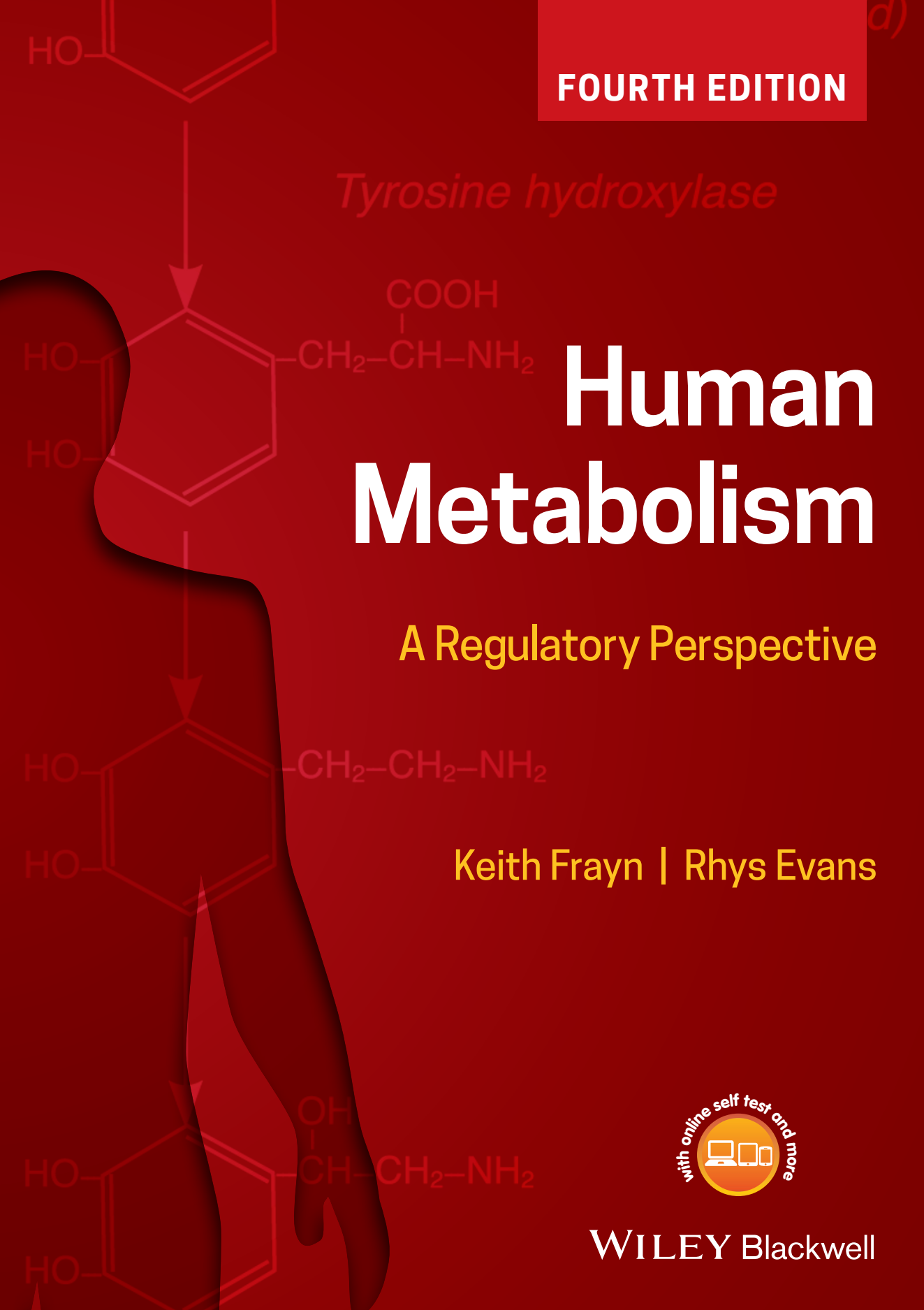
FOURTH EDITION



Human Metabolism

A Regulatory Perspective

Keith Frayn | Rhys Evans

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Human Metabolism

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A Regulatory Perspective

Fourth Edition

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This edition first published 2019 © 2019 Keith N. Frayn and Rhys D. Evans

Edition History
Portland Press (1e, 1996); Blackwell Science (2e, 2003); Wiley-Blackwell (3e, 2010).
(Editions 1 to 3 published under the title of *Metabolic Regulation: A Human Perspective*.)

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data
Names: Frayn, K. N. (Keith N.), author. | Evans, Rhys D. (Rhys David), author.
Title: Human metabolism : a regulatory perspective / Keith N. Frayn and Rhys D. Evans.
Other titles: Metabolic regulation
Description: Fourth edition. | Hoboken, NJ : Wiley-Blackwell, 2019. | Preceded by Metabolic regulation / Keith N. Frayn. 3rd ed. 2010. | Includes bibliographical references and index. |
Identifiers: LCCN 2018039797 (print) | LCCN 2018041323 (ebook) | ISBN 9781119331445 (Adobe PDF) | ISBN 9781119331469 (ePub) | ISBN 9781119331438 (paperback)
Subjects: | MESH: Metabolism—physiology | Metabolic Diseases—physiopathology | Metabolic Networks and Pathways—physiology
Classification: LCC QP171 (ebook) | LCC QP171 (print) | NLM QU 120 | DDC 612.3/9—dc23
LC record available at https://lccn.loc.gov/2018039797

Cover images: courtesy of Keith Frayn and Rhys Evans, © John Wiley & Sons, Inc.
Cover design by Wiley

Set in 10/12pt Adobe Garamond Pro by Aptara Inc., New Delhi, India

10 9 8 7 6 5 4 3 2 1

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Preface

The first edition of *Metabolic Regulation: A Human Perspective* appeared in 1996. (It was pink.) When the second edition was published (in green) in 2003, it seemed that a revolution was taking place in metabolism. Tissues that we always thought were 'doing metabolism' turned out to be secreting hormones, adipose tissue and leptin being the prime example. By 2010, when the third (blue) edition was published, there were yet more changes in our understanding of metabolism and its regulation. The regulation of gene expression by nutrients (including, for instance, the carbohydrate-response element binding protein) was much better understood than previously. The techniques of genetic manipulation had also increased our understanding of metabolic pathways. In 1996, nobody could have guessed that a mouse without the adipose tissue enzyme hormone-sensitive lipase would be viable, let alone relatively normal: that finding led to the discovery of another enzyme of fat mobilisation, adipose triglyceride lipase. Similar studies made us revise our ideas about other 'well-established' enzymes such as phosphoenolpyruvate carboxykinase. Now, in 2018, we see more radical developments in the field. We always thought that hormones were hormones and metabolites were metabolites – now we know that the distinction is far from clear, with many compounds we regard as metabolites signalling through receptors as do 'true hormones,' thereby modulating metabolism. (We note in passing that the late Derek Williamson – colleague to both of us, and mentor to one [RDE], would not have been surprised: he had long predicted that the ketone bodies had a signalling role.)

We have always recognised that this textbook needed to be regarded as a complement to a more conventional biochemistry textbook, which would give details of pathways rather than just notes on their regulation. We have both taught metabolism to biochemistry and medical students in Oxford, and for this edition decided to combine our areas of expertise and to add material to the book that would enable it to be used more independently. Thus, in Chapter 1 of this new edition, we have provided overviews of metabolic pathways that will then be described in more detail in subsequent chapters. A particular emphasis of the later chapters, as in previous editions, is the tissue-specificity of these metabolic pathways. We are aware that this textbook is used by medical and nursing students and that has prompted us to include more material relevant to metabolism in clinical situations such as cancer, sepsis, and trauma. We hope this material will be of interest to all students, including those of nutrition and sports science, as it illustrates how metabolism may be perturbed. The small revision to the title of the book reflects these changes.

