

30 Synthesis of Glycosides, Lactose, Glycoproteins and Glycolipids

Many of the pathways for interconversion of sugars or the formation of sugar derivatives use activated sugars attached to nucleotides. Both **UDP-glucose** and **UDP-galactose** are used for **glycosyltransferase** reactions in many systems. Lactose, for example, is synthesized from UDP-galactose and glucose in the mammary gland. UDP-glucose also can be oxidized to form UDP-glucuronate, which is used to form **glucuronide derivatives** of bilirubin and xenobiotic compounds. Glucuronide derivatives are generally more readily excreted in urine or bile than the parent compound.

In addition to serving as fuel, carbohydrates are often found in **glycoproteins** (carbohydrate chains attached to proteins) and **glycolipids** (carbohydrate chains attached to lipids). **Nucleotide sugars** are used to donate sugar residues for the formation of the glycosidic bonds in both glycoproteins and glycolipids. These carbohydrate groups have many different types of functions.

Glycoproteins contain short chains of carbohydrates (oligosaccharides) that are usually branched. These oligosaccharides are generally composed of glucose, galactose, and their amino derivatives. In addition, mannose, L-fucose, and N-acetylneuraminic acid (NANA) are frequently present. The carbohydrate chains grow by the sequential addition of sugars to a **serine** or **threonine** residue of the protein. Nucleotide-sugars are the precursors. Branched carbohydrate chains also may be attached to the amide nitrogen of **asparagine** in the protein. In this case, the chains are synthesized on **dolichol phosphate** and subsequently transferred to the protein. Glycoproteins are found in mucus, in the blood, in compartments within the cell (such as lysosomes), in the extracellular matrix, and embedded in the cell membrane with the carbohydrate portion extending into the extracellular space.

Glycolipids belong to the class of **sphingolipids**. They are synthesized from nucleotide-sugars that add monosaccharides sequentially to the hydroxymethyl group of the lipid ceramide (related to sphingosine). They often contain branches of N-acetylneuraminic acid produced from CMP-NANA. They are found in the cell membrane with the carbohydrate portion extruding from the cell surface. These carbohydrates, as well as some of the carbohydrates of glycoproteins, serve as **cell recognition factors**.



THE WAITING ROOM



To help support herself through medical school, **Erna Nemdy** works evenings in a hospital blood bank. She is responsible for assuring that compatible donor blood is available to patients needing blood transfusions.

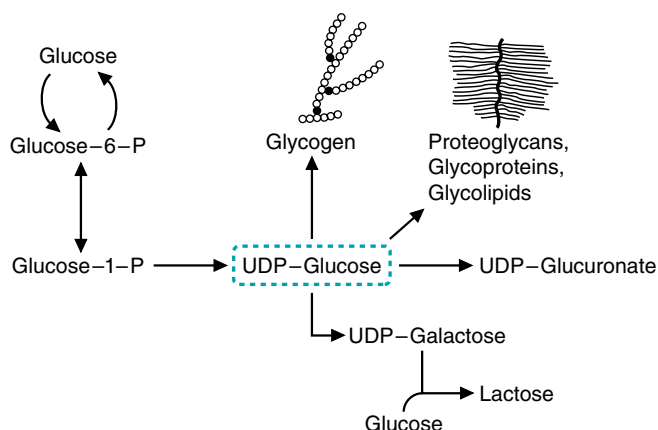


Fig. 30.1. Metabolism of UDP-glucose. The activated glucose moiety of UDP-glucose can be attached by a glycosidic bond to other sugars, as in glycogen or the sugar oligosaccharide and polysaccharide side chains of proteoglycans, glycoproteins, and glycolipids. UDP-glucose also can be oxidized to UDP-glucuronate, or epimerized to UDP-galactose, a precursor of lactose.

As part of her training, Erna has learned that the external surfaces of all blood cells contain large numbers of antigenic determinants. These determinants are often glycoproteins or glycolipids that differ from one individual to another. As a result, all blood transfusions expose the recipient to many foreign immunogens. Most of these, fortunately, do not induce antibodies, or they induce antibodies that elicit little or no immunologic response. For routine blood transfusions, therefore, tests are performed only for the presence of antigens that determine whether the patient's blood type is A, B, AB, or O.



Jay Sakz's psychomotor development has become progressively more abnormal. At 2 years of age, he is obviously mentally retarded and nearly blind. His muscle weakness has progressed to the point that he cannot sit up or even crawl. As the result of a weak cough reflex, he is unable to clear his normal respiratory secretions and has had recurrent respiratory infections.

I. INTERCONVERSIONS INVOLVING NUCLEOTIDE-SUGARS

Activated sugars attached to nucleotides are converted to other sugars, oxidized to sugar acids, and joined to proteins, lipids, or other sugars through glycosidic bonds.

A. Reactions of UDP-Glucose

UDP-glucose is an activated sugar nucleotide that is a precursor of glycogen and lactose, UDP-glucuronate and glucuronides, and the carbohydrate chains in proteoglycans, glycoproteins, and glycolipids (Fig. 30.1). Both proteoglycans and glycosaminoglycans are discussed further in Chapter 49. In the synthesis of many of the carbohydrate portions of these compounds, a sugar is transferred from the nucleotide sugar to an alcohol or other nucleophilic group to form a glycosidic bond (Fig. 30.2). The use of UDP as a leaving group in this reaction provides the energy for formation of the new bond. The enzymes that form glycosidic bonds are sugar transferases (for example, glycogen synthase is a glucosyltransferase). Transferases are also involved in the formation of the glycosidic bonds in bilirubin glucuronides, proteoglycans, and lactose.

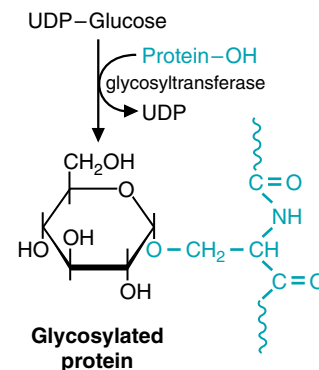


Fig. 30.2. Glycosyltransferases. These enzymes transfer sugars from nucleotide sugars to nucleophilic amino acid residues on proteins, such as the hydroxyl group of serine or the amide group of asparagine. Other transferases transfer specific sugars from a nucleotide sugar to a hydroxyl group of other sugars. The bond formed between the anomeric carbon of the sugar and the nucleophilic group of another compound is a glycosidic bond.



How does glucuronic acid differ from gluconic acid?

