

UNIT 14

DISORDERS OF LIPID METABOLISM

Structure

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14.1 INTRODUCTION

You learnt about various pathways of lipid metabolism. We also explained about the enzymes that mediate their synthesis and storage, breakdown and utilization. In addition, we also described role of proteins like carnitine which act as shuttle system for transport of fatty acyl CoA complex across the mitochondrial membranes. Any defect or deficiency of these components may result in disruption of energy metabolism and manifest into certain disorders. In this unit, we shall deal with some of these disorders and understand their basis.

Expected Learning Outcomes

After studying this unit, you should be able to:

- ❖ indicate the primary cause of some disorders associated with lipid metabolism;
- ❖ describe the symptoms of these disorders; and
- ❖ highlight the strategies for management / treatment and ways of early detection.

14.2 DISORDERS OF LIPID METABOLISM

Disorders of lipid metabolism are generally inherited disorders which occur due to defect or deficiency of a particular enzyme or protein involved in metabolic pathways. We shall discuss them in three broad categories which is based on the metabolic pathway affected:

1. Fatty acid oxidation disorders
2. Lipid storage diseases with reference to sphingolipid catabolism
3. Disorders associated with lipoprotein metabolism

Let us discuss these disorders in more details

14.2.1 Defects in β oxidation of fatty acids

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency

MCAD is the most common error of fatty acid β -oxidation. It catalyses the first step in mitochondrial β -oxidation. It is prevalent in individuals of European descent (especially northern), Portuguese with gypsy ancestry and native Americans of California.

Lipid stores are utilized after the carbohydrate reserves in the body are exhausted. Since children with MCAD deficiency are not able to utilize lipids, therefore, they are most likely to develop symptoms if they go without food for a long period of time or have an increased need for calories because of exercise or illness. Blood sugar levels drop significantly, causing weakness, lethargy, vomiting, seizures, confusion and coma. Symptoms usually develop between birth and age 3. Clinically they have hypoketotic hypoglycemia.

Most fatty acid oxidation (FAO) disorders including MCAD deficiency manifest with sudden and unexpected death. Taking into account the severity of the problem, it is mandatory in the United States for all newborns to be screened for MCAD with a blood test since 2007. Long-term management includes consumption of high carbohydrates and low fat diet and to avoid skipping meals. Supplements of the amino acid carnitine may also be helpful. In case of emergency they are injected glucose intravenously.

Carnitine acyl transferase-I (CAT-I) deficiency

You have studied this enzyme as a component of carnitine shuttle involved in translocation of long chain fatty acyl chains from cytosol into mitochondrial matrix. Its deficiency results in a rare autosomal recessive disorder. The organs which are most affected in this disorder are muscle, heart and kidney. The symptoms range from mild muscle cramping to severe muscle weakness and even death. The levels of both glucose and ketone bodies are low. They have enlarged liver and elevated levels of carnitine in blood. As medium chain fatty acids are not dependent on carnitine shuttle for translocation to mitochondrial matrix, they are processed normally in these individuals.

Carnitine deficiency

L-Carnitine is the carrier of activated long chain fatty acids across the mitochondrial inner membrane for β -oxidation. In mammals, carnitine

About 10% of sudden infant death syndrome (SIDS) cases were found to have MCAD deficiency in autopsy.

Carnitine acyl transferase-I (CAT-I) is also known as carnitine palmitoyl transferase-I (CPT-I).

homeostasis is maintained by endogenous synthesis, absorption from dietary sources and re-absorption by kidneys. It is a zwitterionic compound which is synthesised from lysine (bound to protein) and methionine exclusively in liver and kidneys. Skeletal and cardiac muscles lack these enzymes and are totally dependent on carnitine present in circulation. Therefore a deficiency of carnitine diminishes the ability of tissues to use long chain fatty acids.

Primary carnitine deficiency is due to defect in membrane carnitine transporter that transports carnitine into cells. As a result skeletal and cardiac muscles and kidneys are unable to take up carnitine from blood. It is an autosomal recessive disorder. The symptoms include muscle weakness with myoglobinemia following prolonged exercise; hypoglycemia, vomiting, damage to liver, heart and muscles due to build up of fatty acids. The severity of the symptoms varies considerably.

