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Influence of Iodide on Cataractogenesis in Emory Mice

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Abstract. Cataract development was studied in two groups of Emory mice by periodical biomicroscopic examinations (beginning at 5 weeks of age) and by a final evaluation of water-soluble SH groups in the lenses. The experimental group was given 256 µg iodide/kg body weight with the drinking water throughout the study. The untreated control group received tap water. Iodide treatment induced a delay of cataract formation, resulting in a significant reduction of the time to progress from cataract degree 1 to degree 2 (iodide-treated group 12.8 ± 1.7 weeks, untreated group 9.9 ± 1.0 weeks; $p < 0.025$). A still significant difference in the degree of cataract was also found between the two groups at week 47 of age. No difference was found in the content of water-soluble SH groups. The results are discussed in relation to the known antioxidant and ·OH-scavenging effect of iodide and to the oxidative changes in the lens occurring during progression of cataract development.

Introduction

One of the major causes of severe declining of visual function is senile cataract. Its pathogenesis is complex, and the disease seems to be multifactorial. Nevertheless, there is evidence that reactive oxygen species and lipid peroxidation reactions play an important role in cataractogenesis [1–3]. It has been reported that persons with poor antioxidant status are at enhanced risk of cataract [4] and that the antioxidant system of the lens decreases with increasing degree of cataract [5, 6].

The Emory mouse proved to be useful for the study of human senile cataract [7], as this strain of mice develops a late-appearing hereditary cataract associated with a decrease of the antioxidative defense of the lens, such as glutathione [8] and glutathione peroxidase [9]. There are also marked differences between Emory mice and 'cataract-resistant

controls' in the activities of lens enzymes before the cataracts develop [9]. In addition, Taylor et al. [10] stressed the similarities in protein alterations and histopathological changes that take place in Emory mouse and human lenses.

Recently we have demonstrated that administration of iodide leads to an increase in glutathione peroxidase activity in the liver which might improve the antioxidant status [11]. In vitro experiments carried out by Elstner et al. [12] also revealed a protective effect of iodide against reactive oxygen species in the lens. It seemed, therefore, interesting to study the development of cataract during increased iodide intake in vivo.

Materials and Methods

Emory mice were obtained from the Emory University (Atlanta, Ga., USA) and bred further in our laboratory. Five-week-old females (i.e., 1 week after weaning) were used and divided randomly into two groups. A continuously registered iodide-containing fluid intake resulted in an average daily uptake of iodide of 256 µg/kg body weight. This corresponds to 18 mg iodide for a 70-kg adult man. The control group received tap water ad libitum. To minimize the basal thyroidal iodine uptake without producing an iodine deficiency, the mice of both groups were fed with oats containing low levels of iodide. A total of 68 mice distributed into seven experimental groups of 4–17 animals were analyzed. The body weight was determined every 2–4 weeks; biomicroscopical examinations with a slit lamp and estimation of the cataract status were performed every 4 weeks by an ophthalmologist. The cataract grading was done in any case by the same investigator in a blind fashion: grade 0: lens completely clear, no turbidiy; grade 1: slight, initiating turbidity; grade 2: moderate turbidity with distinct white areas in greater parts of the lens; grade 3: dense turbidity with large interconnected opaque areas; grade 4: very dense, uniform turbidity, complete opaqueness of the lens.

The grading scale corresponds to that used by other authors [10]. Also intermediate values were used for characterization of the cataract degree. The cataract development showed individual differences as demonstrated by Takizawa and Sasaki [13].

After 34–54 weeks of treatment (corresponding to an age of 39–59 weeks) the animals had a final biomicroscopical examination and were subsequently killed under CO_2 anesthesia. Both lenses were immediately removed, and blood samples were obtained for determination of the serum concentration of thyroxine (T_4) by radioimmunoassay (Becton Dickinson, Basel, Switzerland) and inorganic iodide according to the method of Buchberger and Winsauer [14].

