A possible role for vitamin C in age-related cataract

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While many experimental studies have shown a protective effect of vitamin C in age-related cataract, other studies have revealed contrasting roles for this nutrient. Oxidative damage in the lens can be prevented by vitamin C. However, a pro-oxidant effect of vitamin C through H_2O_2 generation has been suggested. Vitamin C has also been shown to play a role in protein glycation, which is observed in cataract formation. A protective effect of dietary energy restriction appears to be inversely related to plasma vitamin C levels in rodents. Moreover, conclusions from human epidemiological and intervention studies are not uniform. The available evidence suggests that maintenance of sufficient plasma vitamin C is needed to prevent oxidative damage in the lens. More research will be needed in order to confirm the relative importance of the different roles of vitamin C in the eye lens.

Vitamin C: Cataract: Antioxidants: Old age

Besides the well-known involvement of vitamin A in eye health, a new role for nutritional factors has emerged. A contributory role of oxidative stress, and protection by antioxidant nutrients has been suspected in the disease process of cataract, the main cause of blindness and visual impairment worldwide (Thylefors *et al.* 1995). The present paper will discuss recent findings with focus on vitamin C after a brief introduction to the subject.

Age-related cataract

Definition

Cataract is an opacification (cloudiness) of the lens of the eye which prevents light from reaching the retina. Cataract is usually treatable surgically, but the large number of operations required impose a great cost on hospital eye services. It has been estimated that if cataract development could be delayed by 10 years, the need for cataract extraction and the cost might be diminished by 50 % (Wynn & Wynn, 1996).

Besides the direct medical costs, visual disability in later life is of major public health importance because it is associated with decreased health status, reduced mobility and activity of daily living competence, and with an increased risk of hip fracture (Dargent-Molina *et al.* 1996; Lee *et al.* 1997).

Risk factors

The main risk factor for cataract is increasing age, although several risk factors have been identified including diabetes, smoking, alcohol use, dark skin colour, dehydration, high or low BMI, hyperoxia, exposure to u.v.-B or i.r. light, corticosteroid use, low socio-economic status, nutritional deficiencies of tryptophan and riboflavin, genetic predisposition, female gender and various systemic diseases (Varma, 1991; Johnson, 1998). However, many subjects develop cataract without any of these predisposing factors. Cataract formation is widely accepted to be a multi-factorial process.

Cataract physiology

The lens is a unique organ because the normal protein repair mechanisms of the body do not exist in the central lens fibres due to loss of DNA and RNA within the cells (Harding, 1991). The lens consists of fibres which are encapsulated in a layer of epithelial cells. The lens is surrounded by fluids, the vitreous humour and aqueous humour (Fig. 1), from which it receives its nourishment (Forrester *et al.* 1996).

In the equatorial region of the lens, epithelial cells differentiate into fibre cells to make up the youngest section of the lens, the lens cortex. Newly-formed fibre cells develop

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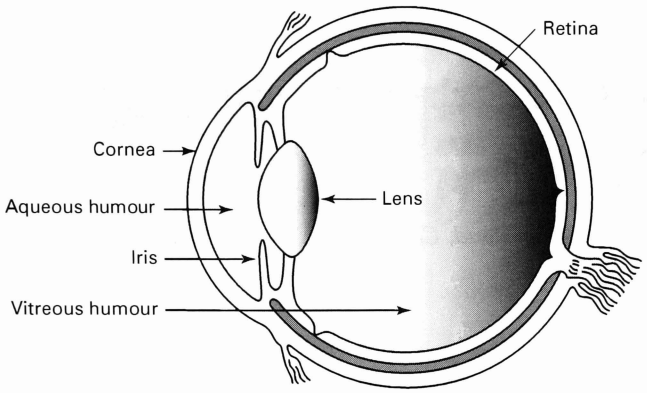

Fig. 1. The human eye.

continuously over the older fibres, which results in an increase in the lens volume and displacement of the older fibres towards the centre of the lens, the lens nucleus. As fibre cells mature, they lose their nucleus and metabolic activity (Spector, 1995).

As the mature fibre cells cannot replace or repair damaged proteins, they have a low defence against external insult. Consequently the gradually-expanding inner region of the lens is dependent on the epithelium and a thin layer of developing fibre cells for maintenance of its environment and protection against insults, and thus for its transparency (Spector, 1995).

The oxidative damage theory

Characteristics

The observation that the prevalence of cataract is greater in people living in areas with a higher intensity and duration of sunlight (Hiller *et al.* 1977; Hollows & Moran, 1981; Sliney, 1986) has prompted many investigations into the role of sunlight and oxidative damage in the cataract process.

