MEDICAL ASPECTS OF CARBOHYDRATES: HETEROPOLYSACCHARIDES

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Abstract

GAGs are long, negatively charged, unbranched heteropolysacchar chains generally composed of a repeating disaccharide unit [acidic sugar-amino sugar]n. The amino sugar is either D-glucosamine or D-galactosamine in which the amino group is usually acetylated, thus eliminating its +ve charge. The amino sugar may also be sulfated on C-4 or 6 or on a non-acetylated nitrogen. The acidic sugar is either D-glucuronic acid or its C-5 epimer, L-iduronic acid. They bind large amounts of water, thereby producing the gel-like matrix that forms the basis of the body’s ground substance. The viscous, lubricating properties of mucous secretions are also caused by the presence of GAGs which led to the original naming of these as mucopolysaccharides. As essential components of cell surfaces, GAGs play an important role in mediating cell-cell signaling & adhesion. There are 6 major classes of GAGs, including chondroitin 4- & 6-sulfates, keratan sulfate, dermatan sulfate, heparin, heparan sulfate & hyaluronic acid. All of the GAGs, except hyaluronic acid, are found covalently attached to protein, forming proteoglycan monomers, which consist of a core protein to which the linear GAG chains are covalently attached. The proteoglycan monomers associate with a molecule of hyaluronic acid to form proteoglycan aggregates. GAGs are synthesized in the ER & Golgi. The polysacchar chains are elongated by sequential addition of alternating acidic & amino sugars, donated by their UDP-derivatives. The last step in synthesis is the sulfation of some of the amino sugars. The source of the sulfate is 3′-phosphoadenosyl-5′-phosphosulfate. GAGs are degraded by lysosomal hydrolases. They are 1st broken down to oligosacchar’s, which are degraded sequentially from the non-reducing end of each chain. A deficiency of one of the hydrolases results in a mucopolysaccharidoses. These are hereditary disorders in which GAGs accumulate in tissues, causing symptoms such as skeletal & extracellular matrix deformities, & mental retardation. Examples of these genetic diseases include Hunter & Hurler syndromes. Glycoproteins are proteins to which oligosacchar’s are covalently attached. They differ from proteoglycans in that length of glycoprotein’s CHO chain is relatively short usually 2-10 sugar residues long. The CHO’s of glycoproteins do not have serial repeats as do GAGs. Memb-bound glycoproteins participate in a broad range of cellular phenomena, including cell surface recognition (by other cells, hormones, viruses), cell surface antigenicity (e.g., blood group antigens), & components of the extracellular matrix & of the mucins of the GI & urogenital tracts, where they act as protective biologic lubricants.

Keywords: GAGs, Glycoproteins, cell surface recognition.

Overview

They are most abundant organic molecules in nature which provide: (i)important part of energy in diet. (ii)Act as the storage form of energy in the body. (iii)structural component of cell membrane

The empiric formula is (CH2O)n – “hydrates of carbon”

Polysaccharides: more than 10 sugar units They are Homopolysaccharides and heteropolysaccharides
Oligosaccharides: 3-10 monosaccharide units
Disaccharides: 2 monosaccharide units
Monosaccharides: Simple sugar

CLASSIFICATION

Monosaccharides Further classification is based on: 1. No. of carbon atoms 2. Functional group: Aldehyde group – aldoses Keto group – ketoses

<table>
<thead>
<tr>
<th>Generic names</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 carbons: trioses</td>
<td>Glyceraldehyde</td>
</tr>
<tr>
<td>4 carbons: tetroses</td>
<td>Erythrose</td>
</tr>
<tr>
<td>5 carbons: pentoses</td>
<td>Ribose</td>
</tr>
<tr>
<td>6 carbons: hexoses</td>
<td>Glucose</td>
</tr>
<tr>
<td>7 carbons: heptoses</td>
<td>Sedoheptulose</td>
</tr>
<tr>
<td>9 carbons: nonoses</td>
<td>Neuraminic acid</td>
</tr>
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Joining of 2 monosaccharides by O-glycosidic bond: Maltose (α-1, 4) = glucose + glucose
Sucrose (α-1, 2) = glucose + fructose
Lactose (β-1, 4) = galactose + glucose

