Carbohydrates of the lens in normal and precataractous states

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The free carbohydrates of the lens are discussed, with particular attention to the normal concentrations. Simple sugar derivatives such as the sugar alcohols are similarly treated. Such metabolic intermediates as the sugar phosphates and the more complex adenosine derivatives are mentioned, as are structural components containing sugar moieties. Experimental procedures, such as special diets, which alter lens sugar levels are briefly outlined.

As far as over-all metabolism is concerned, glucose is the most important free hexose in the lens which derives its supply chiefly by diffusion from the aqueous humor. The normal concentration of glucose in the lens, as determined by glucose oxidase on a Nelson-Somogyi filtrate, is rarely above 15 mg. per 100 Gm. At this level a lens removed from contact with its aqueous and vitreous humors uses up about one third of its endogenous store of glucose in five minutes. Unless a lens is well cleaned of adhering humors by rinsing and blotting, contamination by exogenous glucose will make an appreciable error in the value for the lens glucose level. Thus to a large extent the concept of lens glucose is operational and published values must be regarded in the light of the techniques used in preparing the lenses. We found that twelve lenses (averaging 240 milligrams each) from 12 rabbits (weighing about 1.5 kilograms each) had a glucose level of 7.2 mg. per 100 Gm. when they were prepared with the above precautions in mind. Anterior aqueous humor samples (drawn from just behind the cornea) of these same rabbits had a glucose level of 137 mg. per 100 ml. All other species examined also have glucose in the lens. Table I shows the level of glucose in the lenses of several species. A possible explanation for the rather remarkable consistency of this value (10 ± 10 mg. per 100 Gm. is that the glucose is chiefly in the extracellular lens water (about 10 per cent of the lens volume) where, at a concentration of 100 mg. per 100 ml., it is in approximate equilibrium with the glucose of the posterior aqueous humor.

The occurrence of fructose appears to be universal in lenses. It seems to have been tacitly assumed on the basis of in vitro incubation studies that the lens is the only tissue of the eye which synthesizes fructose, although limited experiments have indicated that whole cornea cannot convert sorbitol to fructose. Although its level is higher than that of glucose in the lenses of some species (e.g., the rabbit) it may be considered less important because it is...
produced from glucose within the lens via the sorbitol pathway, and because normally it is not appreciably utilized but appears to be lost by diffusion into the aqueous and vitreous humors. In the 12 rabbits in our study referred to above, the lenses had a fructose level of 14.5 mg. per 100 Gm., whereas the level in the anterior aqueous humor was 2.2 mg. per 100 ml. The lens fructose levels are given in Table I for other species.

The formation of fructose in the lens via the sorbitol pathway implies that both sorbitol and fructose will occur together. This is true for the few lenses of the various species which have been investigated (Table I). It appears that the sorbitol concentration is usually higher than either the glucose or fructose concentration. This situation is to be expected from a consideration of the properties of the dehydrogenases involved which would favor the conversion to the sugar alcohol. Lens sorbitol may not be useful to the lens since it is not appreciably converted to lactate and its occurrence at high levels in certain abnormal states may be a definite embarrassment because of its osmotic effect. Thus the importance of the sorbitol pathway in lens metabolism must hinge upon the utilization of the fructose produced or the importance of the pathway in toto, including the pyridine nucleotide conversions involved. Any speculation concerning fructose utilization must give proper weight to these facts: that fructokinase activity in the lens is minimal and that the availability of fructose depends on the supply of glucose. Thus it is difficult to conclude that the sorbitol pathway functions as a mechanism for the conversion of glucose. However, the possibility should be considered that some other eye tissue in contact with the aqueous or vitreous humors may find fructose an essential metabolite. Van Heyningen1 has recently reviewed the sorbitol pathway in the lens, and Levari and associates2 have discussed some interrelations of this pathway with other pathways of glucose metabolism.

Traces of glycogen occur in mammalian lenses (5 mg. per 100 Gm. in the rat)3 but the lenses of birds with active flying habits may contain up to 300 mg. per 100 Gm. It is concentrated in the nucleus where it increases the refractive index.