It is now widely accepted that oxidative free-radical damage, for example through exposure to u.v. light, is an initiating or very early event in the overall sequence that leads to cataract (Sarma *et al.* 1994). Oxidative damage may cause lipid peroxidation in the lens epithelium, resulting in disturbances of osmotic balances, and it may cause modifications of the inner lens proteins, such as cross-linking, aggregation and precipitation, or DNA damage (Young, 1991; Reddy *et al.* 1998). To date, the exact sequence of events which leads to opacification has not been clearly defined.

Photochemical insult and defence

Laboratory studies have shown that high levels of the oxygen radicals superoxide and H_2O_2 are generated in the lens of photochemically-induced cataracts (Varma *et al.* 1979; Spector *et al.* 1993). H_2O_2 is also called a 'mobile time bomb' as it can react in a Fenton reaction to form the highly-damaging hydroxyl radical (Gutteridge & Halliwell, 1994).

The lens may defend itself against oxidative stress by means of antioxidants like vitamin C, vitamin E, carotenoids, GSH, and antioxidant enzymes such as superoxide dismutase (*EC* 1.15.1.1), catalase (*EC* 1.11.1.6) and Se-dependent GSH peroxidase (*EC* 1.11.1.9; Sarma *et al.* 1994). Detoxification of H_2O_2 is probably organized through a co-operative scheme between GSH, which is found in low concentrations in the aqueous humour, and the abundantly available (1–2 mM) ascorbate (Brown & Bron, 1996).

Vitamin E is present in the lens in very low concentrations (Yeum *et al.* 1995; Bates *et al.* 1996). Several *in vitro* experiments have suggested a protective role against cataract, possibly through protection of membrane lipids against peroxidation (Varma *et al.* 1984; Ohta *et al.* 1996; Sanderson *et al.* 1996), but very little evidence is available from *in vivo* experiments. Human epidemiological studies have suggested a protective effect of high plasma vitamin E levels (Knekt *et al.* 1992; Leske *et al.* 1995, 1998; Rouhiainen *et al.* 1998), but a recent intervention study did not show a protective effect of vitamin E supplementation (Teikari *et al.* 1998).

Vitamin C and cataract

Characteristics

Diurnal animals and man have ascorbate concentrations in the lens and aqueous humour which are ten to twenty times those in plasma, indicating active transport into the eye (Brown & Bron, 1996). Nocturnal animals, however, have much lower concentrations of ascorbic acid in the lens than diurnal animals (Reddy *et al.* 1998), suggesting a protective role for ascorbic acid against (oxidative) damage caused by sunlight exposure.

A relationship between ascorbate and cataract has been shown by the observed decrease in lens ascorbate levels with increasing age and with increasing cataract severity (Chandra *et al.* 1985; Bates & Cowen, 1988; Tessier *et al.* 1998). Thus far it has not been confirmed whether this drop in vitamin C is a preliminary event or a late consequence of cataract onset (Tessier *et al.* 1998), but experimentally-induced cataracts can be prevented or delayed by administration of ascorbate (Varma *et al.* 1979; Blondin *et al.* 1986; Devamanoharan *et al.* 1991).

Protective role

Direct evidence of a protective effect of ascorbate *in vivo* is still scarce. Many studies of cataractogenesis are carried out *in vitro*, where the validity of extrapolation to *in vivo* situations remains unclear. The following are examples of some recent well-designed studies showing a direct protective effect of ascorbic acid *in vivo*.

Reddy *et al.* (1998) recently showed that guinea-pigs, which have a diurnal lifestyle and have high ascorbate levels in the lens and aqueous humour, are indeed better protected against u.v.-B-induced DNA damage in the lens epithelium than the nocturnal rat (which has low lens ascorbate levels). Injections of ascorbate were associated with reduced levels of DNA damage in the lens epithelium after u.v.-B exposure in the rat, while ascorbate-deficient guinea-pigs showed 50 % more DNA damage than the normal controls (Reddy

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et al. 1998). However, these effects were achieved at radiation levels many times higher than could be expected under normal conditions, while lower u.v.-B exposure levels did not cause significant DNA damage in normal guinea-pigs (although they did in the normal nocturnal rat lens) over the same exposure time period.

A similar study by Devamanoharan *et al.* (1991) showed that cataract formation induced by administration of selenite to rats (causing lipid peroxidation and formation of H_2O_2) could be prevented by intraperitoneal administration of ascorbate.

Diabetic rats show a large increase in protein leakage from the lens into the aqueous and vitreous humour compared with normal controls (Linklater *et al.* 1990). In their experiments, Linklater *et al.* (1990) found that addition of 10 g vitamin C/kg to the diet of diabetic rats significantly decreased protein leakage and cataract formation, but paradoxically they found an increased protein leakage in vitamin C-supplemented normal control rats.