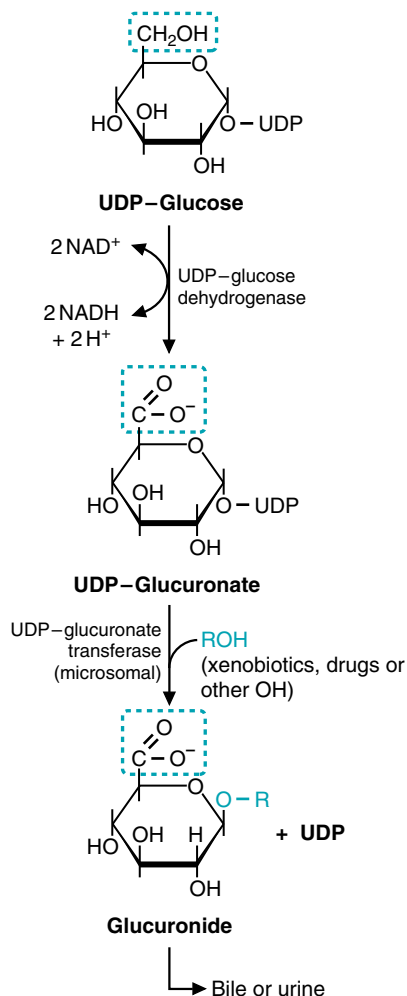


Fig. 30.4. Formation of glucuronate and glucuronides. A glycosidic bond is formed between the anomeric hydroxyl of glucuronate and the hydroxyl group of a nonpolar compound. The negatively charged carboxyl group of the glucuronate increases the water solubility and allows otherwise nonpolar compounds to be excreted in the urine or bile.



High concentrations of galactose 1-phosphate inhibit phosphoglucosyltransferase, the enzyme that converts glucose 6-phosphate to glucose 1-phosphate. How can this inhibition account for the hypoglycemia and jaundice that accompany galactose 1-phosphate uridylyltransferase deficiency?



When bilirubin levels are measured in the blood, one can measure either indirect bilirubin (this is the nonconjugated form of bilirubin, which is bound to albumin), direct bilirubin (the conjugated, water-soluble form), or total bilirubin (the sum of the direct and indirect levels). If total bilirubin levels are high, then a determination of direct and indirect bilirubin is needed to appropriately determine a cause for the elevation of total bilirubin.

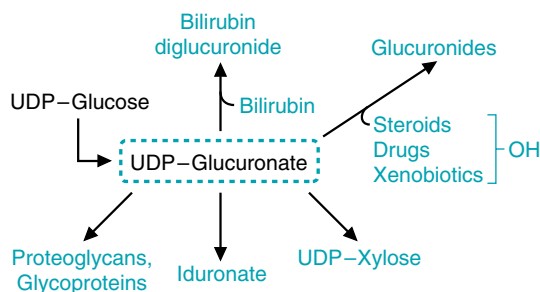


Fig. 30.3. Metabolic routes of UDP-glucuronate. UDP-glucuronate is formed from UDP-glucose (shown in black). Glucuronate from UDP-glucuronate is incorporated into glycosaminoglycans, where certain of the glucuronate residues are converted to iduronate (see Chapter 49). UDP-glucuronate is a precursor of UDP-xylose, another sugar residue incorporated into glycosaminoglycans. Glucuronate is also transferred to the carboxyl groups of bilirubin or the alcohol groups of steroids, drugs, and xenobiotics to form glucuronides. The “ide” in the name glucuronide denotes that these compounds are glycosides. Xenobiotics are pharmacologically, endocrinologically, or toxicologically active substances not endogenously produced and therefore foreign to an organism. Drugs are an example of a xenobiotic.

B. UDP-Glucuronate: A Source of Negative Charges

One of the major routes of UDP-glucose metabolism is the formation of UDP-glucuronate, which serves as a precursor of other sugars and of glucuronides (Fig. 30.3). Glucuronate is formed by the oxidation of the alcohol on C6 of glucose to an acid (through two oxidation states) by an NAD^+ -dependent dehydrogenase (Fig. 30.4). Glucuronate is also present in the diet and can be formed from the degradation of inositol (the sugar alcohol that forms inositol trisphosphate (IP₃), an intracellular second messenger for many hormones).

C. Formation of Glucuronides

The function of glucuronate in the excretion of bilirubin, drugs, xenobiotics, and other compounds containing a hydroxyl group is to add negative charges and increase their solubility. Bilirubin is a degradation product of heme that is formed in the reticuloendothelial system and is only slightly soluble in plasma. It is transported to the liver bound to albumin. In the liver, glucuronate residues are transferred from UDP-glucuronate to two carboxyl groups on bilirubin, sequentially forming bilirubin monoglucuronide and bilirubin diglucuronide, the “conjugated” forms of bilirubin (Fig. 30.5). The more soluble bilirubin diglucuronide (as compared with unconjugated bilirubin) is then actively transported into the bile for excretion.

Many xenobiotics, drugs, steroids, and other compounds with hydroxyl groups and a low solubility in water are converted to glucuronides in a similar fashion by glucuronyltransferases present in the endoplasmic reticulum and cytoplasm of the liver and kidney (Table 30.1). This is one of the major conjugation pathways for excretion of these compounds.



A failure of the liver to transport, store, or conjugate bilirubin results in the accumulation of unconjugated bilirubin in the blood. Jaundice, the yellowish tinge to the skin and the whites of the eyes (sclera) experienced by **Erin Galway**, occurs when plasma becomes supersaturated with bilirubin ($>2\text{--}2.5$ mg/dL), and the excess diffuses into tissues.

Glucuronate, once formed, can reenter the pathways of glucose metabolism through reactions that eventually convert it to D-xylulose 5-phosphate, an intermediate of the pentose phosphate pathway. In most mammals other than humans, an intermediate of this pathway is the precursor of ascorbic acid (vitamin C). Humans, however, are deficient in this pathway and cannot synthesize vitamin C.

D. Synthesis of UDP-Galactose and Lactose from Glucose

Lactose is synthesized from UDP-galactose and glucose (Fig. 30.6). However, galactose is not required in the diet for lactose synthesis because galactose can be synthesized from glucose.

1. CONVERSION OF GLUCOSE TO GALACTOSE

Galactose and glucose are epimers; they differ only in the stereochemical position of one hydroxyl group. Thus, the formation of UDP-galactose from UDP-glucose is an epimerization (Fig. 30.7). The epimerase does not actually transfer the hydroxyl group; it oxidizes the hydroxyl to a ketone by transferring electrons to NAD^+ , and then donates electrons back to re-form the alcohol group on the other side of the carbon.

2. LACTOSE SYNTHESIS

Lactose is unique in that it is synthesized only in the mammary gland of the adult for short periods during lactation. Lactose synthase, an enzyme present in the endoplasmic reticulum of the lactating mammary gland, catalyzes the last step in lactose biosynthesis, the transfer of galactose from UDP-galactose to glucose (see Fig. 30.6). Lactose synthase has two protein subunits, a galactosyltransferase and α -lactalbumin. α -Lactalbumin is a modifier protein synthesized after parturition (childbirth) in response to the hormone prolactin. This enzyme subunit lowers the K_m of the galactosyltransferase for glucose from 1,200 to 1 mM, thereby increasing the rate of lactose synthesis. In the absence of α -lactalbumin, galactosyltransferase transfers galactosyl units to glycoproteins.



