Glycosaminoglycan Sulfotransferases of the Developing Chick Cornea*

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Glycosaminoglycan sulfotransferases prepared from chick corneas were studied throughout embryonic development. Assay conditions were established using keratan sulfates (bovine cornea), heparan sulfates (human umbilicus), mixed isomer chondroitin sulfates (shark and whale cartilage), and chondroitin sulfates A (whale cartilage) as exogenous acceptors of $^3$S from phosphoadenylyl-$^3$Sisulfate. The $^3$S-glycosaminoglycans formed with each exogenous substrate were characterized. The specific activities of corneal glycosaminoglycan sulfotransferases were determined throughout corneal development, using each exogenous acceptor as substrate. Effects of serum factors or thyroid hormones, or both, on the in vitro and in vivo activity of the enzymes also were investigated.

The data with each exogenous acceptor indicate that glycosaminoglycan sulfotransferase specific activity changes only slightly during corneal development, and that embryonic chick sera of various ages contain substantial amounts of glycosaminoglycan sulfotransferase activity. Addition of exogenous glycosaminoglycan acceptors to preparations of corneal enzymes resulted in a 5- to 128-fold stimulation in the formation of $^3$S-glycosaminoglycans above endogenous levels. Dermatan sulfates and chemically desulfated keratan sulfates were not acceptors of $^3$S in these assays. The apparent $K_m$ of corneal glycosaminoglycan sulfotransferases for 3'-phosphoadenylyl-$^3$Sisulfate (with keratan sulfates as exogenous acceptors) did not change significantly during corneal development. The $^3$S-glycosaminoglycan products formed in the standard sulfotransferase assays were identified as those expected for each exogenous substrate. Thyroid hormones or serum factors, or both, from various age embryonic chick sera did not significantly affect the in vitro glycosaminoglycan sulfotransferase activity of enzymes obtained from embryonic corneas or from chick sera. Thyroid hormones injected in ovo on Day 6 did not affect sulfotransferase activities found in Day 8 corneas.

The degree of sulfation of corneal glycosaminoglycans during development may be regulated by the availability of 3'-phosphoadenylylsulfate, rather than by the activity of sulfotransferases.

The polysaccharide chains (glycosaminoglycans) of proteoglycan molecules are strongly polyanionic because of the presence of sulfate or carboxylic acid moieties, or both, on the disaccharide units along their length. The negative charges on these ubiquitous extracellular macromolecules dominate their physical properties and their interactions with other molecules (1, 2). Proteoglycans or glycosaminoglycans are thought to be involved in interactions during normal morphogenesis and development of many tissues (3). The location and density of sulfate residues along the polysaccharide backbone appear to play a major role in the biological function of these polyanionic polyelectrolytes by affecting their interactions with proteins and inorganic or organic ions, by affecting their osmotic contributions to the extracellular matrix, and by regulating their ability to form complex higher order aggregates with other matrix components (2, 4, 5). The enzymes which catalyze the sulfation of these polysaccharide chains therefore are important to study in understanding tissue morphogenesis.

In a recent study of glycosaminoglycan biosynthesis in the developing chick cornea (6), I observed that the apparent relative degree of sulfation of corneal keratan sulfates increased on and after Day 14 of development, coincident with the onset of transparency, increase in dehydration, and appearance of metachromatic staining in the cornea. In addition, previous data suggested that a similar increase in sulfation also may occur in chondroitin sulfates synthesized by corneas after this pivotal period in corneal morphogenesis (7). Coulombre and Coulombre (8) demonstrated that the specific hydration, thickness, metachromasia, and transparency of the cornea are regulated by thyroxine. Matthews and Hinds (9) suggested that thyroxine may regulate sulfation of glycosaminoglycans in tadpole metamorphosis. I therefore have suggested that thyroxine may affect corneal transparency by activation of specific sulfotransferase activity or synthesis (6).

The aim of this study was to establish conditions for the assay of embryonic corneal glycosaminoglycan sulfotransferases, with defined exogenous substrates as acceptors, and then to determine the relative specific activities of these enzymes throughout corneal development. In addition, the in...
Corneal Glycosaminoglycan Sulfotransferases

The present study represents the first time that glycosaminoglycan sulfotransferases have been examined directly throughout the development of a tissue, especially a tissue in which glycosaminoglycans have been implicated in the regulation and maintenance of normal morphogenesis (6, 31-33). The results strongly suggest that the increase in the apparent degree of sulfation of corneal glycosaminoglycans, which occurs coincident with the onset of transparency and increased dehydration of the cornea (6), does not arise because of an increase in the specific activities of glycosaminoglycan sulfotransferases obtained from corneas at these same stages of development. Taken together with our knowledge of the reactions which lead to sulfation of glycosaminoglycans (34-38), these observations suggest that the degree of sulfation of corneal glycosaminoglycans may be regulated by the availability of the sulfate donor, 3'-phosphoadenylyl sulfate, rather than by the specific activity of sulfotransferases.

