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ROLE OF ASPIRIN IN CATARACT

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ABSTRACT

Role of aspirin in cataract is continuously being investigated. Epidemiological studies indicated that regular use of aspirin and aspirin like analgesics decrease the incidence of cataract. Laboratory studies offer several possible mechanisms by which aspirin exert its effect (A) via modification of glucose metabolism (B) via changes in physical behaviour of proteins within the lens fibers or (C) in the communication between lens epithelial cells. Disorder of each of these processes is associated with lens opacification and can be modified by aspirin. Aspirin is particularly appealing as anti-cataract drug because it has relatively few side effects and is inexpensive. However, various case studies indicated that aspirin has no role to play in cataract prevention rather it may cause cataract, which invoked a continuous debate regarding its role.

KEY WORDS: Cataract, Aspirin, Post-translational modifications, Protein aggregation.

INTRODUCTION

Cataract is defined as the opacification of the lens and may occur at any age, but its incidence is clearly associated with aging.[1] The Framingham Eye study[2] showed a prevalence of 17.6 % in less than 65 years age group, 47.1% in 65-74 years age group and 73.3% in those older than 75 years. Through out the world, blindness due to cataract presents enormous problems not only in terms of human mortality but also in terms of economic and social burden.[3] Number of blind people due to cataract was estimated 2.5 million in the year 2000.[4] In India out of 12 million cases of blindness, cataract alone accounted for 81%.[5] The only present remedy of cataract is surgery.[6] Surgery although an effective means of reversing cataract has not however eliminated the problem because of many reasons like (i) long waiting list[7], cost of surgery[8], risk of complications[9], lack of technical hand and equipments[10], etc. The problem of cataract remains consistent in the population despite surgical intervention, also because of continued aging and consequent addition of new ones.[11] Cataract, the leading cause of blindness, is not only an important public health problem but also a socio-economic one especially in the tropical countries including India.[12] Prevention or delay in its progression would present a major achievement for human welfare and is therefore one of the priorities of medical research in this country.[13] It was found that an increased risk of cataract is associated with lower educational achievement, diet low in specific nutrients, high blood pressure and use of cheaper cooking fuels.[12] However, once cataract has developed its reversal by a drug is considered not possible.[11] Prophylaxis against the development of cataract may therefore, is the only ideal pharmacological recourse. The disadvantage of this route, however, is the number of years a person would have to be on prophylaxis. Therefore the person will have to be maintained on a prophylactic drug for the rest of his/her life.[11]

Mechanism of cataract formation

Cataract is a complication that accompanies diabetes mellitus and aging process.[14] Current evidences support the views that cataractogenesis is a process in which many inexorably linked factors induce subtle post-translational modifications in the lens structural proteins (crystallins).[15] Such post-translational protein modifications even at low levels are of particular importance, since due to the negligible turnover of lens proteins, they accumulate in the lens enhancing crystallin aggregation, fragmentation and precipitation.[16] This aggregation disrupts the short-range order of crystallin structure, adversely affecting the transparency of the lens.[17] The mechanism proposed to explain the cataract associated with aging, suggest that the lysyl residues of lens crystallins react with dehydroascorbic acid which is higher in older subjects because the reduced glutathione (GSH), needed to keep ascorbic acid in its reduced form, is depleted.[18] Also subjects with recurring severe diarrhoea, impaired renal function and diabetes all have high incidence of cataract.[14, 17] Harding and Rixon, in 1980[19] have suggested that carbamylation of lysine residues of lens crystallins may contribute to the high incidence of cataract in countries where severe diarrhea is a recurring problem. These subjects are similar to those with renal failure in that they experience elevated