In addition to the above, other carbohydrates or their derivatives have been found in the normal lens. Ascorbic acid is found at a level of the order of 10 mg. per 100 Gm. (from 3 mg. per 100 Gm. in the rat to 57 mg. in the horse).4, 5 Heath6 has reviewed comprehensively the distribution and role of lens ascorbic acid, and Kinoshita7 has discussed its possible function in the metabolism of lens glutathione. Although we can say that ascorbic acid occurs at relatively high levels in the lenses of some species of animals, it apparently is not synthesized there and its functions and ultimate disposal remain unknown.

Another sugar derivative occurring at
unusually high levels in the lenses of some species is inositol (30 mg. per 100 Gm. in rabbits to 300 mg. in sheep, guinea pig, and adult human). Unlike ascorbic acid, its concentration in the aqueous humor is not excessive compared with the blood concentration, hence the high levels in the lens must arise either from synthesis there or from a most efficient concentrating mechanism. Nothing is known of the function or metabolism of inositol in the lens. Pirie and van Heyningen have shown that in senile cataractous human lenses the inositol appears to be leached out as glucose diffuses in, probably because of altered permeability. It is a sugar alcohol, but its metabolism does not appear to involve the sorbitol pathway; only one conversion product is possible, the corresponding ketocyclitol.

Other compounds occurring in the lens in trace amounts are glucosamine (1.5 mg. per 100 Gm. in bovine lens, 2.6 mg. in rat lens) and gluconic acid which was found in the human lens by van Heyningen.

In addition to the free carbohydrates, the lens contains significant amounts of carbohydrates which are moieties of larger structural elements. Because of the small nuclear volume compared to the cell volume in the lens, there is only a very low concentration of deoxyribose (in DNA); there is much more ribose in the RNA. The glycoproteins, extensively studied by Dische and co-workers, have been postulated to be linked to the collagen of the capsule or to make up the cement lubricant of the lens fibers. The sugars involved are chiefly galactose and glucose, with smaller amounts of mannose, fucose, sialic acid, and glucosamine. Feldman has recently found proteolipids in the lens. This fraction is made up partly of glycolipids, including gangliosides. The gangliosides are ceramide monosialo di- and trihexosides containing glucose and galactose but no N-acetylhexosamine. The other glycolipids are ceramide polyhexosides.

Because of the predominance of glycolysis in lens metabolism, all the intermediate phosphate esters between glucose and the trioses are found in the lens. In some cases the steady state concentration of a particular sugar phosphate may be appreciable, but rarely over 8.0 mg. per 100 Gm. expressed as glucose-phosphate. Of this fraction of difficultly hydrolyzable phosphate, the great majority is α-glycerophosphate and glucose-6-phosphate. The concentrations of individual esters in this group have been tabulated by Nordmann and by Pirie and van Heyningen. The high energy phosphate compounds in the lens, such as ATP, are chiefly derivatives of ribose phosphate. Hockwin has studied these compounds in the lens.

It is probable that future research will discover small amounts of carbohydrates not now known to occur in the lens. Gas chromatography of sugar derivatives shows promise of having the high sensitivity and specificity needed for such a task. For instance, several investigators have evidence that in the rabbit lens there is some material which reduces copper but which is not completely accounted for by the sum of glucose and fructose present. The amount of this unknown material is of the same order of magnitude as the combined errors of the methods, so that there is no certainty that it exists, much less that it is a carbohydrate. Such a problem is a challenge to develop better analytical methods.

The levels of carbohydrates in the lens may be altered by the administration of drugs and the imposition of special diets, including starvation. The feeding of rats with high levels of certain carbohydrates not normally in the diet may result in the formation in the lens of significant amounts of carbohydrates normally not detectable there. Van Heyningen found that young rats after a few days on 35 per cent galactose exhibited a level of dulcitol in the lens of up to 6 per cent of the lens dry weight which is the osmotic equivalent of the lens total potassium. Hart and Peckham have shown by gas chromatography that the lens galactose level under such circumstances...
The lens glucose level is approximately 10 mg. per 100 Gm. wet weight. We have shown that a galactose diet, without increasing the aqueous glucose level, will cause the lens glucose level to increase by a factor of 2 to 3 with a corresponding increase in the fructose level. Since the rate of glycolysis appears normal, the increased level of glucose in the lens may be due only to higher lens permeability to glucose. Under these circumstances the aqueous polyol level is about ten times normal, indicating a marked increase in the throughput of the first half of the sorbitol pathway; on the other hand, an increase of only 20 per cent in the aqueous fructose level indicates no marked enhancement of the second half of the sorbitol pathway. It is evident that a fraction of the lens polyol in this case must be sorbitol, a fact which has escaped notice and which points up the deficiency of present methods of detecting and determining small amounts of polyhydroxy compounds.