Properties of Solubilized Corneal Sulfotransferases—In preliminary experiments, various detergents were tested for their ability to solubilize active corneal sulfotransferases: Triton X-100 (Sigma), Tween-20 (Atlas Chem. Co.), and Nonidet P-40 (Shell Chemical Co.), at concentrations from 0.5 to 4% (v/v) in buffer (0.01 M phosphate/citrate, pH 7.0, containing 20 mM KF, 2 mM MgCl₂, and 2 mM MnCl₂). These preliminary experiments indicated that up to one-quarter of the detectable sulfotransferase activity was soluble (25,000 × g supernatant) after homogenization in buffer without detergents. The presence of a broad temperature optimum with two peaks evidently, one at 22°C and another at 37°C, may have been due to the presence of proteases in these crude enzyme preparations. Alternatively, these peaks may have reflected the presence of different sulfotransferases acting on exogenous substrate.

The transfer of 35S from 3'-phosphoadenylyl[35S]sulfate to glycosaminoglycans took place at significant rates even at 4°C (2 to 4 times lower than at optimal temperatures), but occurred at only very low rates at temperatures above 45°C. Under standard assay conditions, with keratan sulfates as exogenous acceptors, incorporation into both trichloroacetic acid-precipitable (mostly endogenous) and trichloroacetic acid-soluble (mostly exogenous) glycosaminoglycans increased in a linear fashion when enzyme concentration was raised, up to at least 4-fold above that used in the standard assay.

Using increasing concentrations of keratan sulfates, chondroitin sulfates A, or chondroitin sulfates (mixed isomers) as exogenous acceptors in the standard assay, the amount of 35S radioactivity incorporated into glycosaminoglycans increased gradually even up to concentrations of 4.6 mg/ml (300 μg/assay). Heparan sulfates, however, caused a sharp increase in the amount of 35S incorporated into glycosaminoglycans up to a concentration of 0.3 mg/ml (20 μg/assay), but the amount of 35S incorporated into glycosaminoglycans leveled off at higher concentrations.

Table I summarizes the relative acceptor activities of 100 μg of each exogenous substrate (50 μg of heparan sulfates), in the standard assay, with enzymes prepared from corneas at different developmental ages. Addition of exogenous glycosaminoglycans resulted in a 5- to 128-fold stimulation of incorporation of radioactivity into the sulfate donor, 3'-phosphoadenylyl[35S]sulfate, to trichloroacetic acid-soluble glycosaminoglycans (mostly exogenous) without, in general, greatly affecting the incorporation of 35S into trichloroacetic acid-precipitable (mostly endogenous proteoglycans) material. Heparan sulfates stimulated incorporation of 35S into glycosaminoglycans by 4- to 18-fold more than other exogenously added glycosaminoglycans under these conditions. Chondroitin sulfates A were generally about 1.5- to 2-fold better substrates than either mixed isomer chondroitin sulfates or keratan sulfates. Keratan sulfates and mixed isomer chondroitin sulfates had similar relative acceptor activities and stimulated the incorporation of 35S into trichloroacetic acid-soluble glycosaminoglycans to levels 5- to 9-fold higher than endogenous substrates. Chemically desulfated, mixed isomer chondroitin sulfates were substantially poorer acceptors, and chemically desulfated keratan sulfates were actually slightly inhibitory, in that they reduced 35S incorporation to levels slightly below that obtained for endogenous substrates. Dermatan sulfates were not acceptors of 35S from corneal sulfotransferases in this system. The large stimulation of 35S incorporation from 3'-phosphoadenylyl[35S]sulfate into glycosaminoglycans, caused by the addition of exogenous substrates to assays saturated with 3'-phosphoadenylyl[35S]sulfate, suggested that the relatively low levels of incorporation of 35S into endogenous substrates was not due to limiting amounts of sulfotransferases. Suzuki and Strominger (13) observed similar stimulation by exogenous glycosaminoglycans in assays of hen oviduct
sulfotransferases. However, in contrast to results described here for corneal sulfotransferases, they noted that heparan sulfates were much poorer acceptors than were chondroitin sulfates; keratan sulfates were not acceptors in the hen oviduct system, results also in contrast with data from cornea. Currently, it is believed that a different sulfotransferase exists for each type of glycosaminoglycan substrate (34, 43; however see Ref. 40). Therefore, it follows that tissues which produce different arrays of glycosaminoglycans also would synthesize different arrays of sulfotransferases. Consistent with this suggestion, recent studies from several different tissues have demonstrated very different relative acceptor activities for the various types of exogenous acceptors added (chick cartilage (40), hen uterus (41), ox lung (44), mouse mastocytoma (45)).