blood urea concentration for prolonged periods. Beswick and Harding, in 1984[20] offered a possible mechanism explaining how isocyanate might cause cataract. They showed that isocynate cause changes in the secondary and tertiary structure of lens alpha-crystallin with subsequent disulfide bonding and aggregate formation that could contribute to opacity. Two mechanisms have been proposed for a cataract in diabetic subjects. These are (i) aldose reductase osmotic mechanism and (ii) non-enzymatic glycosylation.[21] In aldose reductase osmotic mechanism, when blood glucose level is elevated, glucose is reduced by aldose reductase to sorbitol, which accumulates within the cell. It is the rapidity with which sorbitol is produced from its hexose precursor and the impermeability of the cell membrane to the sugar alcohol (sorbitol) that create a hypertonic milieu within the cell which leads to the cellular swelling, rupture and disintegration.[22] There are considerable doubts about the role of aldose reductase and the accumulation of sorbitol in cataract patients with diabetes for a number of reasons. First, the activity measured for aldose reductase is very low in human lens, whereas the activity of polyol dehydrogenase, an enzyme that would remove any sorbitol formed, is high, so no sorbitol could accumulate.[23] Levels of sorbitol found in human cataracts from hyperglycemic patients are low and human lens incubated in high glucose media accumulate trivial concentration of sorbitol.[24]

According to the second method the high incidence of cataract among diabetics may be due to the glycation of lens crystalline.[25] A variety of glycating reagents have been investigated. It has been proposed that glucose[26], glucose 6-phosphate[27] glucosamine[21] and galactose[28], all react with alpha-amino and epsilon-amino groups of proteins, to form schiff-base adduct which undergo Amadori re-arrangement to form the more stable Amadori product. The Amadori product can undergo further dehydration and re-arrangement reactions to form irreversible products termed advanced glycation end products (AGEPs) thus reducing positive charge on the surface of protein and causing conformational changes which eventually lead to irreversible crystallin damage by promoting covalent protein-protein cross links[29, 30], and would affect the lens ability to focus light on the retina.[31]

Prevention of cataract

It has been suggested that there is no need to prevent cataract because there is a perfectly good surgical procedures available.[8] Cataract surgery has not however eliminated the problem. The major drawback of the surgery is the risk of complications. In percentage terms, the risk of most complications is small but given the enormous number of procedures-about 2 million per annum in both United States and India, for example, the overall number of even serious complications is great.[8] One of the complications is the posterior capsular opacification (PCO). It occurs in up to 50% of patients and almost 100% in younger patients.[9] In many of countries with severe cataract problems, the equipment to deal with this complication is a rarity, a point that is ignored by those advocating greater use of the latest western surgical techniques in developing countries.[10] In Nepal the outcome of surgery with intraocular lenses was no better than that without and 50% of impaired vision in operated eyes was attributed to surgical complications including PCO.[32] Accepting that prevention of cataract is desirable; the next question is how to achieve this objective. There would seem to be two major possibilities (1) elimination of risk factors and (2) an anti-cataract drug.[8]

(1)Elimination of risk factors: Abandoning the use of phospholine iodide for the treatment of glaucoma has prevented tens of thousands of cataract.[33] The scope for further prevention in western countries is limited because there is not a single predominant cause of cataract and even major causes are somewhat intractable.[8] If diabetes accounts for about 12% of cataract in West, only wiping out diabetes could eliminate that proportion. Of course it is likely that steps that fall short of elimination could provide tangible benefits. Better control of blood sugar levels would probably decrease the amount of cataract in the following decades. Developing countries has different risk factor and there is evidence that 50% of cataract may be attributable to life threatening diarrhea.[34] In this case the possibility of eliminating this proportion by prevention of diarrhea arises. The greatest advantage of elimination of risk factors is that this would not normally lead to side effects. Indeed better control of diabetes and elimination of diarrhea, heavy smoking and drinking could only bring additional benefits.[8] Xiaoning Yu, et al., 2014 showed an increase in risk of cataract in hypertensive subjects. Thus advocated that controlling hypertension would help to decrease cataract occurrence and cataract surgery costs.[35]

