MEDICAL BIOCHEMISTRY

HUMAN METABOLISM IN HEALTH AND DISEASE

MIRIAM D. ROSENTHAL
ROBERT H. GLEW

WILEY

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MEDICAL BIOCHEMISTRY

PREFACE

Human metabolism is a key component of the basic science knowledge that underlies the practice of medicine and allied health professions. It is fundamental to understanding how the body adapts to physiologic stress, how defects in metabolism result in disease, and why data from the clinical chemistry laboratory are useful to diagnose disease and monitor the efficacy of treatment. Over the more than three decades that each of the authors has been teaching biochemistry to medical students, we have found students increasingly overwhelmed with details that tend to obscure rather than elucidate principles of human metabolism.

Our main aim in writing this book was to provide students in the health professions with a concise resource that will help them understand and appreciate the functions, constituent reactions, and regulatory aspects of the core pathways that constitute human metabolism and which are responsible for maintaining homeostasis and well-being in humans. We have tried to accomplish this by emphasizing function, regulation, and disease processes, while minimizing discussion of reaction mechanisms and details of enzyme structure.

Each chapter is organized in a consistent manner beginning with an explanation of the main functions of the pathway under discussion. Next comes a brief accounting of the cells, tissues, and organs in which the pathway is expressed and the conditions under which the normal function of the pathway is especially important. The bulk of each chapter is devoted to the reactions that account for the function of the pathway, with emphasis on key steps in the pathway. The next section of each chapter discusses the ways in which the activity of the pathway is regulated by hormones, genetic factors, or changes in the intracellular concentration of key metabolites. Each chapter concludes with a discussion of the more common and illustrative diseases that result from defects in or derangements of regulation of the pathway.

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This volume is deliberately modest in size. Instead of providing exhaustive coverage of all the reactions that human cells and tissues are capable of executing, we have chosen examples that illustrate the physiologic and pathophysiologic significance of the topic. The authors' expectation is that each chapter will be read for comprehension rather than to provide abundant fact and detail. During their subsequent education and professional careers, the readers will undoubtably have need for more information on many topics discussed in this book. We hope that this book will provide them with the tools to comprehend and appreciate the detailed resources—both print and electronic—that contain the ever-expanding body of knowledge on human metabolism in health and disease.

MIRIAM D. ROSENTHAL
ROBERT H. GLEW

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THE AUTHORS

Miriam D. Rosenthal, Ph.D., is Professor of Biochemistry at Eastern Virginia Medical School. She received her B.A. in biology from Swarthmore College in 1963, followed by M.S. (1968) and Ph.D. (1974) degrees in biology from Brandeis University. Since 1977, Dr. Rosenthal has developed curricula, provided instruction, and conducted assessment of medical and other health professions students in biochemistry, molecular biology, cell biology, and human genetics. She has served as Course Director of Medical Biochemistry since 1997.

Robert H. Glew, Ph.D., is Emeritus Professor of Biochemistry and Molecular Biology at the University of New Mexico School of Medicine, where he was chair of the department from 1990 to 1998. He received a B.S. in food science from the University of Massachusetts, Amherst in 1962, M.S. in nutrition and food science from the Massachusetts Institute of Technology in 1964, and Ph.D. in biochemistry from the University of California, Davis in 1968. Dr. Glew has taught medical biochemistry at half a dozen medical schools and teaching hospitals in the United States and West Africa.

Drs. Rosenthal and Glew previously coedited *Clinical Studies in Medical Biochemistry* (3rd ed., 2006, Oxford University Press, New York). The book uses case presentations to develop the contextual basis of human metabolism, nutrition, and the molecular bases of disease.

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CHAPTER 1

INTRODUCTION TO METABOLISM

1.1 INTRODUCTION

Intermediary metabolism is the name given to the sequences of biochemical reactions that degrade, synthesize, or interconvert small molecules inside living cells. Knowledge of the core metabolic pathways and their interrelations is critical to understanding both normal function and the metabolic basis of most human diseases. Rational interpretation and application of data from the clinical chemistry laboratory also requires a sound grasp of the major metabolic pathways. Furthermore, knowledge of key biochemical reactions in the two dozen or so core metabolic pathways in humans is essential for an understanding of the molecular basis of drug action, drug interactions, and the many genetic diseases that are caused by the absence of the activity of a particular protein or enzyme.