Many (60%) full-term newborns develop jaundice, termed neonatal jaundice. This is usually caused by an increased destruction of red blood cells after birth (the fetus has an unusually large number of red blood cells) and an immature bilirubin conjugating system in the liver. This leads to elevated levels of nonconjugated bilirubin, which is deposited in hydrophobic (fat) environments. If bilirubin levels reach a certain threshold at the age of 48 hours, the newborn is a candidate for phototherapy, in which the child is placed under lamps that emit light between the wavelengths of 425 and 475 nm. Bilirubin absorbs this light, undergoes chemical changes, and becomes more water soluble. Usually, within a week of birth, the newborn's liver can handle the load generated from red blood cell turnover.



The inhibition of phosphoglucomutase results in hypoglycemia by interfering with both the formation of UDP-glucose (the glycogen precursor) and the degradation of glycogen back to glucose 6-phosphate. Ninety percent of glycogen degradation leads to glucose 1-phosphate, which can only be converted to glucose 6-phosphate by phosphoglucomutase. When phosphoglucomutase activity is inhibited, less glucose-6-P production occurs, and hence, less glucose is available for export. Thus, the stored glycogen is only approximately 10% efficient in raising blood glucose levels, and hypoglycemia results. UDP-glucose levels are reduced because glucose-1-P is required to synthesize UDP-glucose, and in the absence of phosphoglucomutase activity glucose-6-P cannot be converted to glucose-1-P. This prevents the formation of UDP-glucuronate, which is necessary to convert bilirubin to the diglucuronide form for transport into the bile. Bilirubin accumulates in tissues, giving them a yellow color (jaundice).

Table 30.1. Some Compounds Degraded and Excreted as Urinary Glucuronides

Estrogen (female sex hormone)
Progesterone (steroid hormone)
Triiodothyronine (thyroid hormone)
Acetylaminofluorene (xenobiotic carcinogen)
Meprobamate (drug for sleep)
Morphine (painkiller)



6-Phosphogluconate is produced by the first oxidative reaction in the pentose phosphate pathway, in which carbon 1 of glucose is oxidized to a carboxylate. In contrast, glucuronic acid is oxidized at carbon 6 to the carboxylate form.



A pregnant woman who was extremely lactose intolerant asked her physician if she would still be able to breastfeed her infant since she could not drink milk or dairy products. What advice should she be given?

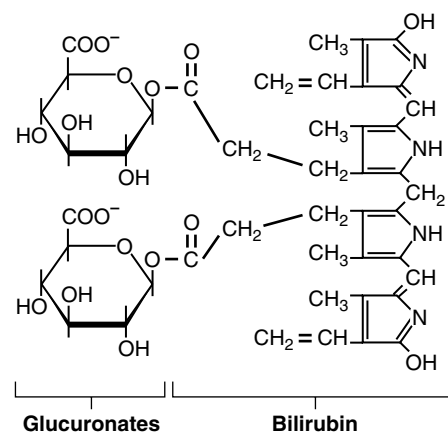


Fig. 30.5. Formation of bilirubin diglucuronide. A glycosidic bond is formed between the anomeric hydroxyl of glucuronate and the carboxylate groups of bilirubin. The addition of the hydrophilic carbohydrate group, and the negatively charged carboxyl group of the glucuronate, increases the water solubility of the conjugated bilirubin and allows the otherwise insoluble bilirubin to be excreted in the urine or bile.

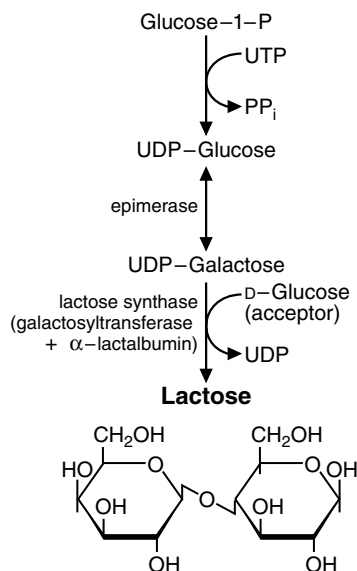


Fig. 30.6. Lactose synthesis. Lactose is a disaccharide composed of galactose and glucose. UDP-galactose for the synthesis of lactose in the mammary gland is usually formed from the epimerization of UDP-glucose. Lactose synthase attaches the anomeric carbon of the galactose to the C4 alcohol group of glucose to form a glycosidic bond. Lactose synthase is composed of a galactosyltransferase and α -lactalbumin, which is a regulatory subunit.

Table 30.2. Some Sugar Nucleotides That Are Precursors for Transferase Reactions

UDP-glucose
UDP-galactose
UDP-glucuronic acid
UDP-xylose
UDP-N-acetylglucosamine
UDP-N-acetylgalactosamine
CMP-N-acetylneuraminic acid
GDP-fucose
GDP-mannose



Although the lactose in dairy products is a major source of galactose, the ingestion of lactose is not required for lactation. UDP-galactose in the mammary gland is derived principally from the epimerization of glucose. Dairy products are, however, a major dietary source of Ca^{2+} , so breastfeeding mothers need increased Ca^{2+} from another source.



N-Acetyltransferases are present in the endoplasmic reticulum and cytosol and provide another means of chemically modifying sugars, metabolites, drugs, and xenobiotic compounds. Individuals may vary greatly in their capacity for acetylation reactions.

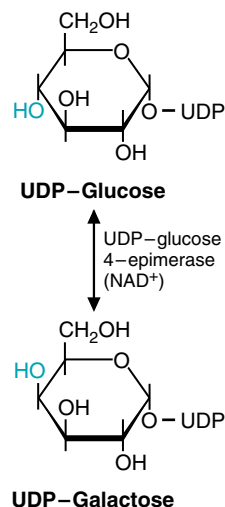


Fig. 30.7. Epimerization of UDP-glucose to UDP-galactose. The epimerization of glucose to galactose occurs on UDP-sugars. The epimerase uses NAD^+ to oxidize the alcohol to a ketone, and then reduce the ketone back to an alcohol. The reaction is reversible; glucose being converted to galactose forms galactose for lactose synthesis, and galactose being converted to glucose is part of the pathway for the metabolism of dietary galactose.

E. Formation of Sugars for Glycolipid and Glycoprotein Synthesis

The transferases that produce the oligosaccharide and polysaccharide side chains of glycolipids and attach sugar residues to proteins are specific for the sugar moiety and for the donating nucleotide (e.g., UDP, CMP, or GDP). Some of the sugar-nucleotides used for glycoprotein, proteoglycan (see Chapter 49) and glycolipid formation are listed in Table 30.2. They include the derivatives of glucose and galactose that we have already discussed, as well as acetylated amino sugars and derivatives of mannose. The reason for the large variety of sugars attached to proteins and lipids is that they have relatively specific and different functions, such as targeting a protein toward a membrane, providing recognition sites on the cell surface for other cells, hormones, or viruses, or acting as lubricants or molecular sieves (see Chapter 42).

