NATIONAL OPEN UNIVERSITY OF NIGERIA

NSC 207

Medical Biochemistry

Module 4

NSC 207 (Medical Biochemistry II)
Module 4

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Published in 2021 by the National Open University of Nigeria

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Unit 1 Sources of Amino Acids

1.0 Introduction

Amino acids are the monomeric units of proteins. Metabolism of amino acids involves the breakdown of amino acids and how amino acids are synthesized. Breakdown of amino acids involves the removal of amino group and utilization of carbon skeleton for the production of other essential biological molecules in the cell. Part of this is also used in the synthesis of other amino acids required.

2.0 Objectives

At the end of this unit, you should be able to:

- discuss the sources and metabolism of amino acids
- describe the fate of free amino acids
- explain the digestion of dietary protein
- explain the degradation of endogenous amino acid.

3.0 Main Content

3.1 Sources of Amino Acids

Amino acids are obtained from dietary proteins (the food). They are also derived from the breakdown of endogenous enzymes, receptors and other cellular proteins. The third source of amino acids is through direct synthesis. This is limited to essential amino acids only. Human diets contain proteins and amino acids; the amino acids that cannot be synthesized must be supplied through the diets. These amino acids are called essential amino acids while those that can be synthesized are called non-essential amino acids; that is, it is not necessary to include them in the diet.

When sufficient quantity of the non-essential amino acids are in the diet, it may not be necessary to synthesize them, synthesis of these amino acids takes place when there is deficiency.

3.2 Fate of Free Amino Acids

The primary source of free amino acids in the body is the breakdown of dietary protein. Free amino acids are used mainly to synthesize proteins, but they also serve as precursors for a variety of nitrogenous compounds. Amino acids present in amount exceeding the quantities needed by the body cannot be stored. Instead they are degraded to yield ammonia and intermediates of carbohydrate and lipid anabolism (synthesis). The intermediates can be converted to glucose or fatty acids or oxidized to yield energy. Ammonia is used to synthesize glutamine (The principal fate of free ammonia) and glutamate. Free excess ammonia is used to make urea which is excreted in the urine.

3.3 Digestion of Dietary Protein

Protein digestion begins in the stomach. Gastric mucosa cells secrete HCl and pepsinogen, (the zymogen precursor of the proteolytic enzyme pepsin). Pepsin requires the acid environment of the stomach for optimal activity (pH 2 to 3). In addition, the acidity of gastric juice probably denatures the proteins in some uncooked foods, rendering them more susceptible to proteolytic attack. Pepsin rapidly attacks the peptide bonds involving the carbonyl group of phenylalanine, tyrosine and tryptophan. It also shows some activity towards peptide bonds involving aliphatic and acidic residues.

The pancrease secretes an alkaline mixture into the small intestine; the mixture contains a number of proteases in inactive form: trypsonogen, several chymotripsinogens, proelastase and pro-carboxypeptidase A and B. Trypsinogen in converted to active trypsin by enteropeptidase. The resulting trypsin then activates the other zymogens to the corresponding active enzymes. The pancreatic enzymes degrade oligopeptides and polypeptide to free amino acids and short oligopeptides which are transported into the intestinal mucoasa cells.

Trypsin cleaves the peptide bonds involving the carboxyl group of lysine or arginine. Chymotrypsins are most active on peptide bonds involving the carboxyl groups of phenylalanine, tyrosine and tryptophan. Elastase is active toward peptide bonds involving neutral aliphatic amino acids. Carboxypepetidase A releases aliphatic and aromatic amino acids one at a time from the c-terminus. Carboxypeptidase B releases c-terminal lysine or arginine residues.

The digestion of small peptides is completed within the intestinal mucosal cells which contain aminopeptidase and dipeptidases. Aminopeptidases release one amino acid at a time from the N-terminus. Prolidase is a dipeptidase specific for dipeptides containing proline in the carboxyl position.

3.4 Degradation of Endogenous Proteins

Endogenous proteins contribute to the supply of free amino acid in two ways. Proteins are degraded in cells by free lysosomal proteases; in addition proteins in the gastric and pancreatic secretions are digested and absorbed in the same way as dietary proteins.

