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, hypoxia, 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...
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; Slaney, 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 \( \text{H}_2\text{O}_2 \) are generated in the lens of photochemically-induced cataracts (Varma et al. 1979; Spector et al. 1993). \( \text{H}_2\text{O}_2 \) 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 \( \text{H}_2\text{O}_2 \) 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; Rouhani 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; Devmanoharan 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 et al. 1998).
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 H₂O₂) 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 H₂O₂ by reducing molecular oxygen, a reaction which is catalysed by metal ions (Halliwell & Gutteridge, 1989; Garland, 1990). Radical species can be generated from the H₂O₂ 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 H₂O₂ generation in the aqueous humour is temperature- and O₂-tension-dependent, and that ascorbic acid and metal ions may make a major contribution to H₂O₂ 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. 1992b; 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. 1992b; 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 O₂ 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 glycat ing agent (Lee et al. 1998) and promote cataract formation. This hypothesis will have to await confirmation by further experimental evidence.

Dietary restriction

Restiction of dietary energy intake has been associated with retardation of various age-related deilities in rodents (Weinruch et al. 1986), including cataracts. Taylor et al. (1995a) 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. 1995b). A recent investigation confirmed that lens epithelial cells from energy-restricted mice are more resistant to H₂O₂-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 supplementation of
Table 1. Epidemiological and intervention studies of vitamin C and cataract

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Study type</th>
<th>Plasma vitamin C</th>
<th>Vitamin C supplement use*</th>
<th>Vitamin C intake</th>
<th>Cataract type</th>
<th>Country</th>
<th>Subjects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Case-control</td>
<td>High levels</td>
<td>N/A</td>
<td>N/A</td>
<td>Posterior subcapsular</td>
<td>USA</td>
<td>Hospital patients, 40–89 years</td>
<td>Jacques et al. (1988)</td>
</tr>
<tr>
<td>2</td>
<td>Case-control</td>
<td>High levels</td>
<td>N/A</td>
<td>N/A</td>
<td>Posterior subcapsular</td>
<td>India</td>
<td>Hospital patients, 37–62 years</td>
<td>Mohan et al. (1999)</td>
</tr>
<tr>
<td>3</td>
<td>Case-control</td>
<td>N/A (multi-vitamin use)</td>
<td>High intake</td>
<td>N/A</td>
<td>All types (multivitamin use), nuclear (vitamin C intake)</td>
<td>USA</td>
<td>Hospital outpatients, 40–79 years</td>
<td>Leske et al. (1991)</td>
</tr>
<tr>
<td>4</td>
<td>Case-control</td>
<td>N/A</td>
<td>Present use</td>
<td>N/A</td>
<td>Not specified</td>
<td>Canada</td>
<td>Hospital patients, ≥55 years</td>
<td>Robertson et al. (1991)</td>
</tr>
<tr>
<td>5</td>
<td>Cohort, 8 year follow-up</td>
<td>N/A</td>
<td>Use ≥ 10 years</td>
<td>N/A</td>
<td>Incidence cataract extraction</td>
<td>USA</td>
<td>Female nurses, 45–67 years at baseline</td>
<td>Hankinson et al. (1992a)</td>
</tr>
<tr>
<td>6</td>
<td>Case-control</td>
<td>High levels</td>
<td>Multivitamin use</td>
<td>N/A</td>
<td>Not specified</td>
<td>USA</td>
<td>Hospital patients, 37–70 years</td>
<td>Schoenfield et al. (1993)</td>
</tr>
<tr>
<td>7</td>
<td>Cohort</td>
<td>No relationship</td>
<td>N/A</td>
<td>N/A</td>
<td>Nuclear</td>
<td>USA</td>
<td>Baltimore residents, ≥40 years</td>
<td>Vitale et al. (1993)</td>
</tr>
<tr>
<td>8</td>
<td>Cohort</td>
<td>N/A</td>
<td>Use 10 years ago</td>
<td>N/A</td>
<td>No relationship</td>
<td>USA</td>
<td>Beaver Dam residents, 43–84 years</td>
<td>Mares-Perlman et al. (1994, 1995)</td>
</tr>
<tr>
<td>9</td>
<td>Cohort</td>
<td>N/A</td>
<td>No relationship (multivitamin use)</td>
<td>N/A</td>
<td>Not specified, self-reported</td>
<td>USA</td>
<td>Male physicians, 40–84 years</td>
<td>Seddon et al. (1994)</td>
</tr>
<tr>
<td>10</td>
<td>Case-control</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Cataract extraction</td>
<td>Italy</td>
<td>Hospital patients, 25–74 years</td>
<td>Tavani et al. (1996)</td>
</tr>
<tr>
<td>11</td>
<td>Cohort</td>
<td>N/A</td>
<td>Use ≥ 10 years</td>
<td>N/A</td>
<td>Any type</td>
<td>USA</td>
<td>Female nurses, 55–69 years</td>
<td>Jacques et al. (1997)</td>
</tr>
<tr>
<td>12</td>
<td>Case-control</td>
<td>N/A</td>
<td>No relationship (multivitamin use)</td>
<td>N/A</td>
<td>Increase in nuclear opacification</td>
<td>USA</td>
<td>Hospital outpatients, 40–79 years</td>
<td>Leske et al. (1998)</td>
</tr>
<tr>
<td>13</td>
<td>Intervention</td>
<td>N/A</td>
<td>Multivitamin supplement</td>
<td>N/A</td>
<td>Nuclear</td>
<td>China</td>
<td>Patients and general population, 45–75 years</td>
<td>Sperduto et al. (1993)</td>
</tr>
<tr>
<td>14</td>
<td>Intervention</td>
<td>Vitamin C</td>
<td>N/A</td>
<td>N/A</td>
<td>Not specified</td>
<td>USA, UK</td>
<td>Hospital outpatients, ≥55 years</td>
<td>Chylack et al. (1998)</td>
</tr>
</tbody>
</table>

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

References


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