The pathways for utilization and formation of many of these sugars are summarized in Figure 30.8. Note that many of the steps are reversible, so that glucose and other dietary sugars enter a common pool from which the diverse sugars can be formed.

The amino sugars are all derived from glucosamine 6-phosphate. To synthesize glucosamine 6-phosphate, an amino group is transferred from the amide of glutamine to fructose 6-phosphate (Fig. 30.9). Amino sugars, such as glucosamine, can then be N-acetylated by an acetyltransferase.

Mannose is found in the diet in small amounts. Like galactose, it is an epimer of glucose, and mannose and glucose are interconverted by epimerization reactions. The interconversion can take place either at the level of fructose 6-phosphate to mannose 6-phosphate, or at the level of the derivatized sugars (see Fig. 30.8).

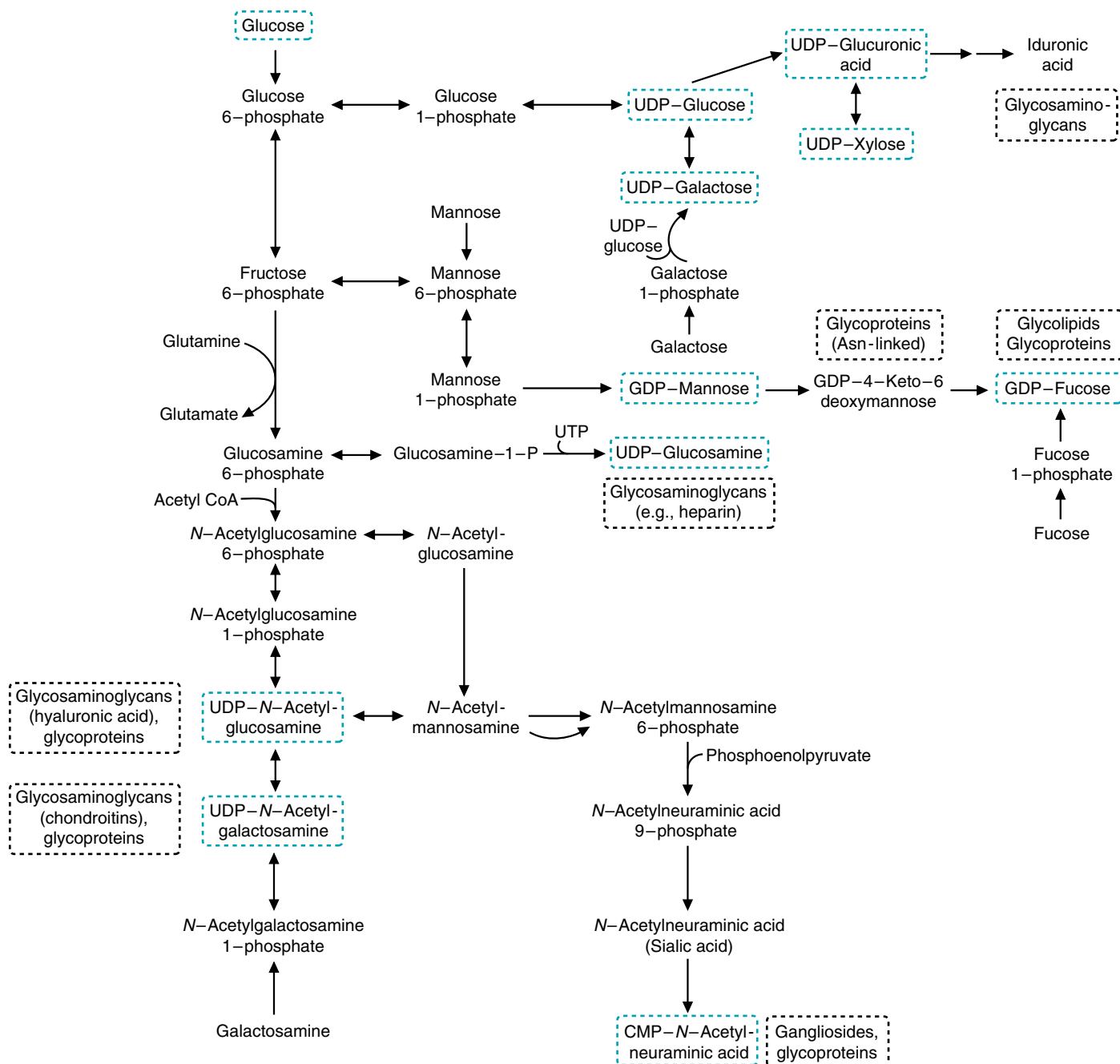


Fig. 30.8. Pathways for the interconversion of sugars. All of the different sugars found in glycosaminoglycans, gangliosides, and other compounds in the body can be synthesized from glucose. Dietary glucose, fructose, galactose, mannose, and other sugars enter a common pool from which other sugars are derived. The activated sugar is transferred from the nucleotide sugar, shown in blue boxes, to form a glycosidic bond with another sugar or amino acid residue. The box next to each nucleotide sugar lists some of the compounds that contain the sugar. Iduronic acid, in the upper right corner of the diagram, is formed only after glucuronic acid is incorporated into a glycosaminoglycan (which is discussed in more detail in Chapter 49).

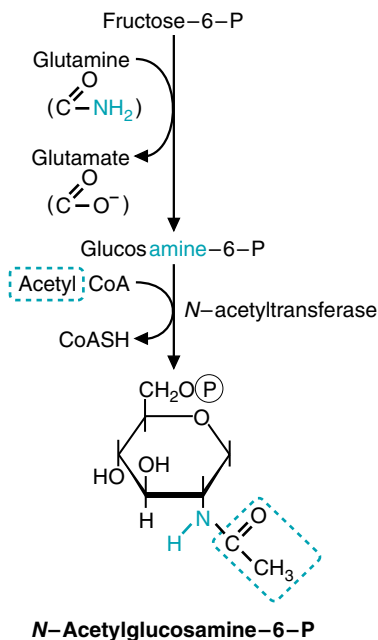


Fig. 30.9. The formation of *N*-acetylglucosamine 6-phosphate. The amino sugar is formed by a transfer of the amino group from the amide of glutamine to a carbon of the sugar. The amino group is acetylated by the transfer of an acetyl group from acetyl CoA.

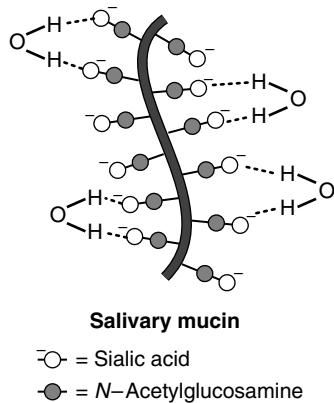


Fig. 30.11. Structure of salivary mucin. The sugars form hydrogen bonds with water. Sialic acid provides a negatively charged carboxylate group. The protein is extremely large, and the negatively charged sialic acids extend the carbohydrate chains so the molecules occupy a large space. All of the salivary glycoproteins are *O*-linked. NANA is a sialic acid.