Disaccharides

Carbohydrates attached to non-carbohydrate structures by glycosidic bonds (O- or N-type) e.g. 1. Purine and pyrimidine bases in nucleic acids 2. Aromatic rings in steroids 3. Proteins in glycoproteins and glycosaminoglycans 4. Lipids found in glycolipids 5. Bilirubin

Complex Carbohydrates

O-Glycosidic
N-Glycosidic
Glycosidic Bonds

4. Amino Sugars (i) D-Glucosamine (ii) D-Galactosamine (iii) N-Acetylneuraminic acid (NANA) is an important component of Glycolipids and Glycoproteins.

Heteropolysaccharides: e.g. glycosaminoglycans (GAGs)
• Homopolysaccharides: Branched: glycogen and starch (α-glycosidic polymer) Unbranched: cellulose (β-glycosidic polymer)
• Polysaccharides

HOMOPOLYSACCHARIDES:

Glycogen • also known as animal starch • stored in muscle and liver (mostly) • present in cells as granules (high MW) • contains both a(1,4) links and a(1,6) branches at every 8 to 12 glucose unit (more frequent than in starch) • complete hydrolysis yields glucose • glycogen and iodine gives a red-violet color • hydrolyzed by both a and b-amylases and by glycogen phosphorylase.

HOMOPOLYSACCHARIDES:

Inulin • b-(1,2) linked fructofuranoses • linear only; no branching • lower molecular weight than starch • colors yellow with iodine • hydrolysis yields fructose • sources include onions, garlic, dandelions and jerusalem artichokes • used as diagnostic agent for the evaluation of GFR (Renal function test).

Jerusalem artichokes
HOMOPOLYSACCHARIDES:

Chitin • chitin is the second most abundant carbohydrate polymer • Like cellulose, chitin is a structural polymer • present in the cell wall of fungi and in the exoskeletons of crustaceans, insects and spiders • chitin is used commercially in coatings (extends the shelf life of fruits and meats) • A chitin derivative binds to iron atoms in meat and slows the rancidity process

Sulfate groups • GAGs are strongly negatively-charged: carboxyl groups of acidic sugars • The acidic sugar is either D-glucuronic acid or L-iduronic acid • The amino sugar (usually sulfated) is either D-glucosamine or D-galactosamine • GAGs are linear polymers of repeating disaccharide units [acidic sugar-amino sugar]n • Glycosaminoglycans (GAGs)

Resilience of GAGs • Being negatively charged GAG chains are extended in solution and repel each other and when brought together, they "slip" past each other • This produces the "slippery" consistency of mucous secretions and synovial fluid • When a solution of GAGs is compressed, the water is "squeezed out" and the GAGs are forced to occupy a smaller volume. When the compression is released, the GAGs spring back to their original, hydrated volume because of the repulsion of their negative charges This property contributes to the resilience of synovial fluid and the vitreous humor of the eye

**CHONDROITIN SULFATES**

1. They are Disaccharide units of Sulfated N-acetylgalactosamine + Glucuronic acid 2. It contains N-AC Galactosamine in stead of N-acetyl glucosamine. 3. Most abundant GAG in the body. 4. Form proteoglycan aggregates. 5. It is present in the ground substance of connective tissues distributed in cartilage, bone, tendons, cornea and skin. 6. In cartilage, they bind collagen and hold fibers in a tight, strong network.
KERATAN SULFATES 1. It is the only GAG which does not contain any uronic acid. 2. Sulfate content is variable and may be present on C-6 of either sugar.

KERATAN SULPHATE 3. Most heterogeneous GAGs. 4. Only N-Acetylglucosamine & Galactose form repeating units of disaccharide. 5. It is found in cornea, Loose CT and tendons.

HYALURONIC ACID

• Disaccharide unit: N-acetylglucosamine Glucuronic acid • Different from other GAGs: they are unsulfated. Not covalently attached to protein The only GAG found in bacteria. • Serves as a lubricant and shock absorber. • Found in synovial fluid of joints, vitreous humor of the eye, the umbilical cord, and cartilage.