Pro-oxidant effects?

Besides a protective role, vitamin C has also been implied to exacerbate cataractogenesis. Ascorbate can generate H_2O_2 by reducing molecular oxygen, a reaction which is catalysed by metal ions (Halliwell & Gutteridge, 1989; Garland, 1990). Radical species can be generated from the H_2O_2 by further reaction of the metal ions in a Fenton reaction, restoring the metal ion into its original state so that it can participate in another cycle of the reactions (Garland, 1990). Recent work by Spector *et al.* (1998) showed that H_2O_2 generation in the aqueous humour is temperature- and O_2-tension-dependent, and that ascorbic acid and metal ions may make a major contribution to H_2O_2 production.

Investigations into the presence of metal ions in the aqueous humour showed that Fe and Cu ions accumulate in cigarette smokers (Christen *et al.* 1992; Hankinson *et al.* 1992*b*; Avunduk *et al.* 1997; Cekic, 1998), supporting the findings of many epidemiological studies that smoking is a strong risk factor for cataract (West *et al.* 1989; Christen *et al.* 1992; Hankinson *et al.* 1992*b*; West, 1992). Further *in vivo* experiments will have to be carried out to investigate the extent to which a pro-oxidant effect of vitamin C can be expected.

Protein glycation

Ascorbate has also been shown to play a role in protein cross-linking and formation of advanced glycation end-products (Ortwerth *et al.* 1988; Saxena *et al.* 1996). It has recently been suggested that, although tempered by the low O_2 pressure in lens tissues, ascorbate can make a much larger contribution to cross-linking than lens glucose (Lee *et al.* 1998). Consequently, in situations where oxidation of the lens tissue occurs, such as those observed in cataract formation, ascorbate could become a significant glycating agent (Lee *et al.* 1998) and promote cataract formation. This hypothesis will have to await confirmation by further experimental evidence.

Dietary restriction

Restriction of dietary energy intake has been associated with retardation of various age-related debilities in rodents (Weinruch *et al.* 1986), including cataracts. Taylor *et al.* (1995*a*) observed that mice fed on an energy-restricted diet developed cataract at a slower rate than mice fed on a normal control diet. Lens ascorbate levels were comparable in both dietary groups, although plasma ascorbate levels were lower in the energy-restricted group. Differences in antioxidant enzyme activities did not explain the observed differences (Gong *et al.* 1997), while biochemical molecular determinants of the cataracts in both groups were similar (Mura *et al.* 1993). As the lens ascorbate levels were comparable in both groups, it is not likely that ascorbate encouraged cataract formation in the control group. The differences may possibly be explained by the differences in plasma glucose levels and glycohaemoglobin levels (27 and 51 % lower respectively in the energy-restricted animals; Taylor *et al.* 1995*b*). A recent investigation confirmed that lens epithelial cells from energy-restricted mice are more resistant to H_2O_2-induced oxidative damage than *ad libitum*-fed mice (Li *et al.* 1998).

Human studies

Table 1 provides an overview of epidemiological and intervention studies which have investigated the relationships between vitamin C and cataract. Although it is often stated that epidemiological studies have shown a protective effect for antioxidant vitamins, Table 1 shows that only a small number of studies confirmed a relationship between dietary vitamin C intake or plasma levels and the risk of cataract. Also, the results of these studies are not uniform.

A larger number of studies showed a relationship between cataract and the use of vitamin C- or multivitamin supplements. However, interpretation of these results should be made carefully, as the use of vitamin supplements has been linked with income, education and health-care-seeking behaviour (Koplan *et al.* 1986), so that potential bias may affect these statistical relationships. Moreover, it has been shown that the human aqueous humour may saturate with vitamin C at intakes up to 250 mg/d (Taylor *et al.* 1997).

Two intervention trials included supplementation with vitamin C (study nos. 13 and 14 in Table 1). The Chinese trial (Sperduto *et al.* 1993) included generally poorly-nourished subjects and an effect of supplementation was only shown in subjects who were identified at high risk for oesophageal cancer. The Roche European–American Cataract Trial (Chylack *et al.* 1998), to date only presented in abstract form, showed a protective effect of supplementation after 2 years in American subjects but not in British subjects. An overall effect of supplementation in the whole study population (USA and UK subjects together) became significant after 3 years of intervention (Chylack *et al.* 1998).