1.1.1 Metabolic Pathways

Metabolism occurs in small discrete steps, each of which is catalyzed by an enzyme. The term *metabolic pathway* refers to a particular set of reactions that carries out a certain function or functions. The pathway of gluconeogenesis or glucose synthesis, for example, operates mainly during a period of fasting, and its primary function is to maintain the concentration of glucose in the circulation at levels that are required by glucose-dependent tissues such as the brain and red blood cells. Another example of a metabolic pathway is the tricarboxylic acid (TCA) cycle, which oxidizes the two

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carbons of acetyl-coenzyme A (acetyl-CoA) to CO_2 and water, thus completing the catabolism of carbohydrates, fats (fatty acids), and proteins (amino acids).

1.1.2 Metabolic Intermediates

Biochemical pathways are comprised of organic compounds called *metabolic intermediates*, all of which contain carbon, hydrogen, and oxygen. Some metabolic intermediates also contain nitrogen or sulfur. In most instances, these compounds themselves have no function. An exception would be a compound such as citric acid, which is both an intermediate in the TCA cycle and a key regulator of other pathways, including oxidation of glucose (glycolysis) and gluconeogenesis.

1.1.3 Homeostasis

Homeostasis refers to an organism's tendency or drive to maintain the normalcy of its internal environment, including maintaining the concentration of nutrients and metabolites within relatively strict limits. A good example is glucose homeostasis. In the face of widely varying physiological conditions, such as fasting or exercise, both of which tend to lower blood glucose, or following the consumption of a carbohydrate meal that raises the blood glucose concentration, the human body activates hormonal mechanisms that operate to maintain blood glucose within rather narrow limits, 80 to 100 mg/dL (Fig. 1-1). Hypoglycemia (low blood glucose) stimulates the release of gluconeogenic hormones such as glucagon and hydrocortisone, which promote the breakdown of liver glycogen and the synthesis of glucose in the liver (gluconeogenesis), followed by the release of glucose into the blood. On the other hand, hyperglycemia (elevated blood glucose) stimulates the release of insulin, which promotes the uptake of glucose and its utilization, storage as glycogen, and conversion to fat.

Maintenance of the blood calcium concentration between strict limits is another example of homeostasis. The normal total plasma calcium concentration is in the range 8.0 to 9.5 mg/dL. If the calcium concentration remains above the upper limit of normal for an extended period of time, calcium may deposit, with pathological consequences in soft tissues such as the heart and pancreas. Hypocalcemia (a.k.a. tetany) can result in muscle paralysis, convulsions, and even death; chronic hypocalcemia causes rickets in children and osteomalacia in adults. The body uses vitamin D and certain hormones (e.g., parathyroid hormone, calcitonin) to maintain calcium homeostasis.

1.2 WHAT DO METABOLIC PATHWAYS ACCOMPLISH?

1.2.1 Generation of Energy

The primary dietary fuels for human beings are carbohydrates and fats (triacylglycerols). The human body also obtains energy from dietary protein and—for some