Essential amino acids	**Non essential amino acids**
Phenylalanine	Glycine
Tryptophan	Alanine
Hisidine	Proline
Valine	Tyrosine
Isoleucine	Serine
Arginine	Cysteine
Threonine	Glutamic acid
Methionine	Glutamine
Lysine	Aspartic acid
Leucine	Asparagines

Tissue Distribution of amino acid metabolism
The principal site of amino acid metabolism is the liver, which is able to take up all the amino acids from the circulation. Muscle shows a preference for the uptake of valine, isoleucine and leucine, brain preferentially takes up valine. Therefore, muscle and brain contribute significantly to the metabolism of branched chain amino acids. Ammonia produced as a result of amino acids degradation in the tissues is excreted in the urine but alanine and serine are transported to the liver for further metabolism.

3.5 Catabolism of Amino Acids

Amino acids are degradation in two steps: Removal of the α-amino group and conversion of the carbon chain to an intermediate of lipid and carbohydrate metabolism.

Removal of the α-amino group (Nitrogen)
Removal of the amino group from amino acids is accomplished by variety of processes such as transamination, oxidative and non-oxidative deamination.

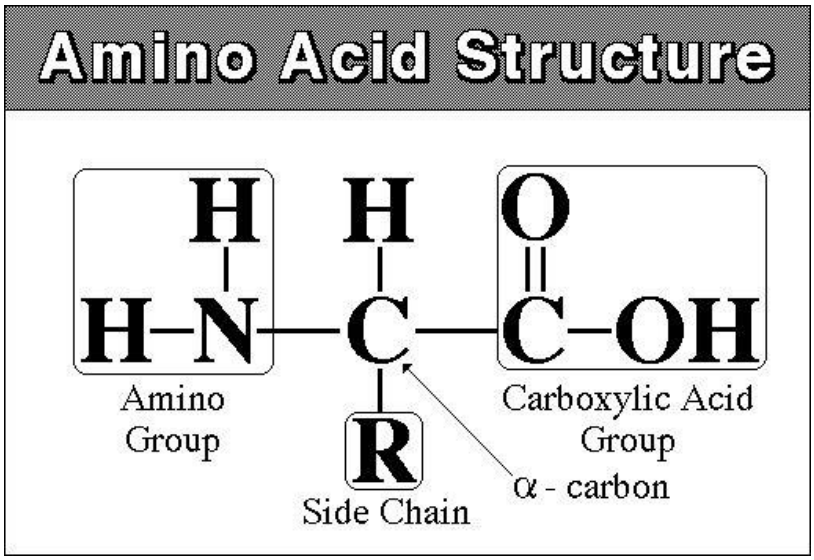
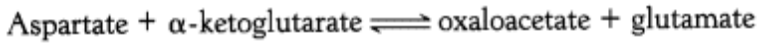


Figure 1.1a: The structure of amino acid (source- google images)

Transamination

Transamination is the transfer of amino group from an amino acid to an α-keto acid or other amino acids.



This reaction is catalysed by aminotransferases that are dependent on the cofactor pyridoxal phosphate, a derivative of vitamine B_6. The importance of transmination reaction is to collect the amino groups from different amino acid in the form of L-glutamate. The glutamate molecules channel amino groups either into biosynthetic pathway or into sequence of reaction to form nitrogenous compounds. Therefore, transamination reactions are particularly important in the eventual removal of the amino group from amino acids.

The oxidative deamination reaction is catalysed by glutamate dehydrogenase. This is the major reaction in mammal cells through which ammonia is synthesized. α-ketoglutarate acts as a sink for amino groups by accepting amino groups from various amino acids, with the resultant formation of glutamate. In mammals, all α- amino acids can undergo transamination, except lysine and threonine. The glutamate dehydrogenase (GDH) in animal tissues occurs in the inner matrix of mitochondria and will utilize NAD^+ or $NADP^+$. GDH system use NAD or NADP but not both. The coupling of transamination and deamination reactions; catalysed by glutamic acid dehydrogenase account for most of the ammonia production in animals. The combined action of amino transferase and glutamate dehydrogenase is referred to as transdeamination and provide a common route for removing and producing nitrogen.