Rats on a xylose diet show lens changes much like those due to galactose but the end results are less severe because xylose can be converted ultimately to xylulose which may escape from the lens. Lerman has found that in xylose feeding the lens does not show the increased levels of glucose and fructose found in galactose feeding. Whether or not this difference in behavior is part of the explanation as to why xylose cataract is reversible while galactose cataract is irreversible remains to be shown. It is worthy of note that the calf lens can convert xylose to xylonic acid but not to xylitol.

In the formation of diabetic cataract in alloxanized rats, the initial changes appear to be due to a lenticular accumulation of glucose, sorbitol, and fructose which are in osmotic imbalance with the aqueous humor glucose. It has been shown that whereas lens glucose rises in direct proportion to the increase in blood sugar, the lens fructose concentration appears to level off at 200 to 250 mg. per 100 Gm. No such systematic study has been made for lens sorbitol in the diabetic rat but a number of isolated analyses indicate, as would be suspected, that the lens sorbitol level may exceed that of glucose and fructose combined. It is not known if the sorbitol concentration reaches a plateau as does fructose.

Other experimental procedures may increase lens sugar levels by producing hyperglycemia. Rats suffering from fluoroacetate intoxication show changes in the lens sugar levels which are indistinguishable from those of mild alloxan diabetes. It has not been possible to produce cataract with sublethal doses of fluoroacetate. Rabbits given chronic methyl prednisolone acetate (Depo-Medrol) treatment may occasionally develop steroid diabetes with consequent effects on lens sugars. One rabbit with an anterior aqueous glucose level of 130 mg. per 100 ml. had a lens glucose level of 33 mg. and fructose of 56 mg. per 100 Gm. Another animal under similar treatment responded differently: The anterior aqueous glucose concentration was only 87 mg. per 100 ml., lens glucose 6.7 mg. per 100 Gm., and lens fructose 42 mg. per 100 Gm.

Recent reports indicate that certain therapeutic drugs may be cataractogenic. We have found that rats on a diet containing triparanol at a level sufficient to reduce total lens sterols by 10 to 15 per cent showed no significant variations from control levels for blood sugar, or lens glucose, fructose, or sorbitol. It seems clear that in the precataractous stage of triparanol feeding there are no aberrations in the levels of lens sugars.

In the process of normal aging, rats and rabbits show increases in the lens level of both sorbitol and fructose even though the glucose levels in the blood and aqueous humor remain relatively constant. This change with aging is capable of being modified by the diet or perhaps other factors. For instance, male rats 18 months old sacrificed shortly after being brought from the farm had a lens fructose level of about 30 mg. per 100 Gm. A similar group kept in the laboratory for the last 8 months of...
life had a lens fructose level of 48 mg. per 100 Gm. Another group of a different strain was kept in individual cages for 11 months. When sacrificed at the age of 15 months the lens fructose was 49 mg. per 100 Gm. Part of this latter group was fed the high fat fructose diet of Patterson for 3 weeks before they were killed. These lenses had a fructose level of 64 mg. per 100 Gm. The control and experimental aqueous fructose levels were 5.3 and 6.4 mg. per 100 ml. Since the blood fructose was low and was increased only slightly by the diet, the slight rise in aqueous humor fructose of rats on the diet may have been a result of the corresponding higher lens fructose. Thus the diet containing 50 per cent fructose increases lens fructose in some indirect manner.

Young (100 gram) rats fasted overnight showed a reduction in lens fructose from 6.3 to 2.8 mg. per 100 Gm. This appears to be a direct consequence of a poorer glucose supply since the blood sugar went from 125 to 85 mg. per 100 ml, the aqueous glucose from 115 to 63 mg. per 100 ml. Fasting had the same effect in the lenses of old rats although the reduction in blood sugar was less.

The results of these studies indicate that normal variations in the diet may affect the lens to a greater degree than has hitherto been supposed, and suggest the possibility that such studies may shed light on the cause of cataracts of unknown etiology.

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REFERENCES