Mucopolysaccharides (Glycosaminoglycans)

Mucopolsaccharides (MPS) or glycosaminoglycans (GAG) **are heteropolysaccharides , containing uronic acid and amino sugars.** Acetylated amino groups , sulfate and carboxyl groups are also generally present . Because of the presence of these charged groups , they attract water molecules and so produce viscous solutions. Glycosaminoglycans have the special ability to bind large amounts of water, thereby producing the gel-like matrix that forms the basis of the body's ground substance, which, along with fibrous structural proteins such as collagen and elastin, and adhesive proteins such as fibronectin, make up the extracellular matrix (ECM).

Mucopolsaccarides in combination with proteins form mucoproteins. Examples of mucopolysaccharides are hyaluronic acid , heparin , chondroitin sulfate , dermatan sulfate and keratan sulfate .

Mucopolysaccharides are essential components of tissues , where they are generally present either in the free form or in combination with proteins. Carbohydrates content varies . When carbohydrates content is > 4% they are called (Mucoproteins) and when < 4% are called (Glycoproteins).

Mucopolysaccharides are excreted in urine in abnormal amounts in the group of lysosomal storage disorders known as mucopolysaccharidoses. They can be detected by 2D gel electrophoresis techniques; some mucopolysaccharides can also be detected by simple urine screening tests like CPC test, Cetavlon test and Alcian blue staining.

Classification of mucopolysacharides.

A- Sulphte free MPS:

1- Hyaluronic Acid

2- Chondroitin

B- Sulphate Containing Acid MPS:

1-Keratan Sulphate

2- Chondroitin Sulphates

3-Heparin

4- Heparin sulphate

A- Sulphates free MPS

1- Hyaluronic Acid

A sulphate free mucopolysacharides. It was first isolated from vitreous humor of eye. Later it was found to be present in synovial fluid, skin, umbilical cord. hemolytic streptococci and in Rheumatic nodule .It occurs both free and salt like combination with proteins and forms so-called "ground substance "of mesenchyme , an integral part of gel like ground substance of connective and other tissues.

Composition: It is composed of repeating units of N-acetyl glucosamine and D-Glucuronic acid.

On hydrolysis, it yields equimolecular quantities of D-Glucosamine, D-Glucuronic acid and acetic acid (Fig. 1).

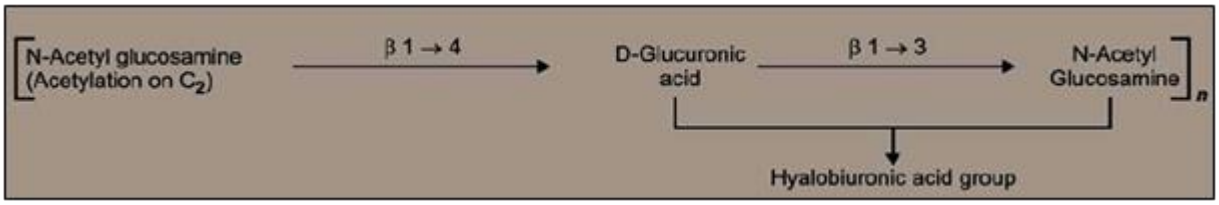

Figure 1: Structure of Hyaluronic acid

Function

Hyaluronic acid acts as a barrier in tissues as a cementing substance and contributes to tissue barrier which metabolites to pass through but resist penetration by bacteria and infective agents. Also Hyaluronic acid present in high concentration in embryonic tissues and is considered to play an important role in cell migration during morphogenesis and wound repair.

Hyaluronic acid is present in basement membrane (BM) of glomerulus of kidney where it plays important role in charge –selectiveness of glomerular filtration (role in glomerular filtration) .