Toxicity of Ammonia

Ammonia is a gas which exists in tissue fluids, predominantly as NH_4^+ (Ammonium). Urea is the main nitrogenous excretory product of amino acids and protein metabolism in most terrestrial vertebrates; these animals are referred to as ureotelic organisms. Birds and reptiles eliminate excess nitrogen by converting it to uric acid which is excreted with little loss of water. These animals are called unicotelic organisms.

Ammonium is absorbed from the upper and lower GIT. The larger quantity of NH_3 is produced in the hepatic cells of the liver primarily by oxidative or non-oxidative deamination of amino acids. The ammonia is absorbed into portal venous blood and rapidly removed from circulation by the liver and converted to urea. Urea is non-toxic and highly water soluble, thus only traces are present in peripheral blood. This is essential, since ammonia is toxic to the central nervous system. Should portal blood bypass the liver, systemic blood ammonia levels may attain toxic levels. This occurs in severely impaired hepatic function. Symptoms of ammonia intoxication include tremor, slured speech, blurred vision, coma and ultimately death. Ammonia may also be toxic to the brain because it reacts with α-ketoglutarate to form glutamate. The resulting depletion of levels of α-ketoglutarate impairs function of the TCA cycle in neurons.

Degradation of carbon chain of Amino Acids

The first phase of amino acid degradation is the removal of amino group through deamination or transamination reactions. The second phase is the conversion of carbon chains to intermediates of carbohydrate or lipid metabolism. All amino acids give rise to one or more of the following substances; pyruvate, *oxaloacetate,* fumarate, succinyl COA, *α-ketoglutarate,* acetyl COA and acetoacetyl COA.

Amino acids whose degradation products make possible a net synthesis of glucose are called *glycogenic or glucogenic*, whereas amino acids whose products can be used for a net synthesis of fatty acids or ketone bodies are called *ketogenics*. Products of glycogenic amino acids are; Pyruvate, oxaloacetate, fumarate, succinyl COA and α-ketoglutarate products of ketogenic amino acids are acetyl COA and acetoacetyl COA. Some amino acids generate products of both groups and are therefore glycogenic and ketogenic.

Glycogenic amino acids are:-

Alamine	Methionine
Asparagines	Proline
Aspartate	Serine
Arginine	Thronine
Cysteine	Tyrosine
Glutamate	Tryptophan
Glutamine	Valine
Histidine	Phenylalanine
Isoleucine	

Ketogenic amino acids are leucine and lysine

Glycogenic and ketogenic amino acids are: isolencine, phenytalanine, tyrosine and tryptophan.

Historically, an amino acid was classified as glycogenic or ketogenic depending whether its administration to diabetic animals resulted in an increase in urinary excretion of glucose or of ketone bodies respectively. In animals that are neither fasted nor diabetic, intermediates of amino acid degradation are oxidized by the TCA cycle to produce energy.

4.0 Conclusion

5.0 Summary

In this unit, you have been taken through the following:

- Sources of Amino Acids
- Fate of Free Amino Acids
- Digestion of Dietary Protein
- Degradation of endogenous proteins
- Catabolism of amino acids.

6.0 Self Assessment Exercise

1. Discuss the sources and Metabolism of Amino Acids
2. Describe the fate of free amino acids
3. Explain the digestion of dietary protein

4. Explain the degradation of endogenous amino acid

Activity: Your course facilitator would contact you on a practical assignment you are to carry out.

7.0 References/Further Reading

Katherine, M. A. Rogers and William N. Scott (2011). Nurses! Test yourself in anatomy and physiology

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Unit 2 Disorders of Amino Acid Metabolism

1.0 Introduction

Disorder of amino acid metabolism results from deficiency or complete absence of a particular enzyme required to complete the metabolism of some amino acids. All of them are genetically inherited diseases. Some of the disorders are as follows:

2.0 Objectives

At the end of this unit, you should be able to:

- explain the following Amino acid metabolism disorders in details.