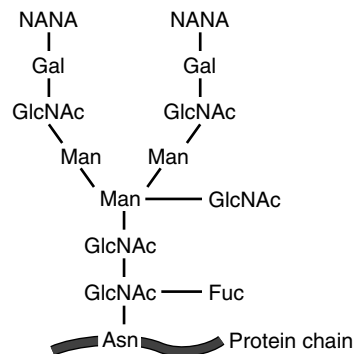


Fig. 30.10. An example of a branched glycoprotein. NANA = *N*-acetylneuraminic acid; Gal = galactose; GlcNAc = *N*-acetylglucosamine; Man = mannose; Fuc = fucose.

N-Acetylmannosamine is the precursor of *N*-acetylneuraminic acid (NANA, a sialic acid) and GDP-mannose is the precursor of GDP-fucose (see Fig. 30.8). The negative charge on NANA is obtained by the addition of a 3-carbon carboxyl moiety from phosphoenolpyruvate.

II. GLYCOPROTEINS

A. Structure and Function

Glycoproteins contain short carbohydrate chains covalently linked to either serine/threonine or asparagine residues in the protein. These oligosaccharide chains are often branched, and they do not contain repeating disaccharides (Fig. 30.10). Most proteins in the blood are glycoproteins. They serve as hormones, antibodies, enzymes (including those of the blood clotting cascade), and as structural components of the extracellular matrix. Collagen contains galactosyl units and disaccharides composed of galactosyl-glucose attached to hydroxylysine residues (see Chapter 49). The secretions of mucus-producing cells, such as salivary mucin, are glycoproteins (Fig. 30.11).

Although most glycoproteins are secreted from cells, some are segregated in lysosomes, where they serve as the lysosomal enzymes that degrade various types of cellular and extracellular material. Other glycoproteins are produced like secretory proteins, but hydrophobic regions of the protein remain attached to the cell membrane, and the carbohydrate portion extends into the extracellular space (Fig. 30.12)(also see Chapter 15, section I). These glycoproteins serve as receptors for compounds such as hormones, as transport proteins, and as cell attachment and cell-cell recognition sites. Bacteria and viruses also bind to these sites.

B. Synthesis

The protein portion of glycoproteins is synthesized on the endoplasmic reticulum (ER). The carbohydrate chains are attached to the protein in the lumen of the ER and the Golgi complex. In some cases, the initial sugar is added to a serine or a threonine residue in the protein, and the carbohydrate chain is extended by the sequential addition of sugar residues to the nonreducing end. As seen previously in Table 2, UDP-sugars are the precursors for the addition of four of the seven sugars that are usually found in glycoproteins—glucose, galactose, *N*-acetylglucosamine, and *N*-acetylgalactosamine. GDP-sugars are the precursors for the addition of mannose and L-fucose, and CMP-NANA is the precursor for NANA.

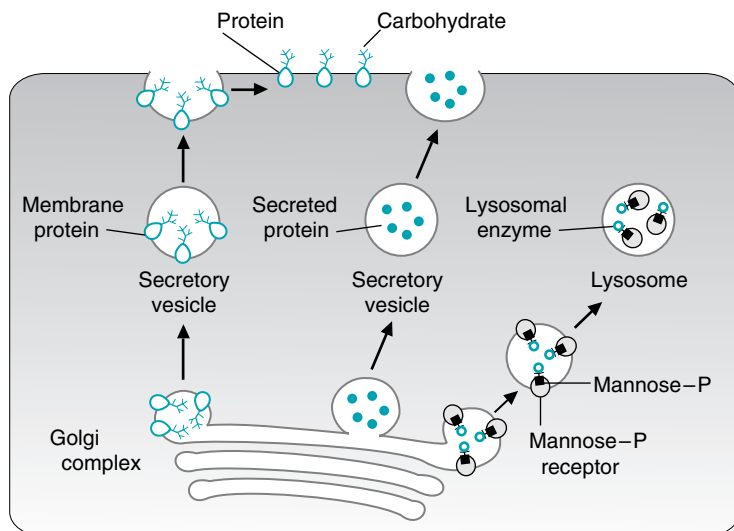


Fig. 30.12. Route from the Golgi complex to the final destination for lysosomal enzymes, cell membrane proteins, and secreted proteins, which include glycoproteins and proteoglycans.

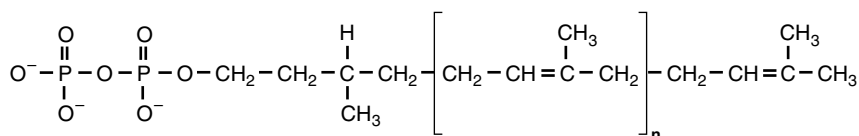


Fig. 30.13. Structure of dolichol phosphate. In humans, the isoprene unit (in brackets) is repeated approximately 17 times ($n \approx 17$).

Dolichol phosphate (Fig. 30.13) (which is synthesized from isoprene units, as discussed in Chapter 34) is involved in transferring branched sugar chains to the amide nitrogen of asparagine residues. Sugars are removed and added as the glycoprotein moves from the ER through the Golgi complex (Fig. 30.14). As discussed in Chapter 10, the carbohydrate chain is used as a targeting marker for lysosomal enzymes.

I-cell (inclusion cell) disease is a rare condition in which lysosomal enzymes lack the mannosephosphate marker that targets them to lysosomes. Consequently, lysosomal enzymes are secreted from the cells. Because lysosomes lack their normal complement of enzymes, undegraded molecules accumulate within membranes inside these cells, forming inclusion bodies.

III. GLYCOLIPIDS

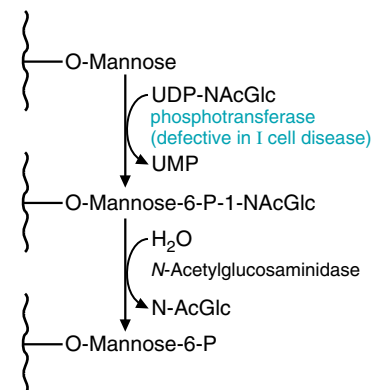
A. Function and Structure

Glycolipids are derivatives of the lipid sphingosine. These sphingolipids include the cerebroside and the gangliosides (Fig. 30.15; see also Fig. 5.22). They contain ceramide, with carbohydrate moieties attached to its hydroxymethyl group.

Glycolipids are involved in intercellular communication. Oligosaccharides of identical composition are present in both the glycolipids and glycoproteins associated with the cell membrane, where they serve as cell recognition factors. For example, carbohydrate residues in these oligosaccharides are the antigens of the ABO blood group substances (Fig. 30.16).



The enzyme that is deficient in I-cell disease is a phosphotransferase located in the Golgi apparatus.