Biomedical Importance

The invasive power of some pathogenic organisms may be increased because they secrete **Hyaluronidase**. **In the testicular secretions, it may dissolve the viscid substances surrounding the ova to permit penetration of spermatozoa. Hyaluronidase is used to increase the efficiency of absorption of solutions administered by clysis**

(the introduction of large amounts of fluid into the body usually by parenteral injection to replace that lost (as from hemorrhage or in dysentery or burns), to provide nutrients, or to maintain blood pressure).

2- **Chondroitin**

Another sulphate free acid mucopolysaccharide. Found in cornea and has been isolated from cranial cartilages. (It differs from hyaluronic acid only in that it contains N- acetyl galactosamine instead of N-acetyl glucosamine).

B- Sulphates containing acid MPS

1-keratan Sulphate (Kerato Sulphate)

A sulphate containing acid MPS. Found in costal cartilage, and cornea has been isolated from bovine cornea. It has been reported to be present in Nucleus pulposus and the wall of aorta. (It is the only GAG, which does not contain any uronic acid).

Composition: It is composed of repeating disaccharide unit consisting of N-acetyl glucosamine and galactose.

Types : They are found in tissues combined with proteins .

a- Keratan SO_4 I : **Occurs in cornea of the eye and lie between the collagen fibrils It plays an important role in maintaining corneal trancparency . In this type linkage is between N-acetyl glucosamine and Asparagine residue to form N- glycosidic bonding.**

b- Keratan SO_4 II : **Occurs in skeletal tissues . In this type , the linkage to protein is by way of OH- groups on serine and threonine residues of protein .**

2- Chondroitin Sulphates

They are principal MPS in the ground substance of mammalian tissues and cartilage.

They occur in combination with proteins and are called as (Chondroproteins). Four chondroitin sulphates have been isolated so far. They are named as chondroitin SO4 A,B,C,D. It is composed of repeating units of glucuronic acid.

Function : Chondroitin sulphates and hyaluronic acids are present in high concentration in cartilages and have a role in compressibility of cartilage weight bearing.

a-Chondrotin SO_4 A

It is present chiefly in cartilages adult bone and cornea.

b- Chondrotin SO_4 B

It is present in skin , cardiac valves and tendons . Also isolated from aortic wall and lung parenchyma .It has L-iduronic acid in place of glucuronic acid which is found in other chondroitin sulphates. It has a weak anticoagulant property , hence sometimes it is called as β-Heparin .(As it is found in skin . it is also called as Dermatan sulphat)e.

c- Chondroitin SO_4 C

It is found in cartilage and tendons . structure of chondroitin SO_4 C is the same as that of chondrotin SO_4 A except that SO_4 group is at position of 6 galactosamine molecule instead of position 4.

d- **Chondroitin SO_4 D**

It has been isolated from the cartilage of shark . It resembles in structure to chondroitin SO_4 C except that it has a second SO_4 attached probably at carbon 2 or 3 of uronic acid moiety.

3- Heparin

It is also called α-Heparin. It is an anticoagulant present in liver and it is produced mainly by most cells of liver (Originally isolated from liver). In addition, it is also found in lungs, thymus, and spleen, walls of large arteries, skin and in small quantities in blood.

It is strongly acidic due to sulphuric acid groups and readily forms salts . Molecular weight of heparin varies from 17000 to 20000. **It occurs in combination with proteins as proteoglycans is unique , consisting chiefly serine and glycine residue Approximately 2/3 of the serine residue contain GAG chains . Linkage with protein molecule is usually with GaIN and serine / sometimes with threonine.**

Function

Role of heparin as anticoagulant in vitro and in vivo

In vitro , heparin is used as an anticoagulant 2 mg/10 ml of blood is used .