We thank Michael Goran, Fredrik Karpe, Denise Robertson and Garry Tan, who have helped us by reading, and commenting on, sections of the book. Any errors remaining are our responsibility. We are enormously grateful to Anne Clark, Mike Symonds and Roy Taylor for providing pictures and data. We give special thanks to Professor Rui Fontes of the University of Porto who translated edition 3 into Portuguese, and in so doing pointed out many errors, most of which had persisted through all the editions. Jenny Seward and James Watson, and their editorial team at Wiley, have been very helpful to us as we prepared this edition. Finally, we thank Theresa and Helen for putting up with us during the hours we spent at the computer producing this new edition.

Abbreviations

Some abbreviations used only within a figure, table or box, and defined there, are not included here. Some abbreviations are given in the text not because the terms are used frequently, but because the substance in question is often better known by its abbreviation. In such cases, if the abbreviation only occurs in one limited section, it will not be listed here.

ABC (G5, G8, etc.)	ATP-binding cassette-containing protein-G5, G8 etc.
ACAT	acyl-Coenzyme A: cholesterol acyltransferase
ACC	acetyl-CoA carboxylase
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACS	acyl-CoA synthase
ACSL	long-chain acyl-CoA synthase
ACTH	adrenocorticotrophic hormone (corticotrophin)
ADH	antidiuretic hormone
ADP	adenosine 5′-diphosphate
AEE	activity energy expenditure
AGE	advanced glycation end-product
AgRP	Agouti-related protein
AIDS	Acquired ImmunoDeficiency Syndrome
ALT	alanine aminotransferase
AMP	adenosine 5′-monophosphate
AMPK	AMP-activated protein kinase
ANP	atrial natriuretic peptide
APOA, B, C, E, etc.	apolipoprotein A,B,C,E, etc.
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
ATGL	adipose triacylglycerol (or triglyceride) lipase
ATP	adenosine 5′-trisphosphate
BAT	brown adipose tissue
BCAA	branched chain amino acid
BCAT	branched chain amino acid aminotransferase
BCKD(C)	branched chain 2-oxoacid (α-ketoacid) dehydrogenase (complex)
BMCP1	brain mitochondria carrier protein 1
BMI	body mass index
BMR	basal metabolic rate
BNP	brain natriuretic peptide
cAMP	cyclic adenosine 3′, 5′-monophosphate (cyclic AMP)
CARS	compensatory anti-inflammatory response syndrome
CAT-1, 2	carnitine-acyl transferase-1, 2
CCK	cholecystokinin
CETP	cholesteryl ester transfer protein
cGMP	cyclic guanosine 3′, 5′-monophosphate (cyclic GMP)
CHD	coronary heart disease
ChRE	carbohydrate response element
ChREBP	carbohydrate response element binding protein
CIM	critical illness myopathy

CIP	critical illness polyneuropathy
CNP	C-type natriuretic peptide
CNS	central nervous system
CoA	coenzyme A
CoASH	coenzyme A reduced form
CoQ10	ubiquinone
CPT-1, 2	carnitine-palmitoyl transferase-1, 2
CSII	continuous subcutaneous insulin infusion
DHA	docosahexaenoic acid (22 : 6 *n*-3)
D-2HG	D-2-hydroxyglutarate
DIT	diet-induced thermogenesis
DPP	Diabetes Prevention Program
EDRF	endothelial-derived relaxing factor
EE	energy expenditure
eIF	eukaryotic initiation factor
eNOS	endothelial NO synthase
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
$FABP(_{pm})$	fatty acid binding protein (plasma membrane isoform)
FAD	flavin adenine dinucleotide (oxidised form)
$FADH_2$	flavin adenine dinucleotide (reduced form)
FAT	fatty acid translocase
FATP	fatty acid transport protein
FFM	fat-free mass
FGF	fibroblast growth factor
FH	familial hypercholesterolaemia
FIL	feedback inhibitor of lactation
FoxO	Forkhead box 'Other'
FQ	food quotient
FSH	follicle-stimulating hormone
FXR	farnesoid X-receptor
G	Gibbs 'free' energy
G6-P	glucose 6-phosphate
GDP	guanosine 5′-diphosphate
GH	growth hormone
GHSR	growth hormone secretagogue receptor
GIP	gastric inhibitory polypeptide, also known as glucose-dependent insulinotrophic polypeptide
GK	glucokinase
GLP (1 and 2)	glucagon-like peptide-1 and -2
GLUT	glucose transporter
GOAT	ghrelin-O-acyltransferase
GPAT	glycerol phosphate-acyl transferase
GPCR	G protein-coupled receptor
GPIHBP1	glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1
GR	glucocorticoid receptor
GSK	glycogen synthase kinase
GTP	guanosine 5′-trisphosphate
HDAC	histone deacetylation/deacetylase

HDL	high density lipoprotein
HIF-1	hypoxia-inducible factor-1
HIV	Human Immunodeficiency Virus
HK	hexokinase
HMG-CoA	3-hydroxy-3-methylglutaryl-CoA
hPL	human placental lactogen
HSL	hormone-sensitive lipase
5-HT	5-hydroxytryptamine
IDDM	insulin-dependent diabetes mellitus
IGF	insulin-like growth factor
IL	interleukin
IMM	inner mitochondrial membrane
JAK	originally Just Another Kinase; redesignated JAnus Kinase
K_a	dissociation constant for an acid
K_m	Michaelis constant
LADA	latent autoimmune diabetes in adults
LCAD	long-chain acyl CoA dehydrogenase
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LH	luteinising hormone
LPL	lipoprotein lipase
LXR	liver X-receptor
MAPK	mitogen-activated protein kinase
MET	(unit of work): 1 MET = resting metabolic rate
MI	myocardial infarction
MODS	multiple organ dysfunction syndrome
MODY	maturity-onset diabetes of the young
M_r	relative molecular mass
mRNA	messenger-RNA
MSH	melanocyte-stimulating hormone
mTOR	mammalian (or mechanistic) Target Of Rapamycin
NAD^+, NADH	nicotinamide adenine dinucleotide (+, oxidised form; H, reduced form)
$NADP^+$, NADPH	nicotinamide adenine dinucleotide phosphate (+, oxidised form; H, reduced form)
NAFLD	non-alcoholic fatty liver disease
Nam	nicotinamide
Nampt	nicotinamide phosphoribosyl transferase
NEAT	non-exercise activity thermogenesis
NEFA	non-esterified fatty acid
NHS DPP	NHS Diabetes Prevention Programme
NIDDM	non-insulin-dependent diabetes mellitus
NPC1L1	Niemann-Pick C1-like protein 1
NPR-A	natriuretic peptide-A receptor
NPY	neuropeptide Y
OMM	outer mitochondrial membrane
PAMPs	pathogen-associated molecular patterns
PCSK9	proprotein convertase subtilisin/kexin type 9
PDC	pyruvate dehydrogenase complex
PDH	pyruvate dehydrogenase
PDX1	pancreatic and duodenal homeobox 1