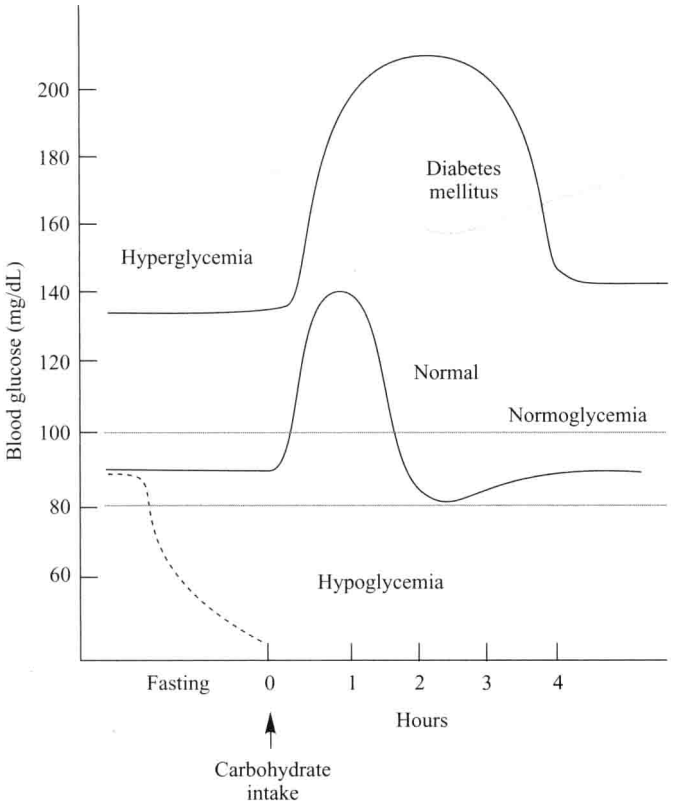

FIGURE 1-1 Changes that occur in the blood glucose concentration in a healthy adult, a person with type II diabetes mellitus, and a person experiencing fasting hypoglycemia. Following ingestion of a carbohydrate-containing meal, there are three features that distinguish the glucose vs. time curve for the person with type II diabetes relative to the healthy adult: (1) the initial blood glucose concentration is higher (approx. 135 vs. 90 mg/dL), (2) the rise in in the glucose level following the meal is greater; and (3) it takes longer for the glucose concentration to return to the fasting glucose level.

people—ethanol. Metabolism of these fuels generates energy, much of which is captured as the high-energy molecule adenosine triphosphate (ATP) (Fig. 1-2). The ATP can be used for biosynthetic processes (e.g., protein synthesis), muscle contraction, and active transport of ions and other solutes across membranes.

1.2.2 Degradation or Catabolism of Organic Molecules

Catabolic pathways usually involve cleavage of C–O, C–N, or C–C bonds. Most intracellular catabolic pathways are oxidative and involve transfer of reducing equivalents (hydrogen atoms) to nicotinamide-adenine dinucleotide (NAD^+) or flavine-adenine dinucleotide (FAD). The reducing equivalents in the resulting NADH or

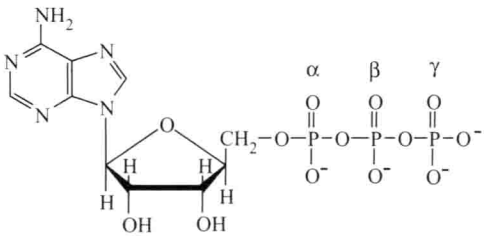

FIGURE 1-2 Structure of adenosine triphosphate.

$FADH_2$ can then be used in biosynthetic reactions or transferred to the mitochondrial electron-transport chain for generation of ATP.

1.2.2.1 Digestion. Before dietary fuels can be absorbed into the body, they must be broken down into simpler molecules. Thus, starch is hydrolyzed to yield glucose, and proteins are hydrolyzed to their constituent amino acids.

1.2.2.2 Glycolysis. Glycolysis is the oxidation of glucose into the three-carbon compound pyruvic acid.

1.2.2.3 Fatty Acid Oxidation. The major route of fatty acid degradation is β-oxidation, which accomplishes stepwise two-carbon cleavage of fatty acids into acetyl-CoA.

1.2.2.4 Amino Acid Catabolism. Breakdown of most of the 20 common amino acids is initiated by removal of the α-amino group of the amino acid via transamination. The resulting carbon skeletons are then further catabolized to generate energy or are used to synthesize other molecules (e.g., glucose, ketones). The nitrogen atoms of amino acids can be utilized for the synthesis of other nitrogenous compounds, such as heme, purines, and pyrimidines. Excess nitrogen is excreted in the form of urea.