(2)Anti-cataract drugs: Anti-Cataract drugs are the alternative option for cataract prevention and have been investigated for many years. The first compound studied systematically were the aldose reductase inhibitors (ARIs).[36] However they have not proved successful and the hypothetical basis for their use has been undermined.[27, 33] The most serious problem with the sorbitol / osmotic stress hypothesis for cataractogenesis is that the pure enzyme isolated or recombinant has never been shown to convert glucose stoichiometrically to sorbitol. That is enzyme cannot perform the reaction that gave its name.[8] Furthermore, the most commonly used assay has a substrate glyceraldehyde that autooxidises.[8] Aldose reductase has a few of the properties expected of an enzyme and the structure has no sign of a sugar binding site.[37] In mitigating cataractogenesis the oral use of amino acids have been found to be beneficial. Lysine alone and other mixture of amino acids (leucine, isoleucine, lysine, phenylalanine, threonine, valine, tryptophan, and methionine) have shown significant prevention of cataract when given orally in diabetes - induced cataract in rats. The amino acids did not only

found anti-cataract but also decreased blood sugar and increased body weight of diabetic animals. The anti-cataract mechanism may be due to the anti-glycating effect of lysine or other essential amino acids competing with lens protein for glycation, scavenging lenticular glucose and thereby decreasing glycation of lens proteins.[38, 39] The next group of potential anti-cataract drugs aspirin or aspirin-like analgesics such as paracetamol (acetaminophen) and ibuprofen arrived on the scene by series of fortuitous observations.[8, 40]

Aspirin as anti-cataract drug

Epidemiological studies have indicated that regular use of aspirin-like analgesics decreases the incidence of cataract[41, 42] and further epidemiological work supported the proposition that those who take aspirin regularly are less likely to need cataract surgery.[43] Aspirin is particularly appealing as an anti-cataract drug because it has relatively few side effects and inexpensive. Aspirin is prescribed as a remedy or prophylactic for a wide range of disorders. Cotlier and Sharma in1981[41] first suggested that aspirin might be the cause of decreased lens opacification in rheumatoid arthritis patients. An increased level of plasma tryptophan and its metabolites have been found in the patients of senile cataracts and the cataractogenic effect of the amino acid has been suspected.[41, 44] Smith and Lakatos[45] found a reduction of 47% in bound plasma tryptophan after oral administration of 1800 mg of aspirin. Thus aspirin may affect the human lens by lowering plasma tryptophan level. It was further speculated that a similar decrease in the incidence of cataract among diabetics taking aspirin was due to salicylate blocking the increase in aldose reductase that causes excess sorbitol formation.[46] Laboratory studies offer several possible mechanisms by which aspirin exert its effect: (a) via modification of glucose metabolism[47, 48] (b) via changes in the physical behavior of proteins within lens fibers[17] or (c) in the communication between lens epithelial cells.[49] Disorder in each of these processes is associated with lens opacification[50- 52] and can be modified by aspirin.[21, 53]

Investigators suggested that the mechanism of the inhibitory effect of aspirin might be through acetylation of the lens proteins, perhaps by competing with carbamylation[17], glycosylation[53, 54] or steroid binding.[46] It has been reported that aspirin can acetylate a variety of proteins including lens proteins.[17, 54-57] Aspirin has been shown to prevent carbamylation of proteins; hence cyanate- induced phase separation temperature and lens opacification.[17] The tight binding of labeled aspirin to lens protein and the preincubation results indicated that aspirin exerts its protective effect by itself reacting with the protein amino group to prevent attack by cyanate. Presumably the reaction is the transfer of acetyl group from aspirin to protein's amino groups.[17] The inhibitory effect of acetylation by aspirin appears to be mediated through a blockage of amino groups that are involved in glycation.[53, 20] In non-enzymic glycosylation of bovine lens proteins, the protection against the reaction was shown by aspirin (acetyl salicylic acid), but not salicylic acid, which is structurally identical except for the absence of acetyl group showing that acetylation may play a role in the protection.[21] Acetylation of lysine of bovine lens α_A – crystallin has been examined after 0 to 48 hours incubation of whole α- crystallin in 100 mM aspirin. For the reaction conditions used in this investigation, acetylated lysyl residues were the principal products. All seven lysyl residues of α_A – crystallin reacted with aspirin, however, the extent of acetylation varied at each lysyl residue.[56] In vivo acetylation has also been identified at lysine 70 of human lens α_A – crystalline.[58]