PET	positron emission tomography
PFK	phosphofructokinase
PGC	PPAR-γ co-activator
Pi, PPi	inorganic phosphate, pyrophosphate
PKA	protein kinase-A (cAMP-dependent protein kinase)
PKC	protein kinase-C
PKG	protein kinase-G (cGMP-dependent protein kinase)
POMC	pro-opiomelanocortin
PPAR	peroxisome proliferator-activated receptor
PPI	proton pump inhibitor
PTHrP	parathyroid hormone-related protein
RAAS	renin-angiotensin-aldosterone system
RAGE	receptor for advanced glycation end-products
RAS	renin-angiotensin system
REE	resting energy expenditure
RER	respiratory exchange ratio
ROS	reactive oxygen species
RQ	respiratory quotient
RXR	retinoid X receptor
SCN	suprachiasmatic nucleus
SGLT	sodium-glucose cotransporter
SIRS	systemic inflammatory response syndrome
SNP	single-nucleotide polymorphism
SOS	Swedish Obesity Study
SR	scavenger receptor
SREBP (-1c, -2)	sterol regulatory element binding protein (1c, 2)
STAT	Signal Transducer and Activator of Transcription
T_3	tri-iodothyronine
T_4	thyroxine
TAG or TG	triacylglycerol
TCA (cycle)	tricarboxylic acid (cycle)
TEE	total energy expenditure
TICE	trans-intestinal cholesterol efflux
TNFα	tumour necrosis factor-α
TNFR1, TNFRSF1A	TNF receptors
TR	thyroid hormone receptor
TSH	thyroid stimulating hormone
TTO (loop)	transcription translation oscillating loop
TZD	thiazolidinedione
UCP1,2,3	uncoupling protein 1, 2, 3
UDP-GlcNAc	uridine diphosphate N-acetylglucosamine
UKPDS	United Kingdom Prospective Diabetes Study
USF-1	upstream stimulatory factor-1
VCO_2	rate of CO_2 production
VLDL	very-low-density lipoprotein
V_{max}	maximal velocity of a reaction
VO_2 (max)	(maximal) rate of O_2 consumption

About the companion website

This book is accompanied by a companion website:

www.wiley.com/go/frayn

The website includes:

- PowerPoint slides of all the figures in the book for downloading
- Multiple choice questions
- Key learning points
- Further reading

CHAPTER 1

The underlying principles of human metabolism

Key learning points

- We eat food. We expend energy doing exercise, sleeping, just being. What happens to the food between it entering our mouths and its being used for energy? That's what metabolism (at least, so far as this book is concerned) is all about.
- In order to cover the periods when we are not eating, we need to store metabolic fuels. We store fuel as fat (triacylglycerol) and as carbohydrate (glycogen). Fat provides considerably more energy per gram stored. Proteins are not stored specifically as energy reserves but they may be utilised as such under certain conditions. We must regulate both the storage and mobilisation of energy to match intake to expenditure. That is what we will refer to as metabolic regulation.
- Molecules involved in metabolism differ in an important property: polarity. Polar molecules (those with some degree of electrical charge) mix with water (which is also polar); non-polar molecules, which include most lipids (fatty substances), usually don't mix with water. This has profound implications for the way they are handled in the body. They also differ in the amount of energy they contain, affecting their efficiency as fuels.
- Some molecules have both polar and non-polar aspects: they are said to be amphipathic. They can form a bridge between polar and non-polar regions. Amphipathic phospholipid molecules can group together to form membranes, such as cell membranes.
- Energy is derived from metabolic substrates derived from food-stuffs principally by oxidation, a chemical process involving electron transfer from electron donor (reducing agent) to electron acceptor (oxidising agent), the final electron acceptor being oxygen.
- The different organs in the body have their own characteristic patterns of metabolism. Substrates flow between them in the bloodstream (circulation). Larger blood vessels divide into fine vessels (capillaries) within the tissues, so that the distances that molecules have to diffuse to or from the cells are relatively small (more detail in Chapter 3).

(*Continued*)

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Key learning points (*continued*)

- The different classes of metabolic substrates have characteristic chemical properties; by utilising all three types of metabolic substrates derived from the three major food energy groups (carbohydrates, fats, and proteins) energy storage (anabolism) and release (catabolism) in many physiological conditions is achieved.
- General features of metabolism include synthesis and breakdown of substrates, and complete breakdown to release energy by oxidation. The tricarboxylic acid cycle (TCA cycle) is the central cellular mechanism for substrate oxidation to H_2O and CO_2, with consumption of O_2. It operates within mitochondria.
- Carbohydrate metabolism centres around the sugar glucose. Carbohydrate metabolic pathways include conversion to glycogen and its reverse, glucose breakdown and oxidation, glucose conversion to lipid, and synthesis of glucose (gluconeogenesis).
- Lipid metabolism for energy centres on the interconversion of fatty acids and triacylglycerol. Triacylglycerol synthesis involves esterification of fatty acids with glycerol; triacylglycerol breakdown (*lipolysis*) involves liberation of fatty acids and glycerol from stored triacylglycerol. The oxidation of fatty acids occurs through a pathway known as β-oxidation.
- Amino acid metabolism involves incorporation of amino acids into protein, and its reverse (protein synthesis and breakdown), and further metabolism of the amino acids, either to convert them to other substrates (e.g. lipids) or final oxidation. The nitrogen component of amino acids is disposed of by conversion to urea in the liver.

1.1 Metabolism in perspective

To many students, metabolism sounds a dull subject. It involves learning pathways with intermediates with difficult names and even more difficult formulae. Metabolic regulation may sound even worse. It involves not just remembering the pathways, but remembering what the enzymes are called, what affects them and how. This book is not simply a repetition of the molecular details of metabolic pathways. Rather, it is an attempt to put metabolism and metabolic regulation together into a physiological context, to help the reader to see the relevance of these subjects. Once their relevance to everyday life becomes apparent, then the details will become easier, and more interesting, to grasp.

This book is written from a human perspective because, as humans, it is natural for us to find our own metabolism interesting – and very important for understanding human health and disease. Nevertheless, many aspects of metabolism and its regulation that are discussed are common to other mammals. Some mammals, such as ruminants, have rather specialised patterns of digestion and absorption of energy; such aspects will not be covered in this book.

Metabolism might be defined as the biochemical reactions involved in converting foodstuffs into fuel. (There are other aspects, but we will concentrate on this one.) As we shall shortly see, that is not a constant process: 'flow' through the metabolic pathways needs to change with time. An important aspect of these pathways is therefore the ability to direct metabolic products into storage, then retrieve them from storage as appropriate. In this chapter we shall give an overview of the major pathways involved in carbohydrate, lipid, and protein metabolism. In later chapters we shall see that these pathways operate within specific tissues – or sometimes between tissues – and not all cells carry out the same set of metabolic reactions. We intend to give enough detail of metabolic pathways that a student will be able to understand them, but inevitably a more detailed biochemistry textbook will provide more. We shall concentrate upon understanding how these pathways operate in human terms, and how they are regulated.

Now we have mentioned metabolic regulation, so we should ask: why is it necessary? An analogy here is with mechanical devices, which require an input of energy, and convert this energy to a different and more useful form. The waterwheel is a simple example. This device takes the potential energy of water in a reservoir – the mill-pond – and converts it into mechanical energy which can be

used for turning machinery, for instance, to grind corn. As long as the water flows, its energy is extracted, and useful work is done. If the water stops, the wheel stops. A motor vehicle has a different pattern of energy intake and energy output (Figure 1.1). Energy is taken in very spasmodically – only when the driver stops at a filling station. Energy is converted into useful work (acceleration and motion) with an entirely different pattern. A long journey might be undertaken without any energy intake. Clearly, the difference from the waterwheel lies in the presence of a storage device – the fuel tank. But the fuel tank alone is not sufficient: there must also be a control mechanism to regulate the flow of energy from the store to the useful-work-producing device (i.e. the engine). In this case, the regulator is in part a human brain deciding when to move, and in part a mechanical system controlling the flow of fuel.

What does this have to do with metabolism? The human body is also a device for taking in energy (chemical energy, in the form of food) and converting it to other forms. Most obviously, this is in the form of physical work, such as lifting heavy objects. However, it can also be in more subtle forms, such as producing and nurturing offspring. Any activity requires energy. Again, this is most obvious if we think about performing mechanical work: lifting a heavy object from the floor onto a shelf requires conversion of chemical energy (ultimately derived from food) into potential energy of the object. But even maintaining life involves work: the work of breathing, of pumping blood around the vascular system, of chewing food and digesting it. At a cellular level, there is constant work performed in the pumping of ions across membranes, and the synthesis and breakdown of the chemical constituents of cells.