✓ Phenylketonuria (PKU)

✓ Albinism

✓ Alkoptonuria

✓ Maple syrup Urine disease.

3.0 Main Content

3.1 Phenylketonuria (PKU)

PKU occurs when phenylalanine hydroxylase activity is absent or significantly reduced (this enzyme is responsible for the degradation of phenylalanine). Phenylalanine (PA) accumulates, which stimulates the metabolism of PA by alternative pathways resulting in urinary excretion of high amounts of phenyllactate, phenylpyruvate, o-hydroxylphenylacetate, and phenyl acetylglutamine as well as phenylalanine. It may lead to neurological problems.

3.2 Albinism

Melanin is the black pigment of human skin, it is synthesized inside the melanocytes from tyrosine. In the first 2 steps of melanin formation, tyrosine is converted to dihydroxy phenylalanine (DOPA) and then to DOPA quinone by tyrosinase. DOPA quinone is then converted to melanin. If there is tyrosinase deficiency, DOPA quinine will not be converted to melanin. Therefore, deficiency of tyrosinase is the cause of certain types of albinism. It is also responsible for gray hair; hair becomes grey in the absence of melanin. Albinism is an example of inborn errors of metabolism.

3.3 Alkoptonuria

In alkaptonuria, the enzyme homogentisate oxidase required for tyrosine metabolism is deficient. High amounts of homogentisate are excreted in the urine which causes the urine to darken gradually or rapidly due to oxidation of homogenetisate. Clinical conditions resulting from this disorder is called ochronosis and in later years arthritis.

3.4 Maple Syrup Urine Disease

The first 2 steps in the degradation of branched chain amino acids such as valine, leucine and isoleucine are identical (Transamination followed by oxidative decarboxylation). The decarboxylation reaction is catalysed by the branched chain α-keto acid dehydrogenase complex. A genetic deficiency of this enzyme causes elevated levels of valine, isoleucine and leucine and their α-keto acids in the blood and urine. The high concentration of α-keto acids gives the urine of these patients a maple syrup odour, leading to the name maple syrup urine disease for the disorder. Clinical symptoms are poor feeding after the 1st week of life, vomiting, muscular hypertonicity and sometimes convulsion.

4.0 Conclusion

5.0 Summary

In this unit, you have been taken through the following Amino acid Metabolism disorders.

- Phenylketonuria (PKU)
- Albinism
- Alkoptonuria
- Maple syrup Urine disease.

6.0 Self Assessment Exercise

Discuss in details the following Amino acid metabolism disorders.

- Phenylketonuria (PKU)
- Albinism
- Alkoptonuria
- Maple syrup Urine disease.

Activity: Your course facilitator would inform you of a practical assignment to be carried out.

7.0 References/Further Reading

Katherine, M. A. Rogers and William N. Scott (2011). Nurses! Test yourself in anatomy and physiology

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Unit 3 Diabetes Mellitus

1.0 Introduction

Diabetes mellitus is a complex disease that affects several hundred million people. Diabetes is characterized by an elevated level of glucose in the blood and in the urine. Glucose is excreted in the urine when the blood glucose level exceeds the reabsorptive capacity of the renal tubules. Water accompanies the excreted glucose, and so an untreated diabetic in the acute phase of the disease is hungry and thirsty. The loss of glucose depletes the carbohydrate stores, which leads to the breakdown of fat and protein.

The mobilization of fats results in the formation of large amounts of acetyl CoA. Ketone bodies (acetoacetate, acetone, and hydroxybutyrate) are formed when acetyl CoA cannot enter the citric acid cycle because there is insufficient oxaloacetate.(oxaloacetate is derived from glucose and some amino acids). The excretion of ketone bodies impairs the acid-base balance and causes further dehydration, which may lead to coma and death in the acute phase of the disease in an untreated diabetic.

2.0 Objectives

At the end of this unit, you should be able to:

- describe the metabolic changes that accompany diabetes mellitus
- explain the classification of diabetes mellitus and distinguish the different types of diabetes in terms of metabolic features, symptoms and time of onset
- describe how diabetes mellitus is diagnosed and the mode of action of medications used in treatment of diabetes.