HYALURONIC ACID

1. Present in connective tissue, tendons, synovial fluid, vitreous humor, umbilical cord & cartilage. 2. Forms ground substance in combination with proteins. 3. Hyaluronidase is an enzyme present in testicular tissue and spleen. It catalyzes depolymerization of hyaluronic acid and reduces its viscosity which defuses into the tissue spaces. So it is known as spreading factors. 4. It dissolve the viscid substance around the ova to permit penetration of spermatozoa. 5. Clinically it is used to increase the efficiency of absorption of solutions administered by clysis.

HEPARIN 1. Disaccharide unit of Glucosamine and Glucuronic or iduronic acids 2. Sulfate is found on glucosamine and uronic acid. 3. Unlike other GAGs that are extracellular, heparin is an intracellular component of mast cells that line arteries, especially liver, lungs and skin.
HEPARIN 4. It activates antithrombin III, which in turn inactivates thrombin, factor X and factor IX. 5. It is an anticoagulant used for taking blood for biochemistry studies. 6. Used in suspected thrombo embolic conditions to prevent intravascular coagulation.

HEPARAN SULPHATE 1. They are components of plasma membrane of the cells they act as receptors and can help in the cell-cell interactions. 2. Chondroitin Sulphate and Hyaluronic acid are present in high concentration in cartilages and help as cushion in the weight bearing joints.

DERMATAN SULFATE

1, 3 linkages. 2. Present in skin, blood vessels and heart valves. 3. This is present in the Sclera of the eye helps in maintaining the shape of the eye. βDERMATAN SULFATE 1. It contains L-iduronic acid and N-acetyl galactosamine in
Proteoglycans and glycoproteins are two kinds of glycoconjugates that contain protein. Glycoconjugates are compounds that covalently link carbohydrates to proteins and lipids.

Glycoconjugates

- Proteoglycans
  - Proteoglycans have a very high carbohydrate to protein ratio, often 95:5, and are found in the extracellular matrix.
  - GAG chains are linked to core proteins by N- and O-glycosidic links.

- Glycoproteins
  - These contain carbohydrate residues on protein chains.
  - Very important examples of these materials are antibodies—chemicals which bind to antigens and immobilize them.
  - The carbohydrate part of the glycoprotein plays a role in determining the part of the antigen molecule to which the antibody binds.

Glycoproteins: The human blood groups A, B, AB, and O depend on the oligosaccharide which form part of the glycoprotein on the surface of erythrocyte cells. The terminal monosaccharide of the glycoprotein at the nonreducing end determines blood group.

Glycoproteins:

- 3 Type Terminal sugar
  - A N-acetylgalactosamine
  - B α-D-galactose
  - AB both the above
  - O neither of the above
  - O is the “universal donor” AB is the “universal acceptor”
Premature death in severe forms. → variable degrees of progressive mental and physical deterioration. → excessive urinary excretion of GAGs, → intralysosomal accumulation of GAGs. → Mucopolysaccharidosis

1. MPS are inheritable storage diseases caused by a deficiency of lysosomal enzymes that degrade glycosaminoglycans (GAGs, previously called mucopolysaccharides). 2. There is excessive accumulation of Granules of MPS in body tissue. 3. The MPSs are a heterogeneous group characterized by the:

Mucopolysaccharidoses

1. Pathogenesis/Pathology comprises:- • a specific lysosomal enzyme deficiency. • and many have variable phenotypic expression. 2. Characteristic degrees of organ involvement and rates of deterioration.

Mucopolysaccharidoses

3. Depending on the enzyme deficiency, the metabolism of:- • dermatan sulfate, heparan sulfate, keratan sulfate may be blocked. • Lysosomal accumulation of the GAGs eventually results in cell, vascular, tissue, and organ dysfunction.