Fig. 1 shows the amount of \(^{35}S\) from 3'-phosphadenyl-\(^{35}S\)sulfate incorporated into glycosaminoglycans by Day 13 corneal sulfotransferases, as a function of incubation time and under standard assay conditions. The results for both trichloroacetic acid-soluble and -precipitable glycosaminoglycans are shown. These results indicated that the assays remained fairly linear for at least 30 min, the time chosen for standard assays in studies designed to determine the relative specific activities of corneal glycosaminoglycan sulfotransferases during corneal development.

In order to determine the relative affinity of corneal glycosaminoglycan sulfotransferases for 3'-phosphoadenylylsulfate during development, the apparent \(K_m\) and \(V_{max}\) were determined with enzymes obtained from corneas at three developmental ages. Keratan sulfates were used as exogenous substrates in these kinetic studies. Fig. 2 shows the effect of increasing concentrations of 3'-phosphoadenylyl[\(^{35}S\)]sulfate on the rate of transfer of \(^{35}S\) to either exogenous or endogenous glycoseaminoglycans, as catalyzed by Day 13 enzyme (Fig. 2B). A double-reciprocal plot of the data from \(^{35}S\) incorporation into exogenous glycosaminoglycans, for enzyme preparations from Days 8, 13, and 18 of corneal development also is shown (Fig. 2A). The \(K_m\) for adenosine 3'-phosphate 5'-phosphosulfate, observed in the present study of corneal sulfotransferases, with keratan sulfates as exogenous substrates, was similar to values described in earlier studies of sulfotransferases from other tissues (34, 35). The high affinity of corneal sulfotransferases for 3'-phosphoadenylylsulfate supports the suggestion that this molecule is the normal sulfate donor in the sulfotransferase reaction mixtures also was excluded from Sephadex G-50. Fig. 3 also shows the results of treating the Sephadex G-50-excluded material, from assays with each respective exogenous substrate, with enzymes or chemicals known to specifically degrade the particular exogenous substrate used. After chondroitinase ABC treatment of the G-50-excluded material from incubations with chondroitin sulfates A or mixed isomer chondroitin sulfates as exogenous substrates, almost all of the \(^{35}S\) radioactivity was eluted in retarded fractions of G-50 (Fig. 3). Similarly, such material from incubations with heparan sulfates or keratan sulfates as exogenous acceptors, was degraded by HNO\(_3\) or keratan sulfate-\(\beta\)-endogalactosidase treatment, respectively, yielding characteristic patterns of retarded peaks on Sephadex G-50. The results suggest that the \(^{35}S\) radioactivity was being transferred from 3'-phosphoadenylyl[\(^{35}S\)]sulfate to the expected substrates, rather than to minor contaminant material.

In sulfotransferase assays with reference standard hyaluronic acids as exogenous substrates, a 2- to 3-fold stimulation of incorporation of \(^{35}S\) from 3'-phosphoadenylyl[\(^{35}S\)]sulfate to exogenous glycosaminoglycans was observed. Since hyaluronic acids are not normally sulfated, it was important to determine the nature of this \(^{35}S\)-labeled material. Table III summarizes the results of treating various standard exogenous glycosaminoglycan acceptors with HNO\(_3\), prior to their use in the standard assay. After HNO\(_3\) treatment, each glycosaminoglycan was subjected to Sephadex G-50 chromatography to separate HNO\(_3\)-resistant glycosaminoglycans from degradation products. Material in the void volume fractions that was pooled and tested for acceptor activity in the standard sulfotransferase assay. Treatment of a relatively crude preparation of umbilical cord hyaluronic acids (Sigma) with HNO\(_3\) reduced its acceptor activity nearly 4-fold. This preparation of hyaluronic acids also has been shown previously to contain small amounts of undersulfated chondroitin sulfates. Treatment of reference standard hyaluronic acids with HNO\(_3\) reduced \(^{35}S\) incorporation into trichloroacetic acid-soluble glycosaminoglycans to near levels obtained with only endogenous substrates. Mixed isomer chondroitin sulfates also were significantly reduced in acceptor activity after HNO\(_3\) treatment. In all other experiments in this study, the mixed isomer chondroitin sulfates were treated with HNO\(_3\) and purified by Sephadex G-50 chromatography, before use as exogenous substrates. The acceptor activity of chondroitin sulfates A (whale cartilage, super special grade, Miles) was not reduced by HNO\(_3\) treatment. Analysis of the products formed in the standard assay with reference standard hyaluronic acids as exogenous substrates (as described above) demonstrated that nearly all of the \(^{35}S\)-labeled material which could be recovered from the origins of the paper chromatograms was excluded from Sephadex G-50 and was degraded by HNO\(_3\) treatment to characteristic products (18). These results suggested that the acceptor activity of untreated preparations of hyaluronic acid was due to heparan sulfates.