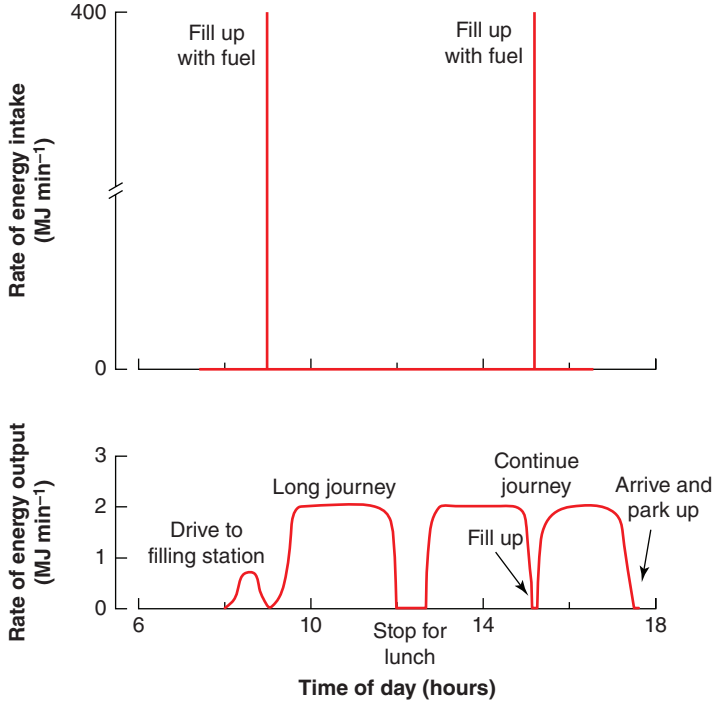


Figure 1.1 Rates of energy intake and output for a motor vehicle. The rate of intake (top panel) is zero except for periods in a filling station, when it is suddenly very high. (Notice that the scales are different for intake and output.) The rate of output is zero while the car is parked with the engine off; it increases as the car is driven to the filling station, and is relatively high during a journey. When totalled up over a long period, the areas under the two curves must be equal (energy intake = energy output) – except for any difference in the amounts of fuel in the tank before and after.

What is your pattern of energy intake in relation to energy output? For most of us, the majority of energy intake occurs in three relatively short periods during each 24 hours, whereas energy expenditure is largely continuous (the *resting metabolism*) with occasional extra bursts of external work (Figure 1.2). It is clear that we, like the motor vehicle, must have some way of storing food energy and releasing it when required. As with the motor vehicle, the human brain may also be at the beginning of the regulatory mechanism, although it is not the conscious part of the brain: we do not have to think when we need to release some energy from our fat stores, for instance. Some of the important regulatory systems that will be covered in this book lie outside the brain, in organs which secrete hormones, particularly the pancreas. But whatever the internal means for achieving this regulation, we manage to store our excess food energy and to release it just as we need.

This applies to the normal 24-hour period in which we eat meals and go about our daily life. But the body also has to cope with less well-organised situations. In many parts of the world, there are times when food is not that easily available, and yet people are able to continue relatively normal lives. Clearly, the body's regulatory mechanisms must recognise that food is not coming in and

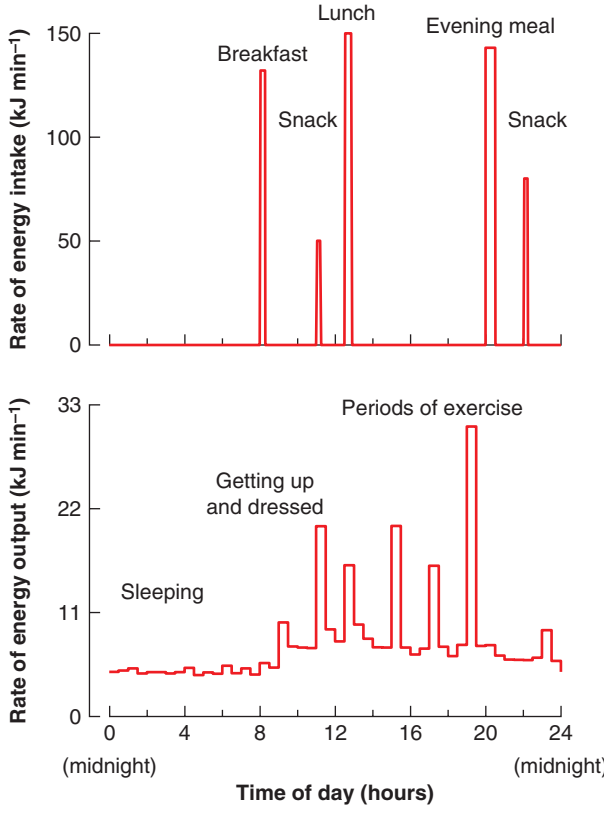


Figure 1.2 Rates of energy intake and output for a person during a typical day. The rate of energy intake (top panel) is zero except when eating or drinking, when it may be very high. The rate of energy output (heat + physical work) (lower panel) is at its lowest during sleep; it increases on waking and even more during physical activity. As with the car, the pattern of energy intake may not resemble that of energy expenditure, but over a long period the areas under the curves will balance – except for any difference in the amounts of energy stored (mainly as body fat) before and after. Source: data for energy expenditure are for a person measured in a calorimetry chamber and were kindly supplied by Prof Susan Jebb of Nuffield Department of Primary Care Health Sciences, Oxford University.

allow an appropriate rate of release of energy from the internal stores. In other situations, the need for energy may be suddenly increased. Strenuous physical exercise may increase the total rate of metabolism in the body to 20 times its resting level. Something must recognise the fact that there is a sudden need to release energy at a high rate from the body's stores. During severe illness, such as infections, the rate of metabolism may also be increased; this is manifested in part by the rise in body temperature. Often the sufferer will not feel like eating normally. Once again, the body must have a way of recognising the situation, and regulating the necessary release of stored energy.

What we are now discussing is, indeed, *metabolic regulation*. Metabolic regulation in human terms covers the means by which we take in nutrients in discrete meals, and deliver energy as required, varying from moment to moment and from tissue to tissue, in a pattern which may have no relationship at all to the pattern of intake. Metabolic regulation works ultimately at a molecular level, mainly by modulation of the activities of enzymes. But one should not lose sight of the fact that these molecular mechanisms are there to enable us to lead normal lives despite fluctuations in our intake and our expenditure of energy. In this book, the emphasis will be on the systems within the human body which sense the balance of energy coming in and energy required, particularly the *endocrine* (hormonal) and the *nervous* systems, and which regulate the distribution and storage of nutrients after meals, and their release from stores and delivery to individual tissues as required.

The intention of this preamble is to illustrate that, underlying our everyday lives, there are precise and beautifully coordinated regulatory systems controlling the flow of energy within our bodies. Metabolic regulation is not a dry, academic subject thought up just to make biochemistry examinations difficult; it is at the centre of human life and affects each one of us every moment of our daily lives.

1.2 The chemistry of food – and of bodies

Energy is taken into the body in the form of food. The components of food may be classified as *macronutrients* and *micronutrients*. Macronutrients are those components present in a typical serving in amounts of grams rather than milligrams or less. They are the well-known carbohydrate, fat, and protein. Water is another important component of many foods, although it is not usually considered a nutrient. Micronutrients are vitamins, minerals, and nucleic acids: they are not oxidised to provide energy, but rather they are used to facilitate biochemical mechanisms of the body. Although these micronutrients play vital roles in the metabolism of the macronutrients, they will not be discussed in any detail in this book, which is concerned with the broader aspects of what is often called *energy metabolism*.

The links between nutrition and energy metabolism are very close. We eat carbohydrates, fats, and proteins. Within the body these relatively large molecules are broken down to smaller components, rearranged, stored, released from stores, and further metabolised, but essentially whether we are discussing food or metabolism the same categories of carbohydrate, fat, and protein can be distinguished. This is not surprising since our food itself is of organic origin, whether plant or animal.