3.0 Main Content

3.1 Diabetes Mellitus

Diabetes mellitus, caused by a deficiency in the secretion or action of insulin, is a relatively common disease: nearly 6% of the United States population shows some degree of abnormality in glucose metabolism that is indicative of diabetes or a tendency toward the condition. There are two major clinical classes of diabetes mellitus: **type I diabetes,** or insulin dependent diabetes mellitus (IDDM), and **type II diabetes,** or non-insulin-dependent diabetes mellitus (NIDDM), also called insulin-resistant diabetes.

Type I Diabetes

In type I diabetes, the disease begins early in life and quickly becomes severe. This disease responds to insulin injection, because the metabolic defect stems from a paucity of pancreatic _ cells and a consequent inability to produce sufficient insulin. IDDM requires insulin therapy and careful, lifelong control of the balance between dietary intake and insulin

dose. Characteristic symptoms of type I (and type II) diabetes are excessive thirst and frequent urination (polyuria), leading to the intake of large volumes of water (polydipsia) ("diabetes mellitus" means "excessive excretion of sweet urine"). These symptoms are due to the excretion of large amounts of glucose in the urine, a condition known as **glucosuria.**

Type II Diabetes

Type II diabetes is slow to develop (typically in older, obese individuals), and the symptoms are milder and often go unrecognized at first. This is really a group of diseases in which the regulatory activity of insulin is defective: insulin is produced, but some feature of the insulin-response system is defective. These individuals are insulin-resistant. The connection between type II diabetes and obesity (discussed below) is an active area of research.

Individuals with either type of diabetes are unable to take up glucose efficiently from the blood; recall that insulin triggers the movement of GLUT4 glucose transporters to the plasma membrane of muscle and adipose tissue. Another characteristic metabolic change in diabetes is excessive but incomplete oxidation of fatty acids in the liver. The acetyl-CoA produced by _ oxidation cannot be completely oxidized by the citric acid cycle, because the high [NADH]/[NAD_] ratio produced by β _ oxidation inhibits the cycle (recall that three steps convert NAD_ to NADH). Accumulation of acetyl-CoA leads to overproduction of the ketone bodies acetoacetate and β-hydroxybutyrate, which cannot be used by extrahepatic tissues as fast as they are made in the liver.

In addition to _ β -hydroxybutyrate and acetoacetate, the blood of diabetics also contains acetone, which results from the spontaneous decarboxylation of acetoacetate: Acetone is volatile and is exhaled, and in uncontrolled diabetes, the breath has a characteristic odor sometimes mistaken for ethanol. A diabetic individual who is experiencing mental confusion due to high blood glucose is occasionally misdiagnosed as intoxicated, an error that can be fatal. The overproduction of ketone bodies, called **ketosis,** results in greatly increased concentrations of ketone bodies in the blood (ketonemia) and urine (ketonuria).

3.2 Classification of Diabetes

Type I DM

About 10% of all diabetic persons are classified as type I. It usually appears in childhood or teenage, but it is not limited to young people.

In this disease, there is very low or complete absence of insulin production by the pancreas, because of defective β-cell function, the result of an autoimmune process. There is severe derangement of carbohydrate, lipid and protein metabolism, leading to

Hyperglycemia: As a result of inability of insulin-dependent tissues to take up glucose and from accelerated hepatic gluconeogenesis from amino acids derived from muscle protein

Hypertriglyceridemia: Because VLDL and Chylomicrons cannot be cleared from the blood by lipoprotein lipase, whose expression is dependent upon insulin.

Severe episodes of Ketoacidosis: This results from increased lipolysis in adipose tissue which increases plasma fatty acid levels and ketone body production by the liver.

In type 1 DM, every tissue plays the catabolic role that it was designed to play in starvation, in spite of adequate or even excess fuel from the gut. This results ultimately in death unless insulin is administered. Administered insulin promotes glucose uptake and inhibits gluconeogenesis, lipolysis and proteolysis. However, it is necessary to adjust the insulin dose to variable dietary intake and physical activity. tight control of blood sugar requires several injections of insulin per day and close blood sugar monitoring by the patient.