The phosphotransferase has the unique ability to recognize lysosomal proteins because of their three-dimensional structure, such that they can all be appropriately tagged for transport to the lysosomes.



By identifying the nature of antigenic determinants on the surface of the donor's red blood cells, **Erna Nemy** is able to classify the donor's blood as belonging to certain specific blood groups. These antigenic determinants are located in the oligosaccharides of the glycoproteins and glycolipids of the cell membranes. The most important blood group in humans is the ABO group, which comprises two antigens, A and B. Individuals with the A antigen on their cells belong to blood group A. Those with B belong to group B, and those with both A and B belong to group AB. The absence of both the A and the B antigen results in blood type O (see Fig. 30.16).

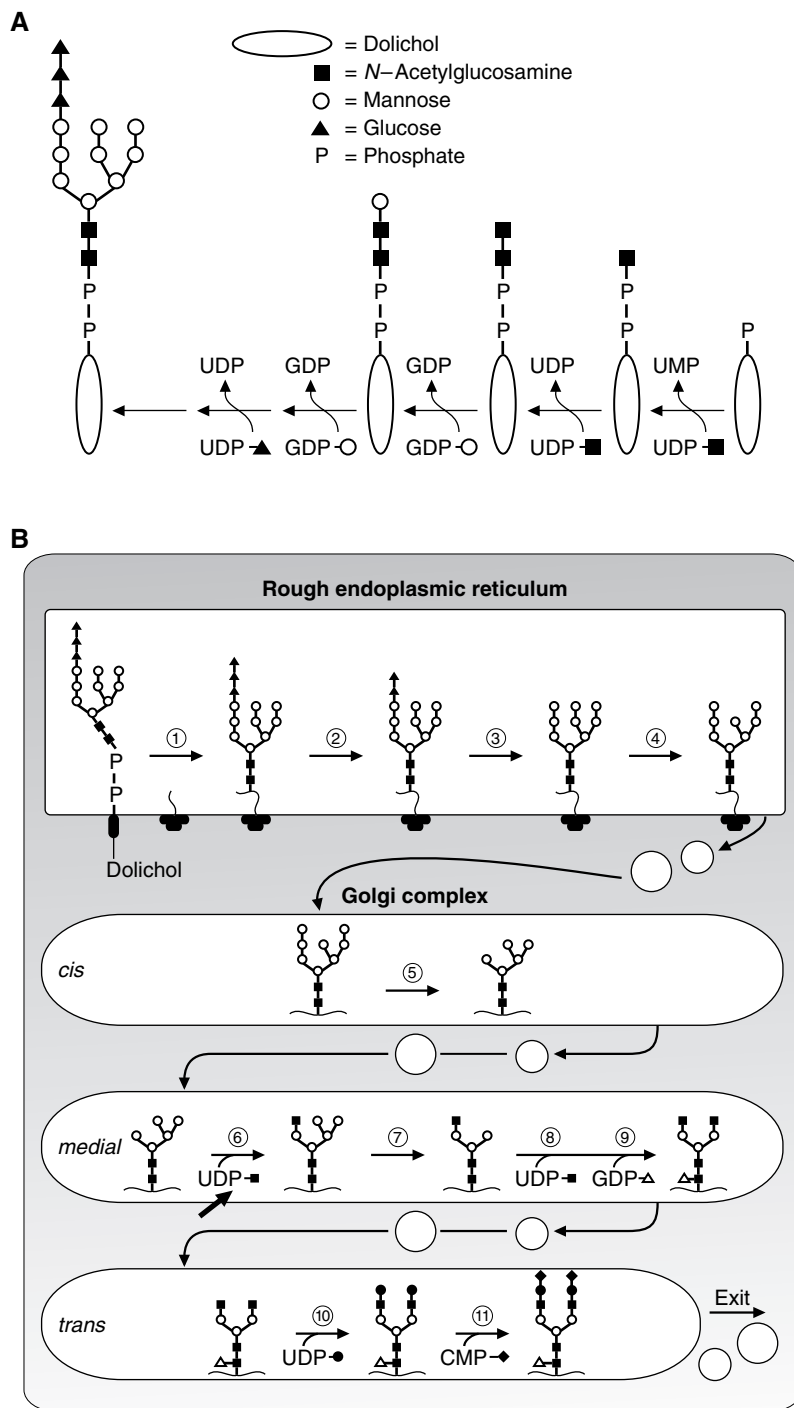


Fig. 30.14. Action of dolichol phosphate in transferring carbohydrate groups to proteins (A) and processing of these carbohydrate groups (B). Transfer of the branched oligosaccharide from dolichol phosphate to a protein in the lumen of the rough endoplasmic reticulum (RER) (step 1) and processing of the oligosaccharide (steps 2–11). Steps 1 through 4 occur in the RER. The glycoprotein is transferred in vesicles to the Golgi complex, where further modifications of the oligosaccharides occur (steps 5–11). B modified with permission from Kornfeld R, Kornfeld S. *Annu Rev Biochem* 1985;54:640. © 1985 by Annual Reviews, Inc. P = phosphate.

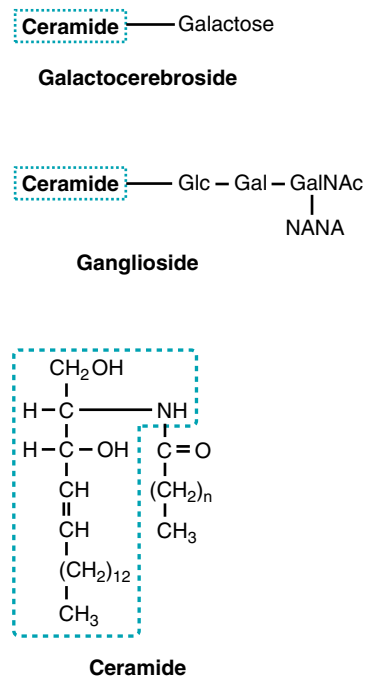


Fig. 30.15. Structures of cerebroside and ganglioside. In these glycolipids, sugars are attached to ceramide (shown below the glycolipids). The boxed portion of ceramide is sphingosine, from which the name *sphingolipids* is derived.