1.2.3 Synthesis of Cellular Building Blocks and Precursors of Macromolecules

1.2.3.1 Gluconeogenesis: Synthesis of Glucose. This pathway produces glucose from glycerol, pyruvate, lactate, and the carbon skeletons of certain (glucogenic) amino acids. Gluconeogenesis is crucial to maintaining an adequate supply of glucose to the brain during fasting and starvation.

1.2.3.2 Synthesis of Fatty Acids. Excess dietary carbohydrates and the carbon skeletons of ketogenic amino acids are catabolized to acetyl-CoA, which is then utilized for the synthesis of long-chain (C16 and C18) fatty acids. Storage of these fatty acids as adipocyte triacylglycerols provides the major fuel source during the fasted state.

1.2.3.3 Synthesis of Heme. Heme is a component of the oxygen-binding proteins hemoglobin and myoglobin. Heme also functions as part of cytochromes, both in the mitochondrial electron transport chain involved in respiration-dependent ATP synthesis and in certain oxidation–reduction enzymes, such as the microsomal mixed-function oxygenases (e.g., cytochrome P450). Although most heme synthesis occurs in hemopoietic tissues (e.g., bone marrow), nearly all cells of the body synthesize heme for their own cytochromes and heme-containing enzymes.

1.2.4 Storage of Energy

Cells have only a modest ability to accumulate ATP, the major high-energy molecule in human metabolism. The human body can store energy in various forms, described below.

1.2.4.1 Creatine Phosphate. Most cells, especially muscle, can store a limited amount of energy in the form of creatine phosphate. This is accomplished by a reversible process catalyzed by creatine kinase:

$$\text{ATP} + \text{creatine} \rightleftharpoons \text{creatine phosphate} + \text{ADP}$$

When a cell's need for energy is at a minimum, the reaction tends toward the right. By contrast, when the cell requires ATP for mechanical work, ion pumping, or as substrate in one biosynthetic pathway or another, the reaction tends to the left, thereby making ATP available.

1.2.4.2 Glycogen. Glycogen is the polymeric, storage form of glucose. Nearly all of the body's glycogen is contained in muscle (approximately 600 g) and liver (approximately 300 g), with small amounts in brain and type II alveolar cells in the lung. Glycogen serves two very different functions in muscle and liver. Liver glycogen is utilized to maintain a constant supply of glucose in the blood. By contrast, muscle glycogen does not serve as a reservoir for blood glucose. Instead, muscle glycogen is broken down when that tissue requires energy, releasing glucose, which is subsequently oxidized to provide energy for muscle work.

1.2.4.3 Fat or Triacylglycerol. Whereas the body's capacity to store energy in the form of glycogen is limited, its capacity for fat storage is almost limitless. After a meal, excess dietary carbohydrates are metabolized to fatty acids in the liver. Whereas some of these endogenously synthesized fatty acids, as well as some of the fatty acids obtained through the digestion of dietary fat, are used directly as fuel by peripheral tissues, most of these fatty acids are stored in adipocytes in the form of triacylglycerols. When additional metabolic fuel is required during periods of fasting or exercise, the triacylglycerol stores in adipose are mobilized and the fatty acids are made available to tissues such as muscle and liver.

1.2.5 Excretion of Potentially Harmful Substances

1.2.5.1 Urea Cycle. This metabolic pathway takes place in the liver and synthesizes urea from the ammonia (ammonium ions) derived from the catabolism of amino acids and pyrimidines. Urea synthesis is one of the body's major mechanisms for detoxifying and excreting ammonia.

1.2.5.2 Bile Acid Synthesis. Metabolism of cholesterol to bile acids in the liver serves two purposes: (1) it provides the intestine with bile salts, whose emulsifying properties facilitate fat digestion and absorption, and (2) it is a mechanism for disposing of excess cholesterol. Humans cannot break open any of the four rings of cholesterol, nor can they oxidize cholesterol to carbon dioxide and water. Thus, biliary excretion of cholesterol—both as cholesterol per se and as bile salts—is the only mechanism the body has for disposing of significant quantities of cholesterol.