Secondary carnitine deficiency is more common than primary carnitine deficiency. There is not enough carnitine in blood that results in heart and liver problems. Disorders of the carnitine cycle / β -oxidation can precipitate secondary carnitine deficiency. A block in β -oxidation leads to accumulation of acyl carnitine which is excreted in urine. Acyl carnitine inhibits carnitine uptake by the carnitine transporter in renal cells that further aggravates the condition. In addition patients with liver disease or CAT-1 deficiency have diminished ability to synthesize carnitine whereas those on anti-seizure drugs like valproic acid have decreased renal reabsorption can develop secondary carnitine deficiency. In fact, CAT-I deficiency affects liver, as a result, these patients not only are unable to use LCFA as fuel but show an impaired ability to synthesize glucose during fasting. This may lead to severe hypoglycemia, coma and death.

Treatment includes oral supplementation of carnitine and diet rich in carbohydrates and low in fats supplemented with medium chain fatty acids. Fasting must be avoided.

Zellweger Syndrome

It is a rare inherited disorder in infants which occurs due to reduction or absence of functional peroxisomes. The most common cause is due to mutation in PEX1 gene (70%) although mutations in many other genes involved in biogenesis and functioning of peroxisomes account for the rest of the known cases. It is an autosomal recessive condition.

Peroxisomes are the primary site for activation and degradation of very long chain fatty acids (>22 carbons) to shorter chain length so that they can be finally degraded by the mitochondrial β -oxidation enzymes. They also synthesise ether phospholipids and participate in the oxidation of branch chain fatty acids. In the absence of peroxisomes, cells are unable to oxidize these fatty acids leading to their accumulation in blood and other organs such as brain, liver, heart and kidney which may be life threatening.

The symptoms include poor feeding, seizures, distinctive facial features, hearing and vision loss and skeletal abnormalities. Usually children do not survive beyond the first year of life. They succumb to respiratory distress, or liver failure. There is no cure for this disease and treatment is largely symptomatic.

14.2.2 Defects in α oxidation of fatty acids

Refsum's disease (phytanic acid storage disease)

Refsum's disease is a rare genetic disease due to deficiency of a peroxisomal phytanoyl CoA hydroxylase. You have learnt in unit 9 that phytanic acid, a constituent of dairy products and animal fats, is a branched chain fatty acid. The presence of an alkyl group at C_β blocks β -oxidation therefore, it is processed by peroxisomal α oxidation that converts it into a product suitable for degradation by β -oxidation. Due to absence of peroxisomal enzyme, phytanic acid accumulates in various tissues leading to serious neurological problems such as retinitis pigmentosa, deafness, unsteady gait, and tremors. The patients are advised to restrict the intake of dairy and meat products.

SAQ 1

Name two disorders of fatty acid oxidation due to peroxisomal defects and also mention the type of oxidation affected in each case.

14.3 LIPID STORAGE DISEASES- SPHINGOLIPIDOSES

Sphingolipidoses refers to inborn errors of metabolism in which there is a deficiency or complete absence of an enzyme involved in the catabolism of sphingolipids. These belong to a subgroup of lysosomal storage disorders as genetic deficiencies result in abnormal accumulation of intermediates of sphingolipid catabolism. Depending on the genetic defect preceding product of the pathway accumulates in lysosomes of the tissue in which catabolism is occurring. The accumulation of incompletely processed lipids accounts for the variety of symptoms observed in affected individuals. All these disorders are rare conditions except some which have much higher prevalence in certain ethnic groups. For instance the incidence of Tay Sachs disease is particularly high among Eastern Europeans and Ashkenazi Jewish populations. Most of them follow an autosomal recessive pattern of inheritance and finding the carrier status of prospective parents is therefore advisable as many are fatal.

The sphingolipids are degraded by hydrolytic enzymes in the lysosomes. The multi step reactions occur at lipid-water interface assisted by non enzymatic proteins. The stepwise breakdown of sphingolipids along with the enzymes is given in Fig.14.1. The genetic diseases associated with enzyme deficiency are also given at each step.