Type 2 Diabetes mellitus

Nearly 90% of diabetic persons are of type 2. It is also called adult-onset diabetes because it usually occurs in middle aged to elderly people.

Aging, physical inactivity, western culture lifestyle, obesity and family history of diabetes are risk factors. It typically occurs in the setting of metabolic syndrome, which also includes abdominal obesity, hypertension and hyperlipidemia

Type 2 diabetics are resistant to insulin and have insufficient production of insulin to overcome the resistance. The majority of patients are obese, and although their insulin levels are high, they are not as high as those of non-diabetic but similarly obese persons.

Recent work implicate increased level of tumor necrosis factorα (TNFα) and resistin as well as reduced secretion of adiponectin as a cause of insulin resistance.The greater the adipose tissue mass, the greater the production of TNFα which impairs insulin action. Uncontrolled glucose production by the liver and low uptake by the skeletal muscle results in hyperglycemia. Hypertriglyceridemia is also seen, as a result of increased VLDL.

Ketoacidosis is rare in this type of diabetes.

Diet alone can control the disease in the obese diabetic as insulin receptors increase and post –receptor abnormalities improve, which will increase tissue sensitivity to insulin and glucose tolerance.

Table 3.1: Type 1 & Type 2 Diabetes

Variable	Type 1	Type 2
Insulin deficiency	Always present	Variable
	Often total	Never absolute
Onset of symptoms	Usually abrupt	Usually insidious
Ketoacidosis	Common	Rare
Need for exogenous insulin	Necessary for life	Not necessary for life

Obesity	Usually absent	Very common
Micro vascular complications	Develop in nearly all	Not a major problem
Macro vascular complications	Develop early in life	Major cause of death and morbidity

Gestational Diabetes
This is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy (especially during the 3rd trimester). It is caused by abnormal function of insulin receptors due to hormonal interference. Such women are at risk of developing Type 2 DM. Babies born are large for gestational age and may develop low blood sugar and jaundice.

3.3 Diagnosis of Diabetes

Table 3.2

Criteria for diagnosis of diabetes using oral glucose test (glucose in plasma , mg/dl, measured before and after a 75g oral glucose load)

Time	Normal adults	Impaired glucose tolerance	Diabetic adults	Gestational diabetic patients	Diabetic children
Fasting	<115	<140	>140	>105	>140
I hour	<200	<200	>200	>195	>200
2 hours	<140	140-200	>200	>165	>200
3 hours	<140	140-200	>200	>145	>200

Measurement of glycated haemoglobin (Hemoglobin A_{1c}) is also used for diagnosis of Diabetes. The reaction occurs by a non enzymatic reaction between glucose and the amino-terminal valine of the Hb α chain and is favoured by high glucose levels. The concentration of Hb1c is a good index of glucose level control. Glycation of proteins may contribute to the development of complications in Diabetes. An HbA1c of 6.5% is recommended as the cut off point for diagnosing diabetes.

Medications are usually targeted at controlling hyperglycemia. These Medications include

Thiazolidinediones: Sensitizes peripheral tissues to insulin action

Metformin: Reduces hepatic gluconeogenesis

Sulfonyl Ureas: Stimulate insulin secretion from β cells.

Insulin administration is essential for treatment of type 1 DM and is often used in selected patients with type 2 diabetes.

4.0 Conclusion

5.0 Summary

In this unit, you have been taken through the following:

- Concept of Diabetes Mellitus
- Classification of Diabetes
- Diagnosis of Diabetes

6.0 Self Assessment Exercise

1. Describe the metabolic changes that accompany Diabetes Mellitus
2. Explain the classification of Diabetes Mellitus and distinguish the different types of Diabetes in terms of metabolic features, symptoms and time of onset
3. Describe how Diabetes mellitus is diagnosed and the mode of action of medications used in treatment of Diabetes.

Activity: Your course facilitator would contact you on a practical assignment you are to perform.

7.0 Reference/Further Reading

Katherine, M. A. Rogers and William N. Scott (2011). Nurses! Test yourself in anatomy and physiology

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