In order to understand metabolism and metabolic regulation, it is useful to have a clear idea of some of the major chemical properties of these components. This is not intended as a treatise in physical or organic chemistry but as a starting point for understanding some of the underlying principles of metabolism. The discussion assumes a basic understanding of the meaning of atoms and molecules, of chemical reactions and catalysis, and some understanding of chemical bonds (particularly the distinction between ionic and covalent bonding).

1.2.1 Some important chemical concepts

1.2.1.1 Polarity

Some aspects of metabolism are more easily understood through an appreciation of the nature of polarity of molecules. *Polarity* refers to the distribution of electrical charge over the molecule. A non-polar molecule has a very even distribution of electrical charge over its surface and is electrically neutral overall (the negative charge on the electrons is balanced by the positive charge of the nucleus). A polar molecule has an overall charge,

or at least an uneven distribution of charge. The most polar small particles are ions – that is, atoms or molecules which have entirely lost or gained one or more electrons. However, even completely covalently bonded organic molecules may have a sufficiently uneven distribution of electrical charge to affect their behaviour. Polarity is not an all-or-none phenomenon; there are gradations, from the polar to the completely non-polar.

Polarity is not difficult to predict in the molecules which are important in biochemistry. We will contrast two simple molecules: water and methane. Their relative molecular masses are similar – 18 for water, 16 for methane – yet their physical properties are very different. Water is a liquid at room temperature, not boiling until 100 °C, whereas methane is a gas ('natural gas') which only liquifies when cooled to −161°C. We might imagine that similar molecules of similar size would have the same tendency to move from the liquid to the gas phase, and that they would have similar boiling points. The reason for their different behaviours lies in their relative polarity. The molecule of methane has the three-dimensional structure shown in Figure 1.3a. The outer electron 'cloud' has a very even distribution over the four hydrogen atoms, all of which have an equal tendency to pull electrons their way. The molecule has no distinct electrical poles – it is non-polar. Because of this very even distribution of electrons, molecules near each other have little tendency to interact. In contrast, in the water molecule (Figure 1.3b) the oxygen atom has a distinct tendency to pull electrons its way, shifting the distribution of the outer electron cloud so that it is more dense over the oxygen atom, and correspondingly less dense elsewhere. Therefore, the molecule has a rather negatively charged region around the central oxygen atom, and correspondingly positively charged regions around the hydrogen atoms. Thus, it has distinct electrical poles – it is a relatively polar molecule. It is easy to imagine that water molecules near to each other will interact. Like electrical charges repel each other, unlike charges attract. This gives water molecules a tendency to line up so that the positive regions of one attract the negative region of an adjacent molecule (Figure 1.3b). So, water molecules, unlike those of methane, tend to 'stick together': the energy needed to break them apart and form a gas is much greater than for methane, and hence water is a liquid while methane is a gas. The latent heat of evaporation of water is 2.5 kJ g^{-1}, whereas that of methane is 0.6 kJ g^{-1}. Note that the polarity of the water molecule is not as extreme as that of an ion – it is merely a rather uneven distribution of electrons, but enough to affect its properties considerably.

The contrast between water and methane may be extended to larger molecules. Organic compounds composed solely of carbon and hydrogen – for instance, the alkanes or 'paraffins' – all have the property of extreme non-polarity: the chemical (covalent) bond between carbon and hydrogen atoms leads to a very even distribution of electrons, and the molecules have little interaction with each other. A result is that polar molecules, such as those of water, and non-polar molecules, such as those of alkanes, do not mix well: the water molecules tend to bond to each other and to exclude the non-polar molecules, which can themselves pack together very closely because of the lack of interaction between them. In fact, there is an additional form of direct attraction between non-polar molecules, the *van der Waals* forces. Random fluctuations in the density of the electron cloud surrounding a molecule lead to minor, transient degrees of polarity; these induce an opposite change in a neighbouring molecule, with the result that there is a transient attraction between them. These are very weak attractions, however, and the effect of the exclusion by water is considerably stronger. The non-polar molecules are said to be *hydrophobic* (water fearing or water hating).

A strong contrast is provided by an inorganic ionic compound such as sodium chloride. The sodium and chlorine atoms in sodium chloride are completely ionised under almost all conditions. They pack very regularly in crystals in a cubic form. The strength of their attraction for each other means that considerable energy is needed to disrupt this regular packing – sodium chloride does not melt until heated above 800 °C. And yet it dissolves very readily in water – that is, the individual ions become separated from their close packing arrangement rather as they would on melting. Why? Because the water molecules, by virtue of their polarity, are able to come between the ions and reduce their attraction for each other.

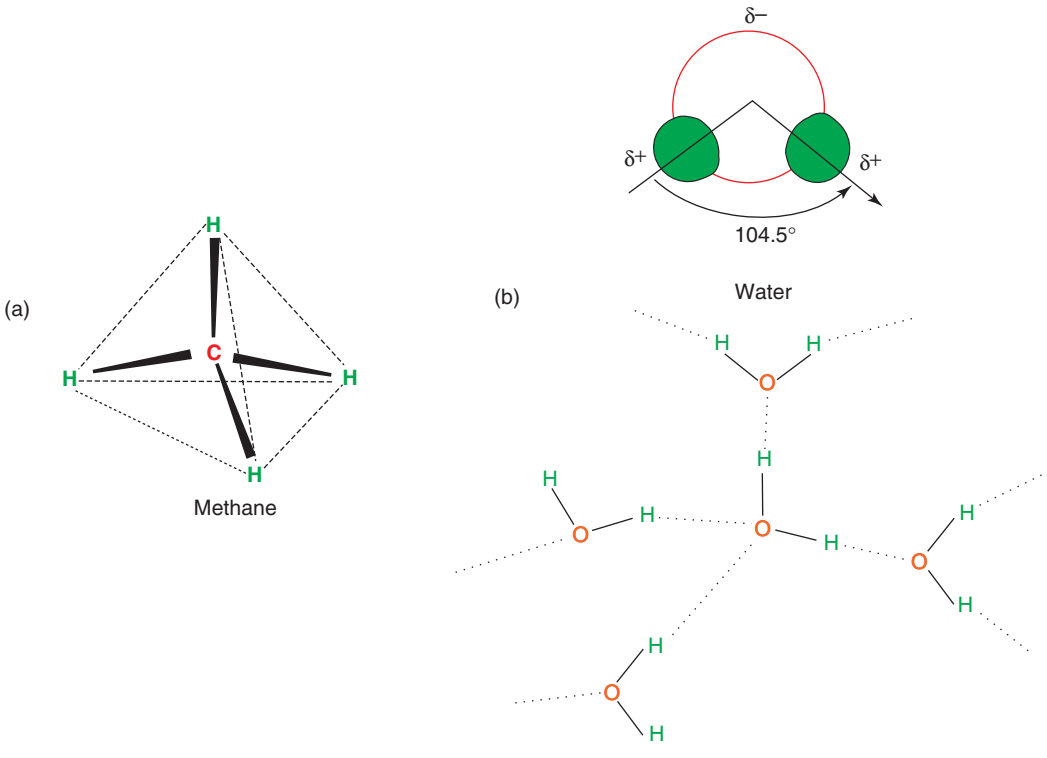


Figure 1.3 (a) Three-dimensional structure of the methane molecule and (b) the molecular structure of water. (a) The hydrogen atoms of methane (CH_4) are arranged symmetrically in space, at the corners of a tetrahedron. (b) The molecular structure of water. Top: view of the 'electron cloud' surrounding the molecule; bottom, interactions between water molecules. The molecule has a degree of *polarity*, and this leads to electrical interactions between neighbouring molecules by the formation of *hydrogen bonds*. These bonds are not strong compared with covalent bonds, and are constantly being formed and broken. Nevertheless, they provide sufficient attraction between the molecules to account for the fact that water is a liquid at room temperature whereas the non-polar methane is a gas.