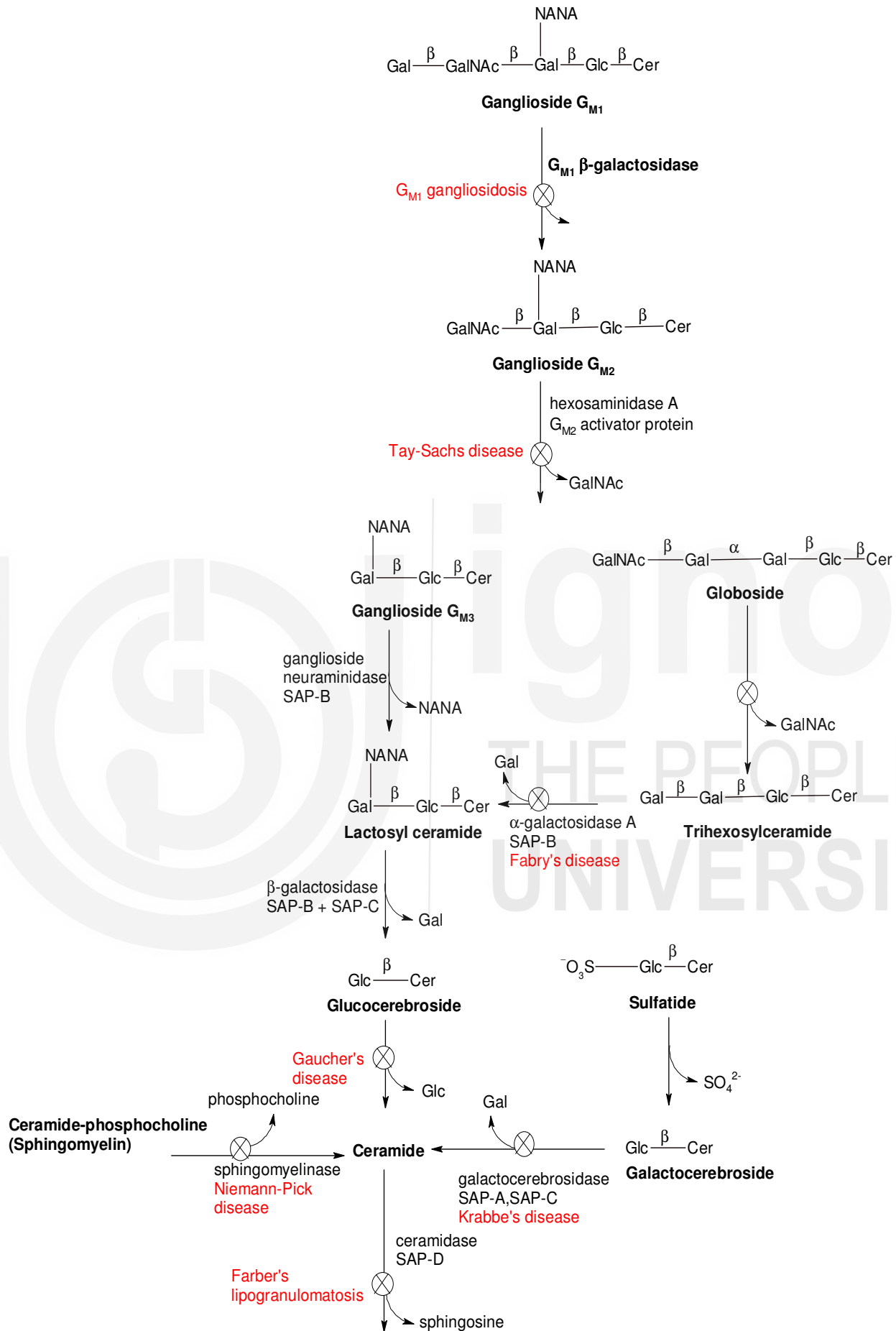


Fig. 14.1: Breakdown of sphingolipids.

The enzyme deficiency and the major symptoms associated with some sphingolipid storage diseases are summarised in Table 14.1.