Mucopolysaccharidoses

3. Main disturbances are:- • Inability to breakdown mucopolysaccharides • Lack or deficiency of enzyme • Inherited • Lack of gene

Mucopolysaccharidosis Results: • many serious physical disorders • Various genetic deformities such as: • Skeletal deformities (especially of the face) • Mental retardation • Decreased life expectancy

Mucopolysaccharidoses Hurler syndrome Hunter syndrome Sanfilippo syndrome Morquio disease Maroteaux-Lamy syndrome SLY Syndrome VII Scheie syndrome

Mucopolysaccharidoses • Mucopolysaccharidoses are hereditary disorders that are clinically progressive. They are characterized by accumulation of GAGs in various tissues, causing varied symptoms, such as skeletal & extracellular matrix deformities, & mental retardation. • Mucopolysaccharidoses are caused by a deficiency of one of the lysosomal hydrolases normally involved in degradation of heparan sulfate and/or dermatan sulfate.

• This results in the presence of oligosaccharide’s in urine, because of incomplete lysosomal degradation of GAGs. These fragments can be used to diagnose the specific mucopolysaccharidosis, namely by identifying the structure present on the non-reducing end of oligosaccharide. That residue would have been the substrate for the missing enz. • Diagnosis can be confirmed by:- 1. Measuring the patients cellular level of lysosomal hydrolases. 2. Children who are homozygous for one of these diseases are apparently normal at birth, then gradually deteriorate. 3. In severe cases, death occurs in childhood. • All of the deficiencies are autosomal & recessively inherited except Hunter syndrome, which is X-linked.
Bone marrow transplants are currently being used successively to treat Hunter syndrome; the transplanted macrophages produce the sulfatase needed to degrade GAGs in the extracellular space. Note: some of lysosomal enzymes required for degradation of GAGs also participate in degradation of glycolipids & glycoproteins. Therefore, an individual suffering from a specific mucopolysaccharidosis may also have a lipidosis or glycoprotein-oligosaccharidosis.

**Hurler syndrome (gargoyleism) type I (Alpha-L-iduronate deficiency)**

- L-Iduronidase accompanied by degradation of dermatan sulphate and heparan sulphate. • Due to deposition of the faulted degradation products in coronary artery leads to ischemia and early death. • Severity varies from mild to most severe. • Storage of abnormal quantities of this material (mucopolysaccharide) in different body tissues is responsible for the symptoms and appearance of the disease. αHurler syndrome (gargoyleism) type I Definition • It is an inherited disorder with deficiency of


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**Hurler syndrome (type I)**

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**Mucopolysaccharidosis I (MPS I) Disease (Hurler, Hurler-Scheie, Scheie Syndromes)**

- Hernia
- Corneal clouding
- Coarse facial
- Claw hand
SYMPTOMES IMAGES OF KEY FEATURES

Hernia corneal clouding Coarse facial Claw hand.

Causes of the Hurler syndrome • Inherited as an autosomal recessive trait. • Metabolic defect: inability of the body to make an enzyme. • The body's to make an enzyme: lysosomal alpha-L-iduronidase.

Incidence & and risk factors Cont. • Approximately 1 in 150,000 infants are affected. • Newborn infants with this defect appear normal at birth. • By the end of the first year, signs of impending problems begin to develop.

MPS (Type I) • The children slowly develop. • Coarse, thick, facial features • Prominent dark eyebrows • Progressive stiffness • Mental retardation.

Prevention • Genetic counseling: important for parents with a family history of Hurler syndrome • Prenatal diagnosis. • An amniocentesis in the amniotic fluid are then cultured and the a-L-iduronidase activity in the cells is determined.

Symptoms • Short stature • Severe mental retardation • Thick, coarse facial features with low nasal bridge • Full lips with a thick, large tongue • Increased body hair (hirsutism).

Symptoms • Umbilical hernia • Deafness • Stiffness (in joints) • Shortness of breath • Abnormal bones of spine and claw hand.

MPS: Signs • Hepatomegaly • Splenomegaly • Enlarged tongue • Retinal pigmentation • Hip dislocation • Kyphosis • Heart murmurs • Heart valve damage from thickening.

Tests that may indicate the syndrome Cont. • Increased excretion of dermatan sulfate and heparan sulfate in the urine. • Absence of lysosomal alpha-L-iduronidase (in cultured fibroblasts). • Culture of cells from amniotic fluid obtained by amniocentesis for enzyme testing (prenatal testing).

Tests that may indicate the syndrome Cont. • Abnormal histological staining of white blood cells called metachromasia • X-ray of the skeleton • X-ray of the spine • X-ray of the chest • ECG.