In vivo, **heprin is an important anticoagulant . it binds with Factor IX and XI, but its important action is with plasma antithrombin III. Binding of heparin to lysine residues in antithrombin III produces conformational change which promotes the binding of the latter to serine protease "thrombin" which is inhibited thus fibrinogen is not converted to fibrin**

Role as a coenzyme : Heparin acts in the body to increase the activity of the enzyme "Lipoprotein Lipase ".Heparin binds specifically to the enzyme present in capillary walls causing a release of the enzyme into the circulation .hence heparin is called as " Clearing factor"

Structure: **It is a polymer of repeating disaccharide units of D-Glucosamine and either of the two uronic acids-D-Glucuronic acid and L-Iduronic acid (Figure 2). The -NH2 group at C2 and OH group at C6 of D-Glucosamine (Glc N) are sulphated.**

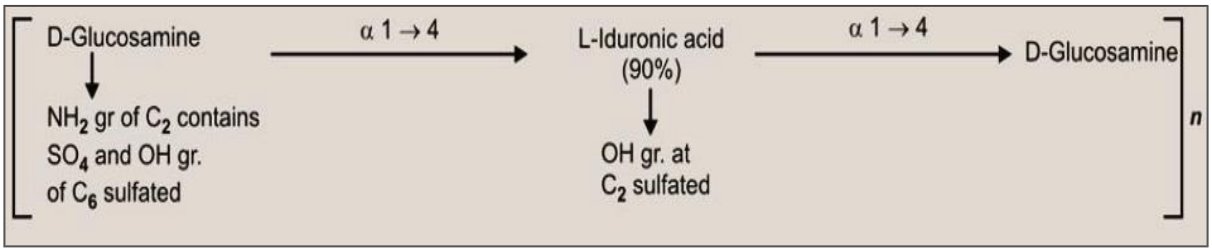

Figure 2 : Structure Heparin

4- Heparin Sulphates

Isolated from amyloid liver, certain normal tissues such as human and cattle aorta, and from the urine , liver and spleen of patients with gargoylism (Hurlers syndrome which is an

inherited lysosomal disorder caused by the absence of alpha-L-iduronidase enzyme which responsible for degradation of glycosaminoglycans (GAG or mucopolysaccharides). This leads to a buildup of dermatan sulfate and heparin sulfate in multiple tissues, resulting in progressive deterioration and, eventually, death). This compound has negligible anticoagulant activity . It seems to be structurally to heparin , but has a :

1-Low m.wt

2-Some of the amino groups , carry acetyl groups and percentages of SO_4 groups are smaller.

3- Unlike heparin , **its predominant uronic acid is D-Glucuronic acid.**

Heparin sulphates are components of plasma membrane of cells , where they may act as "receptors " and can participate in cell adhesion and cell –cell interactions.

Mucpolysaccharidoses

The mucopolysaccharidoses are a group of related disorders , due to inherited defect , in which skeletal changes , mental retardation , visceral involvement and corneal clouding are manifested to varying degrees. Defect/ defects in these disorders result in :

Widespread deposits in tissues of a particular MPS.

In excessive excretion of MPS in urine.

Types of Mucopolysaccharidoses

1- MPS-I (Hurler's syndrome).

2-MPS-II(Hunter's syndrome).

3-MPS-III(SAN Filipos syndrome A,B and C).

4-MPS-IV(Morquio syndrome).

5-MPS-V(Scheie syndrome).

6- MPS –VI (Marteaux –Lamy syndrome).

Glycoproteins and Mucoproteins

When the carbohydrate chains are attached to a polypeptide chain it is called a proteoglycans . They are seen in almost all tissues and cell membrane. About 5% of the weight of the cell membrane is carbohydrates . If the carbohydrate groups cover the

entire surface of the cell membrane , they are called (glycocalyx) . Glycoprotein act as enzymes , hormones , transport proteins , structural proteins and receptors.

Carbohydrate group is attached to proteins either as O-glycosidic linkage or as N-glycosidic linkages . The O-glycosidic linkage is N-acetylated galactoseamine (GalNAc) to serine or threonine residues of usual protein . However , galactose is added to hydroxylysine residues of collagen. The N-glycosidic linkages are made of carbohydrate group to nitrogen atom of asparagine or glutamine residue of proteins.