In vitro studies with rat lens crystallins showed that there was two to four fold faster glycation of gamma-crystallin than all other crystallins from one month old rats and aspirin inhibited glycation of gamma- crystallin four times more than alpha- and beta- crystallins, thus showing preferential glycation of gamma- crystallin and its selective inhibition by aspirin.[59] (14C) acetyl incorporation showed increased acetylation of gamma-crystallin in one-month-old rats, whereas in older lenses acetylation of other crystallins predominated. Treatment with 10 mM aspirin showed 35% decrease in free NH_2 groups but protein thiols remained unchanged.[59]

Aspirin besides acetylating crystalline and preventing glycation has also been proposed to act by another route. It has also been shown to inhibit prostaglandin synthesis, a characteristic of diabetes, responsible for increase in malondialdehyde (MDA) production. MDA can posttranslationally modify proteins leading to aggregation. Thus mechanism of binding of aspirin might be of two types (1) by acetylating the protein and (2) by inhibiting prostaglandin synthesis in platelets which would also lower MDA formation and reduce the amount of MDA available to attack the lens.[60]

A recent study with zeta- crystalline purified from camel lens, has shown that aspirin acetylated zeta- crystallin as well, but this modification has little impact on the enzyme activity. However, acetylation by aspirin may inhibit a variety of posttranslational modifications thought to be harmful to proteins, and it is possible that acetylation of gamma- crystallin might be important for cataract delaying action of aspirin.[61]

These experiments clearly indicated that the eye lens crystallins are acetylated with aspirin and also suggested covalent type of binding of acetyl moiety of aspirin to the lens crystallin. The significant decrease of free epsilon- amino groups of aspirin treated crystallins further suggests the probable site of acetylation in the crystalline.[57] However, it has also been reported that alpha- amino groups of proteins are more reactive than epsilon- amino groups in all these reactions which are general reactions affecting all proteins, so the masking of alpha- amino groups of many long lived proteins such as alpha- and beta- crystallins, collagen and basic protein of

myelin can be seen as a protective mechanism against these chemical modifications.[17]

Aspirin has been shown to delay experimental cataracts in laboratory animals. It delayed naphthalene-induced cataract in rabbits and galactose-induced cataract in rats.[62] It showed protection in diabetic rats against the development of cataract.[48] In this experiment, aspirin decreased glycation of lens without lowering blood glucose level, and helped to maintain gluthathione level in lens.[48] Topical aspirin delayed cataractogenisis in galactose fed rats.[63]

Perhaps the strongest support for the view that aspirin-like analgesics protect against cataract came from case-control studies of cataract in human populations.[42] The first of these studies seeking risk factors in England had a single question about drugs taken regularly which elicited the unexpected protective associations between the consumption of aspirin, paracetamol and ibuprofen and protection against cataract.[42, 64] A second study in the same area confirmed the result and provided more information on the relevant dosage, showing that even low lifetime doses were associated with protection against cataract.[65]