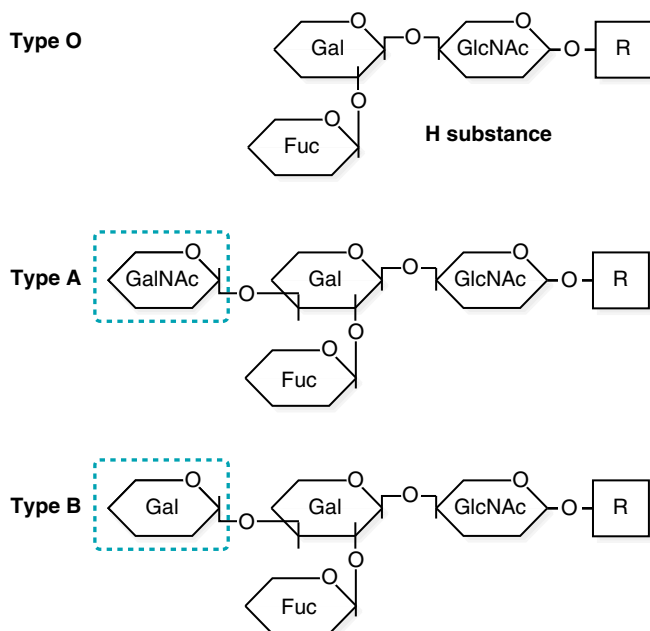
Blood Type

Fig. 30.16. Structures of the blood group substances. Note that these structures are the same except that type A has *N*-acetylgalactosamine (GalNAc) at the nonreducing end, type B has galactose (Gal), and type O has neither. R is either a protein or the lipid ceramide. Each antigenic determinant is boxed. Fuc = fucose; GlcNAc = *N*-acetylglucosamine; Gal = galactose.



The blood group substances are oligosaccharide components of glycolipids and glycoproteins found in most cell membranes. Those located on red blood cells have been studied extensively. A single genetic locus with two alleles determines an individual's blood type. These genes encode glycosyltransferases involved in the synthesis of the oligosaccharides of the blood group substances.

Most individuals can synthesize the H substance, an oligosaccharide that contains a fucose linked to a galactose at the nonreducing end of the blood group substance (see Fig. 30.16). Type A individuals produce an *N*-acetylgalactosamine transferase (encoded by the A gene) that attaches *N*-acetylgalactosamine to the galactose residue of the H substance. Type B individuals produce a galactosyltransferase (encoded by the B gene) that links galactose to the galactose residue of the H substance. Type AB individuals have both alleles and produce both transferases. Thus, some of the oligosaccharides of their blood group substances contain *N*-acetylgalactosamine and some contain galactose. Type O individuals produce a defective transferase, and, therefore, they do not attach either *N*-acetylgalactosamine or galactose to the H substance. Thus, individuals of blood type O have only the H substance.

B. Synthesis

Cerebrosides are synthesized from ceramide and UDP-glucose or UDP-galactose. They contain a single sugar (a monosaccharide). Gangliosides contain oligosaccharides produced from UDP-sugars and CMP-NANA, which is the precursor for the *N*-acetylneuraminic acid residues that branch from the linear chain. The synthesis of the sphingolipids is described in more detail in Chapter 33.

Sphingolipids are produced in the Golgi complex. Their lipid component becomes part of the membrane of the secretory vesicle that buds from the *trans* face of the Golgi. After the vesicle membrane fuses with the cell membrane, the lipid component of the glycolipid remains in the outer layer of the cell membrane, and the carbohydrate component extends into the extracellular space.



Cholera toxin binds to the carbohydrate portion of the GM1 ganglioside to allow its catalytic subunit to enter the cell.



Q: Erna Nemdy determined that a patient's blood type was AB. The new surgical resident was eager to give this patient a blood transfusion and, because AB blood is rare and an adequate amount was not available in the blood bank, he requested type A blood. Should Erna give him type A blood for his patient?



Jay Sakz has Tay-Sachs disease, which belongs to a group of gangliosidoses that include Fabry's and Gaucher's diseases. They mainly affect the brain, the skin, and the reticuloendothelial system (e.g., liver and spleen). In these diseases, complex lipids accumulate. Each of these lipids contains a ceramide as part of its structure (Table 30.3). The rate at which the lipid is synthesized is normal. However, the lysosomal enzyme required to degrade it is not very active, either because it is made in deficient quantities because of a mutation in a gene that specifically codes for the enzyme or because a critical protein required to activate the enzyme is deficient. Because the lipid cannot be degraded, it accumulates and causes degeneration of the affected tissues with progressive malfunction, such as the psychomotor deficits that occur as a result of the central nervous system involvement seen in most of these storage diseases.

Table 30.3. Defective Enzymes in the Gangliosidoses

Disease	Enzyme Deficiency	Accumulated Lipid
Fucosidosis	α -Fucosidase	Cer-Glc-Gal-GalNAc-Gal:Fuc H-isoantigen
Generalized gangliosidosis	G_{M1} - β -galactosidase	Cer-Glc-Gal(NeuAc)-GalNAc:Gal G_{M1} ganglioside
Tay-Sachs disease	Hexosaminidase A	Cer-Glc-Gal(NeuAc):GalNAc G_{M2} ganglioside
Tay-Sachs variant or Sandhoff disease	Hexosaminidase A and B	Cer-Glc-Gal-Gal:GalNAc Globoside plus G_{M2} ganglioside
Fabry's disease	α -Galactosidase	Cer-Glc-Gal:Gal Globotriaosylceramide
Ceramide lactoside lipidosis	Ceramide lactosidase (β -galactosidase)	Cer-Glc:Gal Ceramide lactoside
Metachromatic leukodystrophy	Arylsulfatase A	Cer-Gal:OSO ₃ 3-Sulfogalactosylceramide
Krabbe's disease	β -Galactosidase	Cer:Gal Galactosylceramide
Gaucher's disease	β -Glucosidase	Cer:Glc Glucosylceramide
Niemann-Pick disease	Sphingomyelinase	Cer:P-choline Sphingomyelin
Farber's disease	Ceramidase	Acyl: sphingosine Ceramide

NeuAc, *N*-acetylneuraminic acid; Cer, ceramide; Glc, glucose; Gal, galactose; Fuc, fucose : site of deficient enzyme reaction.

CLINICAL COMMENTS



During her stint in the hospital blood bank, **Erna Nemdy** learned that the importance of the ABO blood group system in transfusion therapy is based on two principles (Table 30.4). (a) Antibodies to A and to B antigens occur naturally in the blood serum of persons whose red blood cell surfaces lack the corresponding antigen (i.e., individuals with A antigens on their red blood cells have B antibodies in their serum and vice versa). These antibodies may arise as a result of previous exposure to cross-reacting antigens in bacteria and foods or to blood transfusions. (b) Antibodies to A and B are usually present in high titers and are capable of activating the entire complement system. As a result, these antibodies may cause intravascular destruction of a large number of incompatible red blood cells given during a blood transfusion. Individuals with type AB blood have both A and B antigens and do not produce antibodies to either. Hence, they are “universal” recipients. They can safely receive red blood cells from individuals of A, B, AB, or O blood type. (However, they cannot safely receive serum from these individuals because it contains antibodies to A or B antigens.) Those with type O blood do not have either antigen. They are “universal” donors; i.e., their red cells can safely be infused into type A, B, O, or AB individuals. (However, their serum contains antibodies to both A and B antigens and cannot safely be used.)



The patient could safely receive type A blood cells from another person because he has both A and B antigens on his own cells and does not have antibodies in his serum to either type A or B cells. However, he should not be given type A serum (or type A whole blood) because type A serum contains antibodies to type B antigens, which are present on his cells.