Identification of \(^{35}S\)-labeled Products with Each Exogenous Substrate—Using the standard sulfotransferase assay with endogenous acceptors or with keratan sulfates, heparan sulfates, HNO\(_3\)-treated chondroitin sulfates (mixed isomers), or chondroitin sulfates A as exogenous acceptors, the specific activities of corneal glycosaminoglycan sulfotransferases were determined throughout corneal development, as described under "Experimental Procedures."
Fig. 4 summarizes the results of using exogenous keratan sulfates or endogenous acceptors, as well as of using boiled enzyme. The percentage of the total detectable (solubilized + particulate) sulfotransferase activity which was solubilized at each age also is shown. The data show that the specific activities of these enzymes changed very little during development. However, the specific activities of enzyme(s) which solubilized exogenous glycosaminoglycans (keratan sulfates as exogenous acceptors) did increase slightly between Day 8 and Day 12 and decline slowly thereafter (Fig. 4). The curve for enzyme(s) which added sulfate to endogenous material had the same general shape, except that the specific activities were similar to those from assays in which only endogenous substrates were present. Fig. 4 also indicates that from Day 8 to Day 12, nearly 90% of the detectable sulfotransferase activity which solubilized exogenous material under these conditions was solubilized. During early development, enzymes which added sulfate to endogenous material were solubilized to the same extent as those sulfating keratan sulfates. However, later in development, I observed lower specific activities for endogenous substrates, perhaps a reflection of decreased solubilization of endogenous substrates from older corneas.

Fig. 5 shows similar data for specific activity determinations using heparan sulfates as exogenous acceptors. Again, only minor changes in specific activities were observed during corneal development. The specific activities of enzyme(s) which added sulfate to both exogenous heparan sulfates and endogenous glycosaminoglycans decreased from Day 8 to Day 10, increased from Day 12 to Day 14, and declined again after Day 14. The proportions of activities solubilized were similar to those described for assays with keratan sulfate as exogenous acceptors (Fig. 4). The specific activities of corneal glycosaminoglycan sulfotransferases during development in the presence of mixed isomer HNO₂-treated chondroitin sulfates (Fig. 6) and chondroitin sulfates A (Fig. 7) as exogenous substrates also remained fairly constant. The shapes of the curves obtained with either of these substrates were similar to those described for assays with keratan sulfates as exogenous acceptors (Fig. 4). The absolute values of specific activities obtained with each of these exogenous substrates were different, however.

Fig. 8 summarizes the specific activities of corneal glycosaminoglycan sulfotransferases during corneal development in the presence of only endogenous substrates. The specific activities of enzymes which added sulfate to endogenous trichloroacetic acid-soluble material were similar to those which added sulfate to endogenous trichloroacetic acid-precipitable material, and in neither case did the activity change substantially during development.

The above observations strongly suggest that the specific activities of the corneal glycosaminoglycan sulfotransferases changed too little during development to account for the increase in the apparent degree of sulfation of corneal glycosaminoglycans that occurs as corneal transparency appears (6, 7). This relative constancy of sulfotransferase specific activity is in sharp contrast with the biochemical and morphological events taking place in the developing cornea (6, 7, 31, 32, 46, 47). The gradual decline in sulfotransferase specific activity seen late in development occurred coincident with an apparent decrease in glycosaminoglycan biosynthesis in the corneal stroma.³

Thus, the degree of sulfation of corneal glycosaminoglycans may not be regulated by changes in the specific activities of the sulfotransferases. However, such regulation might occur at the level of the availability of sulfate donor. Phosphorylation of adenylylsulfate by ATP:adenylylsulfate 5'-phosphotransferase (EC 2.7.1.25) and removal of pyrophosphates by pyrophosphatase phosphohydrolase (EC 3.6.1.1), are both reactions thought to drive the sulfate activation process (35). They therefore are logical places to begin to test this suggestion.