RADIOLOGY depicts: • Large skull, with thickened calvarium. • Shallow orbits. • Abnormal spacing of teeth with dentigerous cysts. • Kyphosis. • The pelvis is usually poorly formed. • The clavicles are short, thickened, and irregular. • The ribs have been described as oar-shaped. • The phalanges are short and trapezoid with widening of the diaphyses.

GENETICS • on chromosome 4p16.3 and spans 19?kb and includes 14 exons. • Mutation analysis has revealed two major alleles, W402X and Q70X, and a minor allele, P533R. • Homozygosity or compound heterozygosity give rise to Hurler syndrome.

Hunter syndrome type II (Sulpho-idoronide sulphatase deficiency )

Hunter syndrome type II

Hunter syndrome type II (Sulpho-idoronide sulphatase deficiency ) This is an X-linked congenital disorder characterised by deficiency of Iduronic Sulphatase comprises by: • wide range of severity • No corneal clouding • Physical deformity is mild to severe • Facial features. • Progressive stiffness • Decreased mental development.
Hepatomegaly (liver enlargement) • Splenomegaly (spleen enlargement) • Abnormal bone x-rays Clinical features are: • Coarse facial features, • short stature, • skeletal deformities, • joint stiffness, • and mental retardation • with onset of disease usually between 2–4 yr of age • chronic diarrhea. • Communicating hydrocephalus

Extensive, slowly progressive neurologic involvement usually precedes death • Death usually occurs between 10–15 yr of age. GENETIC:- • The gene encoding IDS contains nine exons that span 24?kb and is mapped to Xq28. • About 20% of patients with the severe form of MPS II have major deletions or rearrangements of the IDS gene.

Type D : N-Acetylglucosamine-6-sulfatase deficiency. • These enzymes help the body get rid of a substance normally found outside of our cells called a mucopolysaccharide • Level of heparan sulfate increased, and in Sanfilippo syndrome, large amounts of it are excreted in the urine • Type C : Glucosamine-N-acetyltransferase deficiency. • Type B : N-Acetylglucosamindase deficiency. • Type A : Heparan Sulfaminidase deficiency

Sanfilippo syndrome type III Definition • Sanfilippo syndrome is one of the hereditary mucopolysaccharide storage diseases • It is characterized by the absence of one of several enzymes. Due to multiple enzyme deficiency this disease is of four types:

This is an autosomal recessive trait • It is possibly the most common of the mucopolysaccharide storage diseases • It has a relatively late onset rather than during the first year of life Sanfilippo syndrome Causes

CLINICAL MANIFESTATION

• Coarse, thick, facial features • Prominent dark eyebrows • Progressive stiffness • Gait disturbances • Speech disturbances • Decreased mental development that progresses to severe mental retardation

An amniocentesis in the amniotic fluid are then cultured and the enzyme activity in the cells is determined. • Genetic counseling is advised to the prospective parents with a family history of Sanfilippo syndrome Prenatal diagnosis:

Prevention Cont.

Symptoms . • Family history of Sanfilippo syndrome. • May have normal growth during first few years, but final height is below average. • Delayed development followed by deteriorating mental status. • Deterioration of gait.

Abnormal bone x-rays such as thickened skull and oval vertebrae • Echocardiogram may show thickened heart • Corneas clear • Splenomegaly (spleen enlargement) • Hepatomegaly (liver enlargement) • Sanfilippo syndrome Signs and tests

Sanfilippo syndrome Signs and tests • Seizures • mental retardation • Activities of one of the enzymes may be low in fibroblast skin cells • Urine may have increased heparan sulfate • Abnormal pathological staining character of white blood cells called metachromasia

Features and Characteristics children with Sanfilippo syndrome • Occasional enlarged head • Coarse facial features • Coarse hair • Excessive hair growth • Joint stiffness

Sanfilippo syndrome • Severe diarrhea or constipation • Severe hearing loss • Hyperactivity • Aggressive and destructive behavior • Poor attention • Physical aggression • Speech and language delay • Sleep disturbance

Vision impairment • Mild growth retardation. • Severe intellectual impairment most often before 6 years of age. • Sanfilippo syndrome (Cont.)