The lenses were weighed and prepared for determination of SH groups using the method of Sedlak and Lindsay [15]. In a few instances, the iodide content in the lenses was extracted with water and its concentration determined with the method utilized for serum iodide. The weight of the thyroid glands was also determined as a rough additional parameter of thyroidal status. Data were expressed as mean values ± SEM. Wilcoxon's U test and linear regression calculation were used for statistical analyses.

Results

Biomicroscopical Examination of the Eyes

Figure 1 shows the progress of cataract formation in relation to age and duration of iodide treatment, based on the 4-weekly optical examinations. The turbidity increased uniformly from the 10th week of age in both treated and untreated groups, with a progressively lower opacity in animals receiving iodide. However, statistical significance between the two groups was observed only during the 47th week of treatment ($p < 0.01$). The number of mice alive at the 47th week was reduced to 14 animals (7 controls and 7 treated) from the initial 68 (33 controls and 35 treated), as a result of intermediate final evaluation after weeks 39 and 43 of age, including 15 cases of spontaneous death during the whole experimental period (at 31.7 ±

Table 1. Number and percentage of mice showing cataract grade 2 between weeks 39 and 51 of age

Week	Iodide		Control	
	n	%	n	%
39[a]	9 (26)	34.6	17 (28)	60.7
43[b]	8 (16)	50.0	10 (15)	66.7
47	5 (7)	71.4	7 (7)	100.0
51	6 (7)	85.7	7 (7)	100.0

Figures in parentheses represent total number of animals.

[a] Sacrifice of 20 animals for final evaluation; 3 spontaneous deaths.

[b] Sacrifice of 17 animals for final evaluation.

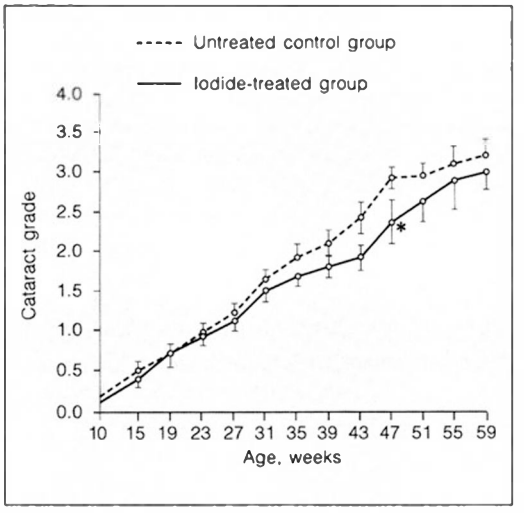

Fig. 1. Effect of chronic oral administration of 256 µg NaI/kg body weight on the cataractogenesis of Emory mice (biomicroscopical evaluation: grades 0–4; see 'Materials and Methods'). Mean values ± SEM from seven experimental series including a total of 68 animals at the onset of the study are shown. The asterisk represents a significant difference ($p < 0.01$; Wilcoxon's U test: $n = 14$). For these calculations, average values from both eyes of each animal were used.

Table 2. Water-soluble SH groups in the lenses

Group	Number of lenses	Fresh weight mg	Water-soluble SH nmol/mg lens
Iodide	52	6.22 ± 0.19	2.42 ± 0.18
Control	60	6.02 ± 0.21	2.36 ± 0.22

4.1 weeks in control mice and at 31.6 ± 3.4 weeks in the iodide-treated group).

As can be seen from table 1, in the iodide-treated group a lower percentage of mice showing cataract degree ⩾2 was found between weeks 39 and 51 of age.

Combining all the final biomicroscopical examinations performed before the termination of the study, we found a lower degree of turbidity in the iodide-treated mice (2.09 ± 0.10 vs. 2.43 ± 0.12 U in the untreated control group; $p \sim 0.15$).

Testing all animals with regard to their time to progress from cataract degree 1 to degree 2 ($n = 34$ usable values), a significant difference was found between the two groups ($p < 0.025$). The iodine-treated mice required, on average, 12.8 ± 1.7 weeks and the controls only 9.9 ± 1.0 weeks. This difference would be even more pronounced, if one might consider that 14 mice of the iodine-treated group did not at all progress to degree 2 during their experimental period as compared with only 9 mice of the control group.