Table 14.1: Sphingolipid storage diseases in humans

Disorder	Enzyme deficiency	Lipid accumulated	Principal Signs and Symptoms
Tay- Sachs disease	Hexosaminidase A	Ganglioside GM ₂	Mental retardation, blindness, cherry red spot on macula, children die by 2-3 years of age.
Gaucher's disease	Glucocere-brosidase	Glucocere-broside	Mental retardation; liver and spleen enlargement; anemia; erosion of pelvic and long bones
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin	Liver and spleen enlargement; mental retardation that may include spasticity, slurred speech, eye paralysis.
Krabbe's disease (globoid leuko-dystrophy)	Galactocerebrosidase	Galacto-cerebroside	Mental retardation; absence of myelin; sudden jerking of limbs; irritability, deafness; paralysis.; globoid bodies in white matter of the brain.
GM ₁ ganglio-sidosis	GM ₁ β-galactosidase	GM ₁ ganglioside	Mental retardation, liver enlargement; red spot in retina in approx.50%.
Farber's Disease	Ceramidase	Ceramide	Painful & deformed joints; hoarse cry; cherry red macula; tissue granulomas; dermatitis; lethargy , sleepiness
Fabry's disease (X-linked disease; affects generally males)	α-Galactosidase A	Trihexoxyl-ceramide	Skin rash, kidney failure; burning pain in arms and legs; cloudiness in cornea; risk of stroke and heart attack.

The diagnosis of these diseases is made from the biopsy of the organ involved, such as liver, brain, bone marrow or on morphological appearance. Enzyme analysis is used to further confirm the particular type of lipid storage disease.

SAQ 2

Name the lipid that accumulates in the following disorders?

- i) Farber disease ii) Gaucher disease iii) Krabbe disease iv) Tay- Sachs disease v) Niemann Pick disease
-

14.4 DISORDERS ASSOCIATED WITH LIPOPROTEIN METABOLISM

Familial hypercholesterolemia (FH)

FH is a common life threatening disease that affects 1 in 500 people in most countries. As the name suggests it is characterised by high levels of LDL (primary carrier of cholesterol in blood) in blood. It is an inborn error of lipid metabolism in which there is deficiency or complete absence of functional **LDL receptors**. The defective gene is present on human chromosome 19 and it is an **autosomal dominant disorder** which means the symptoms appear even if a child inherits only one mutant copy. In rare cases a child is homozygous for the mutant gene and the symptoms show up early in life and are more severe. The heterozygotes are more common than homozygotes. It occurs with a higher frequency in some populations (French Canadians, Lebanese). FH can also be caused by defects in proteins essential for normal function of LDL receptors such as mutations in apoB-100.

A deficiency of LDL receptors raises blood LDL levels due to decreased uptake by the liver and increased conversion of IDL to LDL. There is deposition of cholesterol in various tissues and nodules of cholesterol called *xanthomas* are prominently seen in skin and tendons. The condition becomes more dangerous when cholesterol is deposited in coronary arteries as atherosclerotic plaques (clumps) leading to a high risk of coronary disease. Excessive intake of cholesterol in diet may also lead to similar problem. This condition is known as atherosclerosis.

A combination of dietary control and drug intervention can reduce cholesterol levels. The treatment involve the use of competitive inhibitors of HMG-CoA reductase such as atorvastatin which bring down endogenous synthesis and anion exchange resins that bind bile salts and excrete them. The increased excretion induces the liver to convert more cholesterol to bile salts. The net effect is reduction in serum cholesterol. Therefore, the use of resins in combination with statins will provide a better management.

Familial chylomicronemia

Lipoprotein lipase found predominantly in adipose tissue and cardiac and skeletal muscles helps in TAG degradation in chylomicrons and VLDL and is

important for HDL metabolism. Deficiency of this enzyme results in accumulation of significantly high amounts of chylomicrons-TAG (≥ 1000 mg/dl) in plasma even in fasting state. Such patients are at high risk for acute pancreatitis. More than 50% of the patients develop yellow fat deposits under the skin called eruptive xanthomas. These fat deposits most commonly appear on the trunk, buttocks, knees, and arms. The condition of such patients generally improves when put on low fat diet.