Table 30.4. Characteristics of the ABO Blood Groups

	O	A	B	AB
Red cell type	O	A	B	AB
Possible genotypes	OO	AA or AO	BB or BO	AB
Antibodies in serum	Anti-A and B	Anti-B	Anti-A	None
Frequency (in Caucasians)	45%	40%	10%	5%
Can accept blood types	O	A, O	B, O	A, B, AB, O

The second important red blood cell group is the Rh group. It is important because one of its antigenic determinants, the D antigen, is a very potent immunogen, stimulating the production of a large number of antibodies.

The unique carbohydrate composition of the glycoproteins that constitute the antigenic determinants on red blood cells in part contributes to the relative immunogenicity of the A, B, and Rh (D) red blood cell groups in human blood.



Tay-Sachs disease, the problem afflicting **Jay Sakz**, is an autosomal recessive disorder that is rare in the general population (1 in 300,000 births), but its prevalence in Jews of Eastern European extraction (who make up 90% of the Jewish population in the United States) is much higher (1 in 3,600 births). One in 28 Ashkenazi Jews carries this defective gene. Its presence can be discovered by measuring the tissue level of the protein produced by the gene (hexosaminidase A) or by recombinant DNA techniques. Skin fibroblasts of concerned couples planning a family are frequently used for these tests.

Carriers of the affected gene have a reduced but functional level of this enzyme that normally hydrolyzes a specific bond between an *N*-acetyl-D-galactosamine and a D-galactose residue in the polar head of the ganglioside.

No effective therapy is available. Enzyme replacement has met with little success because of the difficulties in getting the enzyme across the blood-brain barrier.

BIOCHEMICAL COMMENTS



Hexosaminidase A, the enzyme defective in Tay-Sachs disease, is actually composed of two subunits, an α and a β chain. The exact stoichiometry of the active enzyme is unknown, but it may be $\alpha_2\beta_2$. The α subunit is coded for by the HexA gene, whereas the β subunit is coded for by the HexB gene. In Tay-Sachs disease, the α subunit is defective, and hexosaminidase A activity is lost. However, the β subunit can form active tetramers in the absence of the α subunit, and this activity, named hexosaminidase B, which cleaves the glycolipid globoside, retains activity in children with Tay-Sachs disease. Thus, children with Tay-Sachs disease accumulate the ganglioside GM₂, but not globoside (Fig. 30.17).

Mutation of the HexB gene, and production of a defective β subunit, leads to inactivation of both hexosaminidase A and B activity. Such a mutation leads to Sandhoff disease. Both activities are lost because both activities require a functional β subunit. The clinical course of this disease is similar to Tay-Sachs but with an accelerated timetable because of the initial accumulation of both GM₂ and globoside in the lysosomes.

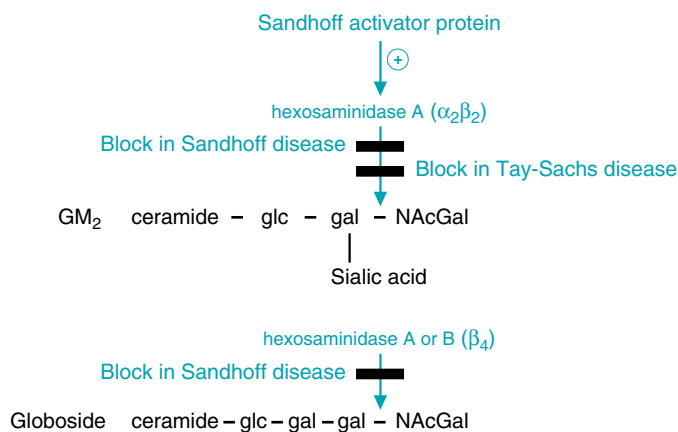
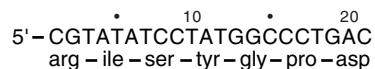


Fig. 30.17. Substrate specificities of hexosaminidase A, B, and the function of the activator protein. Glc = glucose; gal = galactose; NAcGal = N-acetylgalactosamine.

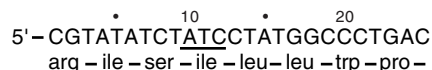
A third type of mutation also can lead to disease symptoms similar to those of Tay-Sachs disease. Children were identified with Tay-Sachs symptoms, but when both hexosaminidase A and B activities were measured in a test tube, they were normal. This disease, ultimately named Sandhoff activator disease, is caused by a mutation in a protein that is needed to activate hexosaminidase A activity. In the absence of the activator, hexosaminidase A activity is minimal, and GM2 initially accumulates in lysosomes. This mutation has no effect on hexosaminidase B activity.

When a glycolipid cannot be degraded because of an enzymatic mutation, it accumulates in residual bodies (vacuoles that contain material that lysosomal enzymes cannot digest). Normal cells contain a small number of residual bodies, but in diseases of lysosomal enzymes, large numbers of residual bodies accumulate within the cell, eventually interfering with normal cell function.

In 70% of the cases of Tay-Sachs disease in persons of Ashkenazai Jewish background, exon 11 of the gene for the α chain of hexosaminidase A contains a mutation. The normal gene sequence encodes a protein with the amino acids arg-ile-ser-tyr-gly-pro-asp in this region, as shown below:



The mutant DNA sequence for this area is shown below:



A four-base insertion (underlined) occurs in the mutated gene, which alters the reading frame of the protein, and also introduces a premature stop codon further down the protein, such that no functional α subunit can be produced.

Suggested References

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- Lloyd KO. The chemistry and immunochemistry of blood group A, B, H and Lewis antigens: past, present and future. *Glycoconjugate J* 2000:531–541.



REVIEW QUESTIONS—CHAPTER 30

- Which of the following best describes a mother with galactosemia caused by a deficiency of galactose 1-phosphate uridylyl transferase?
 - She can convert galactose to UDP-galactose for lactose synthesis during lactation.
 - She can form galactose 1-phosphate from galactose.
 - She can use galactose as a precursor to glucose production.
 - She can use galactose to produce glycogen.
 - She will have lower than normal levels of serum galactose after drinking milk.

2. The immediate carbohydrate precursors for glycolipid and glycoprotein synthesis are which of the following?
 - (A) Sugar phosphates
 - (B) Sugar acids
 - (C) Sugar alcohols
 - (D) Nucleotide sugars
 - (E) Acyl-sugars

3. A newborn is diagnosed with neonatal jaundice. In this patient, the bilirubin produced lacks which of the following carbohydrates?
 - (A) Glucose
 - (B) Gluconate
 - (C) Glucuronate
 - (D) Galactose
 - (E) Galactitol

4. The nitrogen donor for the formation of amino sugars is which of the following?
 - (A) Ammonia
 - (B) Asparagine
 - (C) Glutamine
 - (D) Adenine
 - (E) Dolichol

5. Which of the following glycolipids would accumulate in a patient with Sandhoff's disease?
 - (A) GM1
 - (B) Lactosyl-ceramide
 - (C) Globoside
 - (D) Glucocerebroside
 - (E) GM3