A currently ongoing large multi-centre intervention trial in the USA (Age-related Eye Disease Study coordinated by the National Eye Institute of the USA) will provide further evidence of the effect of long-term supplemention of

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Table 1. Epidemiological and intervention studies of vitamin C and cataract

Study no.	Study type	Plasma vitamin C	Vitamin C supplement use*	Vitamin C intake	Cataract type	Country	Subjects	Reference
1	Case–control (*n* 112)	High levels → ↓ risk	N/A	N/A	Posterior subcapsular	USA	Hospital patients, 40–89 years	Jacques *et al.* (1988)
2	Case–control (*n* 1990)	High levels → ↑ risk	N/A	N/A	Posterior subcapsular and nuclear	India	Hospital patients, 37–62 years	Mohan *et al.* (1989)
3	Case–control (*n* 1380)	N/A	N/A (multi-vitamin use → ↓ risk)	High intake → ↓ risk	All types (multivitamin use), nuclear (vitamin C intake)	USA	Hospital outpatients 40–79 years	Leske *et al.* (1991)
4	Case–control (*n* 350)	N/A	Present use → ↓ risk	N/A	Not specified	Canada	Hospital patients, ≥55 years	Robertson *et al.* (1991)
5	Cohort, 8 year follow-up (*n* 50828)	N/A	Use ≥10 years → ↓ risk	No relationship	Incidence cataract extraction	USA	Female nurses, 45–67 years at baseline	Hankinson *et al.* (1992*a*)
6	Case–control (*n* 4847)	High levels → ↑ risk (in Indian subjects only)	Multivitamin use → ↓ risk in USA subjects, no relationship in Italian subjects, Indian subjects N/A	N/A	Not specified	India, Italy, USA	Hospital patients, 37–70 years	Schoenfield *et al.* (1993)
7	Cohort (*n* 660)	No relationship	N/A	N/A	Nuclear	USA	Baltimore residents, ≥40 years	Vitale *et al.* (1993)
8	Cohort (*n* 2152)	N/A	Use 10 years ago → ↓ risk (as single vitamin or in multivitamin supplement)	No relationship	Nuclear	USA	Beaver Dam residents, 43–84 years	Mares-Perlman *et al.* (1994, 1995)
9	Cohort (*n* 17744)	N/A	No relationship (multivitamin use → ↓ risk)	N/A	Not specified, self-reported	USA	Male physicians, 40–84 years	Seddon *et al.* (1994)
10	Case–control (*n* 913)	N/A	N/A	No relationship	Cataract extraction	Italy	Hospital patients, 25–74 years	Tavani *et al.* (1996)
11	Cohort (*n* 247)	N/A	Use ≥10 years → ↓ risk	N/A	Any type	USA	Female nurses, 55–69 years (subsample of seven)	Jacques *et al.* (1997)
12	Case–control, 5 year follow-up (*n* 764)	N/A	No relationship (multivitamin use → ↓ risk)	N/A	Increase in nuclear opacification	USA	Hospital outpatients, 40–79 years (subsample of six)	Leske *et al.* (1998)
13	Intervention, 5 and 6 years (*n* 35390)	N/A	Multivitamin supplement (including vitamin C) → ↓ risk in subjects 65–74 years; vitamin C + Mo supplement no effect	N/A	Nuclear	China	Patients and general population, 45–75 years	Sperduto *et al.* (1993)
14	Intervention, 3 years (*n* 231 after 2 years, *n* 158 after 3 years)	N/A	Vitamin C (+β-carotene + vitamin E) supplement → ↓ risk	N/A	Not specified	USA, UK	Hospital outpatients, ≥55 years	Chylack *et al.* (1998)

N/A, not assessed or presented; ↑, increased; ↓, decreased.
* As a single vitamin supplement unless otherwise stated.

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high-dose vitamins and minerals on the cataract process in human subjects.

Conclusion

The unknown (to date) latency period for cataract development could extend over a lifetime, possibly starting in the first months of life (Evans *et al.* 1998). There is no doubt that many different factors are involved in the cataract process, each with varying importance depending on the absence or presence of other factors, and possibly varying over different periods of a lifetime.

The required optimal level of plasma ascorbic acid to guarantee a healthy lens metabolism cannot be concluded from the available evidence, but could vary with different exposure levels to oxidative events and resulting losses of lens ascorbic acid. If this situation were true, relationships between intake or plasma levels of vitamin C and cataract status would only show in population studies when exposure to oxidative insult in some of the subjects studied causes a demand for vitamin C in the lens which exceeds the available quantities. Only then would statistical relationships show in population studies.

The available evidence suggests that maintenance of sufficient plasma vitamin C levels is needed to prevent oxidative damage to the lens and to allow active transport of ascorbate into the eye tissues. An optimum vitamin C intake would guarantee continuous eye tissue saturation. However, at present we cannot estimate the benefits:risk value of higher than normal intake levels. More research is needed in order to identify the relative importance of the different roles of vitamin C and other protective factors in various risk situations.

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