Familial hypobetalipoproteinemia (FHBL)

Defective synthesis of apolipoprotein B48 and B100 results into a rare but more severe disease FHBL as these is an important component of chylomicrons and VLDL. As a result, fats absorption and transport does not take place. The condition is characterized by low levels of cholesterol in plasma. There is build up of fats in liver known as liver steatosis or fatty liver which in severe cases leads to chronic liver cirrhosis. Growth is stunted, absorption of fats and fat soluble vitamins A and E is disrupted and excessive fats are excreted in feaces (steatorrhea). Neuropathy and red blood cell deformities are also seen in such patients.

14.5 SUMMARY

- Disorders of lipid metabolism are generally inherited autosomal recessive disorders which occur due to defect or deficiency of a particular enzyme or protein involved in metabolic pathways.
- Fatty acid oxidation disorders are due to absence or deficiency of the enzymes needed to break down fatty acids for energy. This leaves the body short of energy and results in accumulation of breakdown products, such as acyl-CoA, to accumulate.
- Disorders at β oxidation of lipids include MCAD deficiency, carnitine acyl transferase-I (CAT-I) deficiency, carnitine deficiency and Zellweger's Syndrome. Refsum's disease is due to deficiency of peroxisomal α hydroxylase enzyme.
- Lipid storage disease are the group of genetic diseases due to defect in some enzyme involved in catabolism of lipids, especially sphingolipids. As a result, product of that pathway accumulates in lysosomes of the tissue in which catabolism occurs leading to various symptoms which may range from muscle weakness, neurological disorders, organ enlargement to failure and finally the death at early age.
- Familial hypercholesterolemia (FH) is an inborn error of lipid metabolism of hyperlipidemia type in which there is absence of deficiency or complete absence of functional LDL receptors resulting in deposition of cholesterol in various tissues including skin and tendons. It may even lead to heart attack if cholesterol is deposited in coronary arteries.
- Deficiency of lipoprotein lipase results in accumulation of significantly high amounts of chylomicrons-TAG (≥ 1000 mg/dl) in plasma even in fasted state resulting in familial chylomicronemia.

- Defective synthesis of apolipoprotein B48 and B100 results into a rare but severe disease FHBL. Fat absorption and transport is disrupted resulting in fatty liver, stunted growth and steatorrhea.

14.6 TERMINAL QUESTIONS

1. What are fatty acid oxidation disorders? Explain with help of specific examples.
2. What is Sphingolipidoses? Describe two disorders of sphingolipid catabolism.
3. What is the genetic basis of familial hypercholesterolemia (FH)? Indicate the symptoms and treatment of FH.

14.7 ANSWERS

Self-Assessment Questions

1.
 - i) Refsum's disease- α oxidation;
 - ii) Zellweger's Syndrome- β - oxidation of very long chain fatty acids.
2.
 - i) Ceramide
 - ii) Glucocerebroside
 - iii) Galactocerebroside
 - iv) Ganglioside GM2
 - v) Sphingomyelin

Terminal Questions

1. Disorders caused by absence or deficiency of the enzymes needed to break down fatty acids at the time of energy requirement are classified as fatty acid oxidation disorders. This leaves the body short of energy and allows breakdown products, such as acyl-CoA, to accumulate. These disorders may further be divided based on whether the defect is at the level of β or α oxidation of lipids. Refer to section 14.2 for more details.
2. These are group of genetic diseases due to defect in some enzyme involved in catabolism of lipids, especially sphingolipids. As a result, product of that pathway accumulates in lysosomes of the tissue in which catabolism occurs leading to various symptoms. Refer to the section 14.3 for more details.
3. Familial hypercholesterolemia is an inborn error of lipid metabolism of hyperlipidemia type in which there is absence of deficiency or complete absence of functional LDL receptors. As a result, LDL cannot enter liver leading to very high plasma levels of LDL- cholesterol. The condition becomes more dangerous when cholesterol is deposited in coronary arteries as atherosclerotic plaques, leading to their narrowing and blockage and finally the heart attack.

SUGGESTED READINGS

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