In fact, each of the charged sodium and chloride ions will become surrounded by a 'shell' of water molecules, shielding it from the attraction or repulsion of other ions. Sodium chloride is said to be *hydrophilic* – water loving. The terms *polar* and *hydrophilic* are for the most part interchangeable. Similarly, the terms *non-polar* and *hydrophobic* are virtually synonymous.

Ionic compounds, the extreme examples of polarity, are not confined to inorganic chemistry. Organic molecules may include ionised groups. These may be almost entirely ionised under normal conditions – for instance, the esters of orthophosphoric acid ('phosphate groups'), as in the compounds AMP, ADP, and ATP, in metabolites such as glucose 6-phosphate, and in phospholipids. Most of the organic acids involved in intermediary metabolism, such as lactic acid, pyruvic acid, and the long-chain carboxylic acids (fatty acids), are also largely ionised at physiological hydrogen ion concentrations (Box 1.1). Thus, generation of lactic acid during exercise raises the hydrogen ion concentration (the acidity) both within the cells where it is produced, and generally within the body, since it is released into the bloodstream.

As stated earlier, polarity is not difficult to predict in organic molecules. It relies upon the fact that certain atoms always have *electronegative* (electron withdrawing) properties in comparison

with hydrogen. The most important of these atoms biochemically are those of oxygen, phosphorus, and nitrogen. Therefore, certain functional groups based around these atoms have polar properties. These include the hydroxyl group (–OH), the amino group ($–NH_2$), and the orthophosphate group ($–OPO_3^{2–}$). Compounds containing these groups will have polar properties, whereas those containing just carbon and hydrogen will have much less polarity. The presence of an electronegative atom does not always give polarity to a molecule – if it is part of a chain and balanced by a similar atom this property may be lost. For instance, the ester link in a triacylglycerol molecule (discussed below) contains two oxygen atoms but has no polar properties.

Examples of relatively polar (and thus water-soluble) compounds, which will be frequent in this book, are sugars (with many –OH groups), organic acids such as lactic acid (with a $COO^–$ group), and most other small metabolites. Most amino acids also fall into this category (with their amino and carboxyl groups), although some fall into the *amphipathic* ('mixed') category discussed below.

Box 1.1 Ionisation state of some acids at normal hydrogen ion concentrations

The normal pH in blood plasma is around 7.4. (It may be somewhat lower within cells, down to about 6.8.) This corresponds to a hydrogen ion concentration of 3.98×10^{-8} mol l^{-1} (since $– \log_{10}$ of 3.98×10^{-8} is 7.4).

The equation for ionisation of an acid HA is:

$$HA \Leftrightarrow H^+ + A^-$$

this equilibrium is described by the equation:

$$\frac{[H^+][A^-]}{[HA]} = K_i$$

where K_i is the dissociation or ionisation constant and is a measure of the strength of the acid: the higher the value of K_i the stronger (i.e. the more dissociated) the acid.

K_i in the equation above relates the concentrations expressed in molar terms (e.g. mol/l). (Strictly, it is not the concentrations but the 'effective ion concentrations' or ion *activities* which are related; these are not quite the same as concentrations because of inter-ion attractions. In most biological systems, however, in which the concentrations are relatively low, it is a close approximation to use concentrations. If activities are used, then the symbol K_a is used for the dissociation constant of an acid.)

Some biological acids and their K_a values are listed in Table 1.1.1, together with a calculation of the proportion ionised at typical pH (7.4).

The calculation is done as follows (using acetic acid as an example):

$$K_a = 1.75 \times 10^{-5} = \frac{[H^+][Ac^-]}{[HAc]}$$

(where HAc represents undissociated acetic acid, $Ac^–$ represents the acetate ion). At pH 7.4, $[H^+] = 3.98 \times 10^{-8}$ mol l^{-1}. Therefore,

$$\frac{[Ac^-]}{[HAc]} = \frac{1.75 \times 10^{-5}}{3.98 \times 10^{-8}} = 440$$

(i.e. the ratio of ionised to undissociated acid is 440:1; it is almost entirely ionised).

The percentage in the ionised form $= \frac{440}{441} \times 100\% = 99.8\%$.

Table 1.1.1

Acid	K_a	% ionised at pH 7.4
Acetic, CH_3COOH	1.75×10^{-5}	99.8
Lactic, $CH_3CHOHCOOH$	0.38×10^{-4}	99.9
Palmitic acid, $CH_3(CH_2)_{14}COOH$	1.58×10^{-5}	99.8
Glycine, CH_2NH_2COOH (carboxyl group)	3.98×10^{-3}	100

Another important point about polarity in organic molecules is that within one molecule there may be both polar and non-polar regions. They are called amphipathic compounds. This category includes phospholipids and long-chain fatty acids (Figure 1.4). Cell membranes are made up of a double layer of phospholipids, interspersed with specific proteins such as transporter molecules, ion channels and hormone receptors, and molecules of the sterol, cholesterol (Figure 1.5). The phospholipid bilayer presents its polar faces – the polar 'heads' of the phospholipid molecules – to the aqueous external environment and to the aqueous internal environment; within the thickness of the membrane is a non-polar, hydrophobic region. The physicochemical nature of such a membrane means that, in general, molecules cannot diffuse freely across it: non-polar molecules would not cross the outer, polar face and polar molecules would not cross the inner, hydrophobic region. Means by which molecules move through membranes are discussed in Chapter 2 (Box 2.1).

The long-chain fatty acids fall into the amphipathic category – they have a long, non-polar hydrocarbon tail but a more polar carboxylic group head ($–COO^-$). Another compound with mixed properties is cholesterol (Figure 1.6); its ring system is very non-polar, but its hydroxyl group gives it some polar properties. However, the long-chain fatty acids and cholesterol may lose their polar aspects completely when they join in ester links. An ester is a compound formed by the condensation (elimination of a molecule of water) of an alcohol (–OH) and an acid (e.g. a carboxylic acid, $–COO^-$). Cholesterol (through its –OH group) may become esterified to a long-chain fatty acid, forming a *cholesteryl ester* (e.g. cholesteryl oleate, Figure 1.6). The cholesteryl esters are extremely non-polar compounds. This fact will be important when we consider the metabolism of cholesterol in Chapter 10. The long-chain fatty acids may also become esterified with glycerol, forming triacylglycerols (Figure 1.4). Again, the polar properties of both partners are lost, and a very non-polar molecule is formed. This fact underlies one of the most fundamental aspects of mammalian metabolism – the use of triacylglycerol as the major form for storage of excess energy.

Among amino acids, the branched-chain amino acids, leucine, isoleucine, and valine, have non-polar side chains and are thus amphipathic. The aromatic amino acids phenylalanine and tyrosine are relatively hydrophobic, and the amino acid tryptophan is so non-polar that it is not carried free in solution in the plasma.

The concept of the polarity or non-polarity of molecules thus has a number of direct consequences for the aspects of metabolism to be considered in later chapters. Some of these consequences are the following:

(1) Lipid fuels – fatty acids and triacylglycerols – are largely hydrophobic and are not soluble in the blood plasma. There are specific routes for their absorption from the intestine and specific mechanisms by which they are transported in blood.

(2) Carbohydrates are hydrophilic. When carbohydrate is stored in cells it is stored in a hydrated form, in association with water. In contrast, fat is stored as a lipid droplet from which water is excluded. Mainly because of this lack of water, fat stores contain considerably more energy per unit weight of store than do carbohydrate stores.

(3) The entry of lipids into the circulation must be coordinated with the availability of the specific carrier mechanisms. In the rare situations in which it arises, uncomplexed fat in the bloodstream may have very adverse consequences.

1.2.1.2 Osmosis

The phenomenon of *osmosis* underlies some aspects of metabolic strategy – it can be seen as one reason why certain aspects of metabolism and metabolic regulation have evolved in the way that they have. It is outlined only briefly here to highlight its relevance.

