacemi, 2000). Epithelial cell apoptosis and DNA modifications are also mechanisms for UVR-B-induced cataract (Michael et al., 1998b; Söderberg et al., 1986).

It is established that UVR induces a cortical cataract and that there is a continuous dose-response relationship for UVR-induced cataract (Söderberg, 1990; Longstreth, 1998; McCarty et al., 2000; Michael and Brismar, 2001; Sliney, 1995). Sun exposure has recently been reported to be a risk factor for nuclear cataract (Hayashi, 2003; Neale, 2003). The higher incidence of nuclear cataract later in life is strongly related to high sun exposure early in life (Neale, 2003). UVR exposure elicits photochemical damage through production of reactive oxygen species (ROS). ROS may lead to enzyme inactivation, protein aggregation (Zigman et al., 1973, 1974), and/or DNA alteration (Söderberg et al. 1986), and as a consequence cell damage (Li and Spector, 1996). The epithelial cells of the lens are the first target for UVR. The epithelial cells divide in the germinative zone and differentiate into fiber cells. Damage to epithelial cells caused by UVR will therefore be mediated to growing lens fibers. A young lens has a high rate of lens cell division and the fast growth of a lens requires intense protein synthesis. This renders the young lens more sensitive to UVR damage. Therefore excessive exposure to UVR in childhood may contribute to age related nuclear cataract, because the cortical lens fibers move to the center of the nucleus with the growth of the lens. UVR can induce DNA modification (Michael et al., 1998b) and unscheduled DNA synthesis (Söderberg et al., 1986). The balance between DNA and protein damage and repair is critical for lens health. Damage induced by UVR at the young age is additive to other age related degenerative processes and may be expressed as age related cataract later in life.

The young rat has a thinner cornea, a shallower anterior chamber, and a smaller lens compared to an old rat. Due to these anatomical differences, it has been shown that lenticular doses are higher in young than in old animals. There is a 25% difference in corneal thickness (Löfgren et al., 2003) between a very young and a very old rat. With an 8 kJ m^{-2} corneal dose, the lens anterior surface receives $3\cdot8$ kJ m^{-2} in the very young rat and $2\cdot9$ kJ m^{-2} in the very old rat (Löfgren et al., 2003). However, in the present study, the $MTD_{2\cdot3:16}$ is $1\cdot4$ kJ m^{-2} for the youngest rat and $5\cdot1$ kJ m^{-2} for the oldest rat. There is thus a nearly five-fold difference in MTD between the youngest rat and the oldest rat. Therefore, the age dependent anatomical dimensions of the eye do not fully explain the sensitivity difference between the young and old rat. The age dependent difference of sensitivity to UVR must exist in the lens itself.

The current study indicates that MTD for avoidance of UVR-B-induced cataract for rat remains constant from the age of 18 weeks and forward. Lenses from age 18–60 weeks may have a comparable rate of cell division and differentiation, and thus similar response to UVR-B.

Our studies show that MTD for avoidance of cataract induced by UVR-B for SD rats increases with increasing age during the first third of the rat life span, and then stabilizes to a constant level during the remaining two thirds. If the current findings are extrapolated to humans, an age factor

has to be introduced in current safety standards (Sliney et al., 2004) for avoidance of development of cataract after exposure to a high dose of UVR. Thus, protection against UVR exposure early in life is important.

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