Thyroid Hormones and Serum Factors—It had been suggested that sulfotransferases might be regulated by thyroxine (6, 9). Thyroid hormones, serum factors, or both components acting synergistically have been shown to increase the incorporation of "³⁵SS into glycosaminoglycans in other systems (9, 48-50). For these reasons, and since thyroxine has also been shown to regulate the onset of transparency and increased dehydration of the cornea (8), the effects of thyroid hormones or serum factors, or both, on the activities of corneal glycosaminoglycan sulfotransferases in vivo were determined as described in "Experimental Procedures." Injection of L-thyroxine (3 μg/egg) into Day 6 eggs did not significantly affect the sulfotransferase activities determined on Day 8 in the presence of each of the exogenous glycosaminoglycans as substrates when compared with 0.9% NaCl (saline)-injected controls. Embryos injected with this dose of L-thyroxine were slightly larger than controls (whole body weight: 0.831 g ± 0.082, thyroxine; 0.803 g ± 0.079, saline-injected control).

Injections of triiodo-L-thyronine (3 μg/egg) arrested embryonic development shortly after injection.

Fig. 9 summarizes the results of adding thyroid hormones, sera from embryonic chicks of various ages, or both to standard assays of Day 8 corneal glycosaminoglycan sulfotransferases in the presence of keratan sulfates as exogenous acceptors. The data clearly suggest that the sera from embryonic chicks of various ages contain substantial amounts of glycosaminoglycan sulfotransferase activity. Furthermore, serum factors alone or together with L-thyroxine or triiodo-L-thyronine, at levels used here, did not significantly affect the activity of corneal glycosaminoglycan sulfotransferase in vitro. In addition, thyroid hormones did not affect significantly the activities of glycosaminoglycan sulfotransferase present in embryonic chick sera collected from embryos at various stages of development. Similarly, Day 8 enzymes alone in the standard assay, using keratan sulfates as exogenous acceptors, were not affected by thyroid hormones at this level (776 ± 31 cpm, control; 751 ± 42 cpm, L-thyroxine; and 986 ± 427 cpm, triiodo-L-thyronine).

The above experiments suggested that thyroid hormones, serum factors, or both components together did not affect the activities of corneal glycosaminoglycan sulfotransferases, with keratan sulfates as exogenous acceptors. However it was unexpectedly found that sera from embryonic chicks of ages Day 8 to Day 20 contained appreciable amounts of glycosaminoglycan sulfotransferase activity. Such activity in serum, with keratan sulfates as exogenous substrates, displayed similar developmental profiles to that form cornea Heat-treated serum lacked sulfotransferase activity. Further work will be required to determine if glycosaminoglycan sulfotransferases also exist in the extracellular matrices of tissues,³

³Preliminary experiments, using exogenous substrates as described here, detected sulfotransferases in the 12,100 × g supernatant (15 min) of nutrient medium (Ham's F-12 with 10% fetal calf serum) from saturated skin fibroblast cultures. I observed a 17-fold (heparan sulfates as exogenous acceptors), a 2-fold (keratan sulfates as exogenous acceptors), and a 4-fold (chondroitin sulfates as exogenous acceptors) increase, respectively, in sulfotransferase activity...
such as the cornea, and, if so, what role such extracellular sulfation systems might play in morphogenesis.

Acknowledgments—I thank Drs. K. Nakazawa and S. Suzuki for helpful advice in the isolation of keratan sulfate-β-endogalactosidase, and Drs. J. A. Cifonelli and M. B. Ma as compared to media which had not been exposed to cells. The latter media, however, did contain considerable sulfotransferase activity with keratan sulfates as exogenous acceptors. Activity from either type of nutrient media was inactivated by boiling.

throughly purified reference standards of glycosaminoglycans. I am especially grateful to Dr. T. Okuyama of the Seikagaku Kogyo Co. for the gift of whale nasal septum keratan sulfates. The excellent technical assistance of Ms. M. L. Hsu is gratefully acknowledged. Finally, I wish to thank Dr. G. W. Conrad for my predoctoral support, and helpful criticisms. His assistance in the preparation of this manuscript is especially appreciated.

REFERENCES

The references can be found on p. 353.
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Table 3

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References

Fig. 1. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.

Fig. 2. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.

Fig. 3. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.

Fig. 4. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.

Fig. 5. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.

Fig. 6. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.

Fig. 7. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.

Fig. 8. Schematic diagram of corneal sulfotransferases. The diagram shows the location of corneal sulfotransferases in the corneal stroma. Corneal sulfotransferases are localized in the corneal stroma, with the majority of enzyme activity detected in the corneal stroma. The distribution of sulfotransferases is shown in the diagram.
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