A case control study performed with a population of patients with a Rheumatoid arthritis (RA) and RA with diabetes was selected. On the treatment with aspirin with 2.7 gram daily for an average of 10.4 years for patients with diabetes alone and 2.3 grams daily for an average of 8.8 years for patients with RA and diabetes, were found to develop cataract significantly less. The study showed prolong aspirin therapy can delay or prevent cataract formation in adult onset RA.[41] In another case control study of 300 patients with cataract associated with diabetes, renal failure, severe diarrhea, steroid and nifedipine administration with 609 control subjects of same age and sex distribution have indicated that long term use of aspirin- like analgesics halves the risk of cataract.[42] A study in senile cataract patients using systemic aspirin and systemic vitamin E has shown that more eyes in systemic aspirin treated group maintained the initial vision and loss of vision in this group was also less marked. Aspirin also caused significant less mean increase in cortical opacity extent, nuclear/opacity and density and posterior sub-capsular opacity extent and density as well as in ophthalmoscopically graded opacity extent and density. Authors suggested that aspirin is a potential drug, which should be further evaluated in large double blind photodocumentated studies.[66] In a similar hospital based case control study of 1441 patients with age related cataract and 549 controls were studied in association with different types of cataract like nuclear, cortical, posterior sub-capsular, and mixed and a number of physiological, behavioral, environmental and biochemical variables were taken into account. The data suggested that use of one or more aspirin a month was protective for posterior sub-capsular cataract and mixed type of cataract, however, the results were not so promising for other cataracts.[67] The Beaver Dam eye study, a population based incidence study, showed a significant decrease in the incidence of nuclear cataract in those who took thiazide and aspirin at base line. The beneficial effect of aspirin for nuclear cataract although weak, is biologically plausible in that aspirin decrease inflammation, a possible cause of human age related cataract.[68]

While there are a number of case-control studies, showing that aspirin protect against cataract[41,42, 66-68], some case-control and cohort studies claimed not to have shown any such effects.[69-72]

Aspirin protects or causes cataract is still debatable

Role of aspirin in cataract prevention or formation is a debatable topic. Many people have opinion that aspirin causes cataract in long run rather than preventing it. It has also been reported that the use of aspirin for a longer time may increase the risk for cataract formation. Researchers have shown that more than 10 years use of aspirin caused a 44% elevation in posterior sub capsular cataracts, compared to nonusers or short-term users. This risk was found to be larger among people less than 65 years of age than older subjects.[73] Further studies also indicated disassociation between aspirin and the cataract prevention[74, 75] and raised a suspicion that aspirin could even cause cataracts, though that is no more than a preliminary finding. Thus further study is needed to ascertain the clear cut role of aspirin in cataract; however its use in heart disease risk cannot be over looked for elder patients.[76] A randomized study conducted with 2435 patients with transient ischemic attack or minor ischemic stroke were treated with aspirin 1200 mg/day and 300 mg/day for few years. Patients were examined for cataract status. There were no difference found in the prevalence of cataracts between patients on aspirin and patients on placebo.[77] The debate continues as another randomized trial of aspirin in relation with cataract has been recently conducted in United States which proposed aspirin as an anti cataract drug or a drug which can delay its progression. They indicated the possible role of aspirin on tryptophan levels in cataract patients, or in lens glycosylation or inhibitory effects on aldose reductase enzyme which plays a crucial role in diabetic cataract formation.[78, 79]

A problem with case-control studies is the ever-present possibility that some variables are not allowed for inmatching.[80] Case-control studies show only associations not a causal relationship, which would normally come from an intervention study for the treatment of cataract.[37] No such study has been reported, although cataract studies have been added to aspirin and heart disease studies.[37] Of course the causal relationship was clearly demonstrated by the protection against experimental cataract. Calculation of attributable risk shows that about 40% of cataract could be prevented if the relationship was causal.[65, 81] The protective

association of aspirin against sight-threatening cataract has been confirmed in India and US.[23, 82]

CONCLUSION

Causes of cataract are multi-factorial and it would be surprising if the ingestion of a single substance could protect against all types of cataract.[8, 42, 43, 64] It is therefore, not surprising that a beneficial effect is not readily apparent in some of the studies. Meanwhile, cataract is the commonest cause of blindness in the world, though operable, treatment is not accessible to the majority of the blinds in the developing world.[80] As an age related problem it can be expected to worsen with an increasingly aged population. One estimate suggested that if cataract could be delayed by 10 years, the number of cataract operation needed would be decreased by 50%.[13] Therefore, any hopeful preventive measure deserves to be studied. In view of the increasing magnitude of the problem to which no solution is in sight, aspirin still deserves a serious look amidst the long ongoing debates.

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