Morquio syndrome Type IV • Deficiency of Galactose-6-sulfatase • Accumulation of Keratan sulfate • Autosomal Recessive. CLINICAL FEATURES • Both types of Morquio syndrome are characterized • by significant, short-trunk dwarfism, • fine corneal deposits,
CLINICAL FEATURES

- a skeletal dysplasia that is distinct from other mucopolysaccharidoses, • and preservation of intelligence. • The appearance of genu valgus, • kyphosis, • growth retardation with short trunk and neck, • and waddling gait with a tendency to fall are early symptoms of MPS IV. • Gene is on chromosome 16q24.3.

- Extraskeletal manifestations may include: • 1. mild corneal clouding, 2. hepatomegaly, 3. cardiac valvular lesions, 4. and small teeth with abnormally thin enamel and frequent caries formation. 

DIAGNOSIS • Analysis of urinary GAGs is an initial diagnostic test (semiquantitative spot test to more precise qualitative and quantitative) • definitive diagnosis established by enzyme assay (Serum, leukocytes, or cultured fibroblasts) • Prenatal diagnosis is available for all MPSs and is carried out on cultured cells from amniotic fluid or chorionic villus biopsy. • Molecular diagnosis is the preferred method of carrier testing provided that the mutation in the family under consideration is known.

TREATMENT

- Unrewarding • Symptomatic • Orthopedic procedures, including femoral osteotomies, acetabular reconstruction, and posterior spinal fusion, are necessary • Bone marrow transplant. • Bone marrow transplantation has resulted in significant clinical improvement of somatic disease in MPS I and increased long-term survival. Resolution or improvements have been noted in hepatosplenomegaly, joint stiffness, facial appearance, obstrucive sleep apnea, heart disease, communicating hydrocephalus, and hearing loss.

Morquio syndrome subtypes A & -Galactosidase deficiency. • Autosomal recessive.ββ Type IV • Type IVA: Galactose-6- sulfatase deficiency. • Type IVB:

Features and Characteristics children with Morquio syndrome • Joint stiffness • Mild growth retardation • Without mental retardation ! • Abnormal x-rays of: - Bone Skeleton Spine Chest

PREVENTION

Genetic counseling: important for prospective parents with a family history of Morquio syndrome Prenatal diagnosis: • An amniocentesis in the amniotic fluid are then cultured and the enzyme activity in the cells is determined.

Morquio's syndrome type IV Mucopolysaccharidosis • presence of keratan sulfate in the urine • short stature due to severe deformity of the spine and the thorax, long bones with irregular epiphyses, enlarged joints, flaccid ligaments, and a waddling gait • Type A: deficiency of the enzyme N-acetylgalactosamine-6-sulfate sulfatase. Type B: deficiency of the enzyme beta-galactosidase

Maroteaux-Lamy syndrome Type V (N-Acetylgalactose-amin-4-sulfatase) (Arylsulfatase B)

synovial fluids→ mucous secretions ← body cells ← A gel-like substance found in: •Definition Cont.
Coarse facial features (N-Acetyl-galactose-amin-4-sulfatase (Arylsulfatase B) These are leading features.

Features and Characteristics Maroteaux-Lamy syndrome

Treatment. • At the present time, there is no cure for MPS disorders. • Enzyme replacement therapy and gene therapy are coming up as two treatments. • Research for suitable treatment is going on in various countries.

mental deficiency → Corneal clouding → Short stature → Skeletal deformity → Splenomegaly → Hepatomegaly → glucuronidase. • There is defective degradation of Dermatan sulfate and heparan sulfate. • The disease is characterised by: βSLY SYNDROME (MPS VII) • In this disease there is congenital deficiency of Mild mental retardation

Skeleton → general dysplasia of the → coarsening of the facies → progressive corneal clouding. →Scheie’s syndrome Type I S Mucopolysaccharidosis • alpha-L iduronidase defect • high levels of chondroitin sulfate B in the urine.

Scheie’s Syndrome • Lysosomal alpha-L-iduronidase • Mildest • Autosomal recessive

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