Osmosis is the way in which solutions of different concentrations tend to even out when they are in contact with one another via a *semipermeable membrane*. In solutions, the *solvent* is the substance in which things dissolve (e.g. water) and the *solute* the substance which dissolves. A semipermeable membrane allows molecules of solvent to pass through, but not those of solute. Thus, it may allow molecules of water but not those of sugar to pass through. Cell membranes have specific protein channels

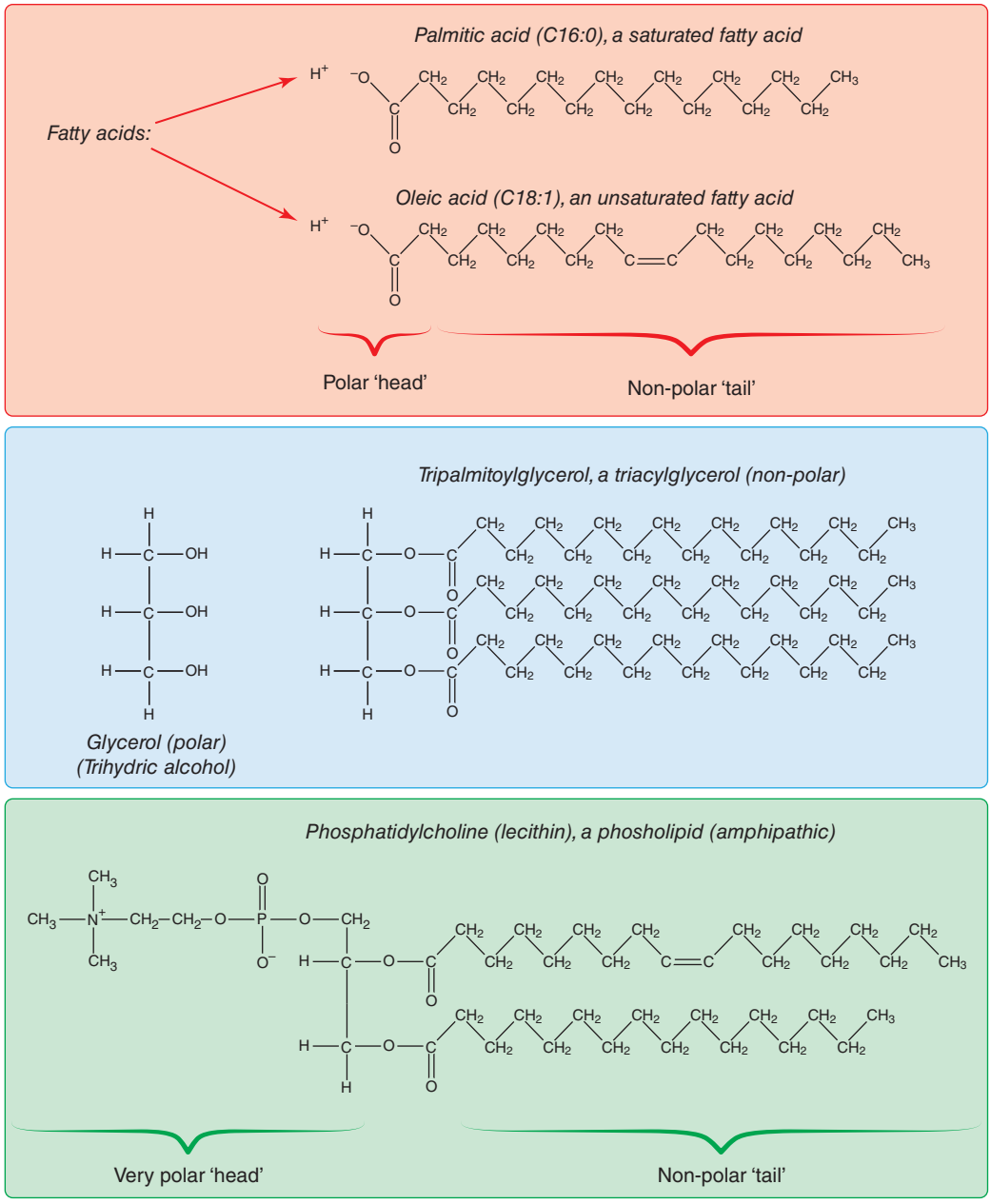


Figure 1.4 Chemical structures of some lipids. A typical saturated fatty acid (palmitic acid) is shown with its polar carboxylic group and non-polar hydrocarbon tail. *Glycerol* is a hydrophilic alcohol. However, it is a component of many lipids as its hydroxyl groups may form ester links with up to three fatty acids, as shown. The resultant *triacylglycerol* has almost no polar qualities. The *phospholipids* are derived from phosphatidic acid (diacylglycerol phosphate) with an additional polar group, usually a nitrogen-containing base such as choline (as shown) or a polyalcohol derivative such as phosphoinositol. Phospholipids commonly have long-chain unsaturated fatty acids on the 2-position; oleic acid (18:1 *n*-9) is shown.

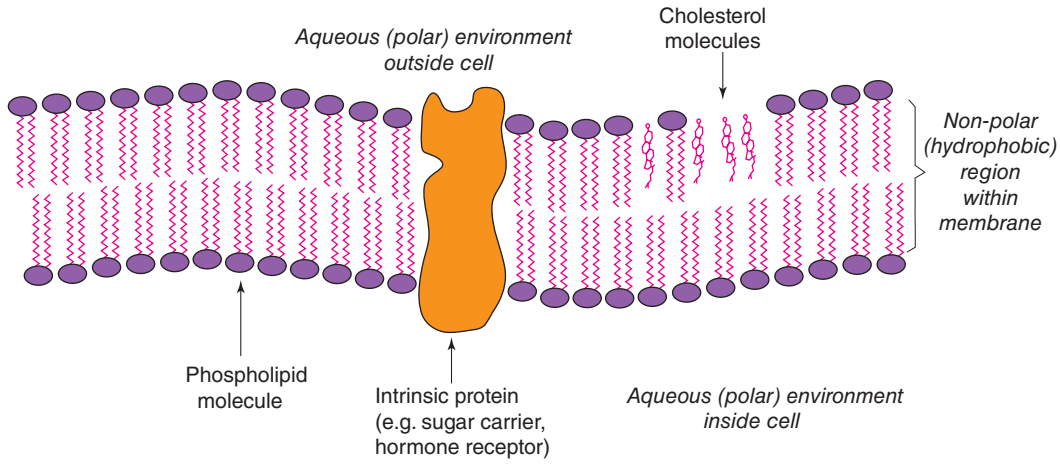


Figure 1.5 Structure of biological membranes in mammalian cells. Cell membranes and intracellular membranes such as the endoplasmic reticulum are composed of bilayers of phospholipid molecules with their polar head-groups facing the aqueous environment on either side and their non-polar 'tails' facing inwards, forming a hydrophobic centre to the membrane. The membrane also contains *intrinsic proteins* such as hormone receptors, ion channels, and sugar transporters, and molecules of cholesterol which reduce the 'fluidity' of the membrane. Modern views of cell membrane structure emphasise that there are domains, known as 'rafts,' in which functional proteins co-locate, enabling interactions between them. These lipid rafts are characterised by high concentrations of cholesterol and of certain phospholipids (glycosphingolipids).