Biochemical Data

Table 2 shows no differences in the content of free SH groups between control and experimental animals that could have been

Table 3. Thyroid parameters and inorganic iodide in serum

Group	Thyroid weight, mg (n = 8)	Serum T_4, µg/dl (n = 14)	Inorganic serum iodide µg/dl
Iodide	7.74 ± 1.29	3.32 ± 0.19	53.8 ± 5.9 (n = 7)
Control	8.16 ± 0.86	3.25 ± 0.25	9.1 (n = 2)

taken as reflecting alterations in iodide-induced antioxidative processes.

Thyroid Parameters and Inorganic Iodide

The iodide-treated group had a six-fold increase in the serum iodide concentration, while serum T_4 levels and thyroid weight were unaffected (table 3).

The concentration of inorganic iodide in the lenses of iodide-treated mice was 0.43 ± 0.16 ng/mg (range 0.12–0.71; n = 4), while in controls it was 0.14 ± 0.05 ng/mg (range 0.03–0.24; n = 4).

Discussion

Despite conflicting results and opinions [12, 16–19] iodide has long been recommended and used for the prevention of cataracts. Nevertheless, evidence derived from in vitro experiments [20–23] would indicate that iodide has an inhibitory role in the formation of cataracts.

Rathbun et al. [9] found a diminished activity in lens glutathione peroxidase in Emory mice as compared with cataract-resistant mice, particularly at the age of 10 weeks (9.9 vs. 18.0 U/g lens), as well as a general tendency to a decline of the glutathione peroxidase activity with progressing age. On the other hand, we found an elevation of the glutathione peroxidase activity in the rat liver after 3 weeks of iodide supply [11] which might be beneficial to an enhancement of the cellular defense system against factors that cause oxidative damages (i.e., H_2O_2, lipid peroxides). The present data, however, failed to demonstrate a relationship between water-soluble SH content in the lenses and cataract development, since the SH concentrations in control and iodide-treated mice were similar. Although several reports postulated that aging lenses are characterized by transformation of nuclear SH to SS groups (by UV irradiation and certain drugs) [see for a review ref. 24], other workers [25] did not find differences in SH profiles in a Raman study between early Emory mice cataracts and clear lenses from age-matched controls. These results support the view that lenses of Emory mice do not undergo accelerated disulfide production; also, the progression of cataractogenesis does not necessarily correlate with increased SS formation. Kuck and Kuck [8] found that the biochemical alterations in the Emory cataracts are very different and often do not correlate with the severity of the in vitro estimated cataracts. Therefore, mechanisms other than SS formation must be involved in cataractogenesis. Korte et al. [26] reported that in normal bovine lenses the free protein-bound SH groups increased during the first period of life and decreased later

and that there was an increase in disulfides in the investigated lenses during the aging process. Nevertheless, a transformation of soluble to insoluble proteins seems to be the most important and characteristic alteration, and this is partly linked to an oxidation of SH groups.

Corresponding data for soluble and insoluble proteins in lenses of Emory mice and cataract-resistant controls were shown by Kuck and Kuck [27]. Even though cataract formation may result from several factors, it seems likely that a prominent role is played by oxidative pathways and deficient protective enzymes and vitamins. Only a few agents have been found to be effective to some extent in preventing certain kinds of cataract formation in vivo. A retardation of cataract development was described for drugs such as penicillamine [27, 28], α-tocopherol [27, 29], certain aldose reductase inhibitors (e.g., flavonoids) [30], and bendazac-lysine [31] as well as caloric restriction [10]. A controlled cataract therapy study in man with a combination of cytochrome C, adenosine, sorbitol, sodium succinate, and nicotinamide [32] found no significant differences between the drug-treated and the placebo groups. For this reason, any delay in the onset or in the progress of cataract must be regarded as a positive result. A delaying effect on cataractogenesis of about 4–8 weeks as seen in our experiments (fig. 1) would correspond to about 5–10 years in human cataract development, assuming a mean life span of the Emory mouse of about 50 weeks. As far as we know, this is the first study showing an inhibitory effect of iodide on cataract development. Nevertheless, one must be aware that there are inherent limitations in transferring animal models to human conditions.

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