1.2.5.3 Heme Catabolism. When heme-containing proteins (e.g., hemoglobin, myoglobin) and enzymes (e.g., catalase) are turned over, the heme moiety is oxidized to bilirubin, which after conjugation with glucuronic acid is excreted via the hepatobiliary system.

1.2.6 Generation of Regulatory Substances

Metabolic pathways generate molecules that play key regulatory roles. As indicated above, citric acid (produced in the TCA cycle) plays a major role in coordinating the activities of the pathways of glycolysis and gluconeogenesis. Another example of a regulatory molecule is 2,3-bisphosphoglyceric acid, which is produced in a side reaction off the glycolytic pathway and modulates the affinity of hemoglobin for oxygen.

1.3 GENERAL PRINCIPLES COMMON TO METABOLIC PATHWAYS

1.3.1 ATP Provides Energy for Synthesis

Anabolic or synthetic pathways require input of energy in the form of the high-energy bonds of ATP, which is generated directly during some catabolic reactions (such as glycolysis) as well as during mitochondrial oxidative phosphorylation.

1.3.2 Many Metabolic Reactions Involve Oxidation or Reduction

During catalysis, oxidative reactions transfer reducing equivalents (hydrogen atoms) to cofactors such as NAD^+, $NADP^+$ (nicotinamide-adenine dinucleotide phosphate) or FAD. Reduced NADH and $FADH_2$ can then be used to generate ATP through oxidative phosphorylation in mitochondria. NADPH is the main source of reducing equivalents for anabolic, energy-requiring pathways such as fatty acid and cholesterol synthesis.

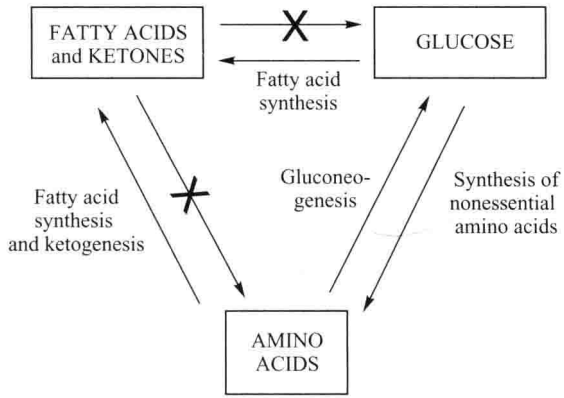

FIGURE 1-3 Possible interconversions of the three major metabolic fuels in humans. Note that glucose and amino acids cannot be synthesized from (even-carbon) fatty acids.

1.3.3 Only Certain Metabolic Reactions Occur in Human Metabolism

It is important to appreciate that although humans possess the machinery to interconvert many dietary components, not all interconversions are possible. Thus, humans can convert glucose into long-chain fatty acids, but they cannot convert even-carbon-numbered long-chain fatty acids into glucose (Fig. 1-3).

1.3.4 Some Organic Molecules Are Nutritionally Essential to Human Health

Certain key cellular components cannot be synthesized in the body and must therefore be provided preformed in the diet and are therefore designated as *essential*. These molecules include two polyunsaturated fatty acids (linoleic and α-linolenic) and the carbon skeletons of some of the amino acids. They also include the vitamins (such as thiamine and niacin), most of which serve as components of enzymatic cofactors. By contrast, other important compounds, such as glucose and palmitic acid, are not essential in the diet. Glucose, whose blood levels are crucial to homeostasis, can be synthesized from glycerol, lactate, pyruvate, and the carbon skeletons of glucogenic amino acids when dietary glucose is not available.

1.3.5 Some Metabolic Pathways Are Irreversible or Contain Irreversible Steps

One example of an irreversible pathway is glycolysis, the multistep catabolic pathway that oxidizes glucose to pyruvate or lactate. Gluconeogenesis is essentially the reverse of glycolysis and is the process by which pyruvate (or a number of other molecules such as lactate and the carbon skeleton of the amino acid alanine) can be used to synthesized glucose. Although glycolysis and gluconeogenesis share many enzymes,

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