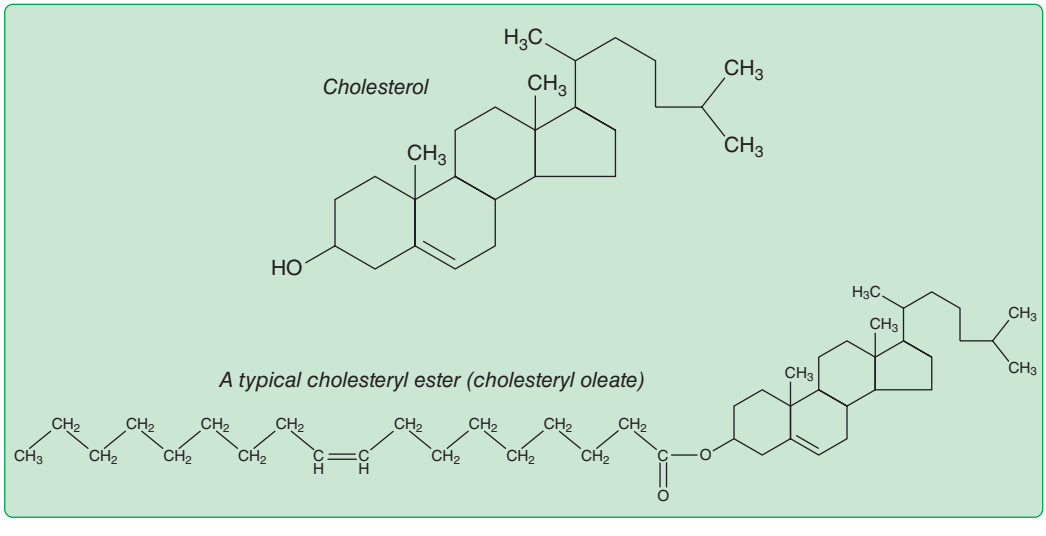


Figure 1.6 Cholesterol and a typical cholesteryl ester (cholesteryl oleate). In the structure of cholesterol, not all atoms are shown (for simplicity); each 'corner' represents a carbon atom, or else –CH or $–CH_2$. Cholesterol itself has amphipathic properties because of its hydroxyl group, but when esterified to a long-chain fatty acid the molecule is very non-polar.

(*aquaporins*, discussed in Section 2.2.2.6) to allow water molecules to pass through; they are close approximations to semipermeable membranes.

If solutions of unequal concentration – for instance, a dilute and a concentrated solution of sugar – are separated by a semipermeable membrane, then molecules of solvent (in this case, water) will tend to pass through the membrane until the concentrations of the solutions have become equal. In order to understand this intuitively, it is necessary to remember that the particles (molecules or ions) of solute are not just moving about freely in the solvent: each is surrounded by molecules of solvent, attracted by virtue of the polarity of the solute particles. (In the case of a non-polar solute in a non-polar solvent, we would have to say that the attraction is by virtue of the non-polarity; it occurs through weaker forces such as the van der Waals.) In the more concentrated solution, the proportion of solvent molecules engaged in such attachment to the solute particles is larger, and there is a net attraction for further solvent molecules to join them, in comparison with the more dilute solution. Solvent molecules will tend to move from one solution to the other until the proportion involved in such interactions with the solute particles is equal.

The consequence of this in real situations is not usually simply the dilution of a more concentrated solution, and the concentration of a more dilute one, until their concentrations are equal. Usually there are physical constraints. This is simply seen if we imagine a single cell, which has accumulated within it, for instance, amino acid molecules taken up from the outside fluid by a transport mechanism which has made them more concentrated inside than outside. Water will then tend to move into the cell to even out this concentration difference. If water moves into the cell, the cell will increase in volume. Cells can swell so much that they burst under some conditions (usually not encountered in the body, fortunately). For instance, red blood cells placed in water will burst (*lyse*) from just this effect: the relatively concentrated mixture of dissolved organic molecules within the cell will attract water from outside the cell, increasing the volume of the cell until its membrane can stretch no further and ruptures.

In the laboratory, we can avoid this by handling cells in solutions which contain solute – usually sodium chloride – at a total concentration of solute particles which matches that found within cells. Solutions which match this osmolarity are referred to as *isotonic*; a common laboratory example is *isotonic saline* containing 9g of NaCl per litre of water, with a molar concentration of 154 mmol l^{-1}. Since this will be fully ionised into Na^+ and Cl^- ions, its particle concentration is 308 'milliparticles' – sometimes called milliosmoles – per litre. We refer to this as an *osmolarity* of 308 mmol l^{-1}, but it is not 308 mmol NaCl per litre. (Sometimes you may see the term *osmolality*, which is very similar to osmolarity, but measured in mmol per kg solvent.)

The phenomenon of osmosis has a number of repercussions in metabolism. Most cells have a number of different 'pumps' or active transporters in their cell membranes which can be used to regulate intracellular osmolarity, and hence cell size. This process requires energy and is one of the components of basal energy expenditure. It may also be important in metabolic regulation; there is increasing evidence that changes in cell volume are part of a signalling mechanism which brings about changes in the activity of intracellular metabolic pathways. The osmolarity of the plasma is maintained within narrow limits by specific mechanisms within the kidney, regulating the loss of water from the body via changes in the concentration of urine. Most importantly, potential problems posed by osmosis can be seen to underlie the metabolic strategy of fuel storage, as will become apparent in later sections.

1.2.1.3 Reduction-oxidation

Metabolic energy in living cells is released by the oxidation of relatively large molecular weight substrates containing substantial amounts of chemically available energy (Gibbs 'free' energy, G). This is a form of combustion: energy-rich carbon-containing fuel (metabolic substrate) is 'burnt' using oxygen, producing water (H_2O) and carbon dioxide (CO_2) as waste products, in the same way as carbon-based domestic fuel (coal, wood) is burnt on a fire using atmospheric oxygen, and releasing its contained energy, with the same end-products. Clearly in metabolism there is no flame, but that is because the gradual release of the energy is controlled so stringently and incrementally.

The term 'oxidation' originally referred to the gain of oxygen in a chemical reaction, and the opposite process, 'reduction,' to the loss of oxygen (e.g. when metal oxides are heated, they are 'reduced' to pure metal, with the loss of oxygen and a reduction in the weight of the ore). However, these terms have now been broadened to encapsulate the general principle of these types of reaction – i.e. the *transfer of electrons*. Oxidation can be thought of as the process of **losing** electrons, and reduction as **gaining** electrons (in an analogous fashion to regarding acids as proton (H^+) donors and bases as proton acceptors). Implicit in gaining an electron is gaining energy, hence reduction actually involves achieving an enhanced energy status. This may sound counter-intuitive as the word 'reduction' implies diminution, but if one considers that chemically it refers to gaining a *negatively* charged entity (an electron, e^-) then this aids understanding. Oxidation and reduction occur simultaneously in a reaction as an electron is transferred, and these reactions are therefore called *redox* reactions. Following on from this, oxidising agents are substances that are relatively electron poor and can gain electrons (indeed, they attract electrons) causing oxidation (electron loss) in another substance, but becoming themselves reduced, becoming electron-enriched. The partner substance, a reducing agent, is electron- (and hence energy-) rich and donates an electron (to the electron acceptor – the oxidising agent) and hence reduces it, becoming itself oxidised: see Box 1.2.

Oxygen is a powerful oxidising agent (the word 'oxidising' derives from oxygen) and is used in metabolism as an electron acceptor. Hydrogen is the reducing agent in many biological reactions and hence reduction could be termed 'hydrogenation' although this term has a specific meaning in chemistry, referring to the addition of hydrogen.

Oxidation and reduction are characterised by a change in the *oxidation state* of the atoms involved. The oxidation state is the (theoretical) charge (its electron status or 'count') that an atom would have if all its bonds were entirely ionic (not true in practice due to covalent bonding) – hence oxidation state denotes the degree of oxidation of an atom; it may be positive, zero, or negative, and an increase in oxidation state during a reaction denotes oxidation of the atom, whilst a decrease denotes reduction, both resulting from electron transfer. The tendency of an atom to attract electrons to itself (i.e. to act as an oxidising agent) is denoted by its *electronegativity*, and is partly a function of the distribution of its own (valence) electrons; by contrast, the tendency of an atom to donate electrons (i.e. to act as a reducing agent) is denoted by its *electropositivity*.

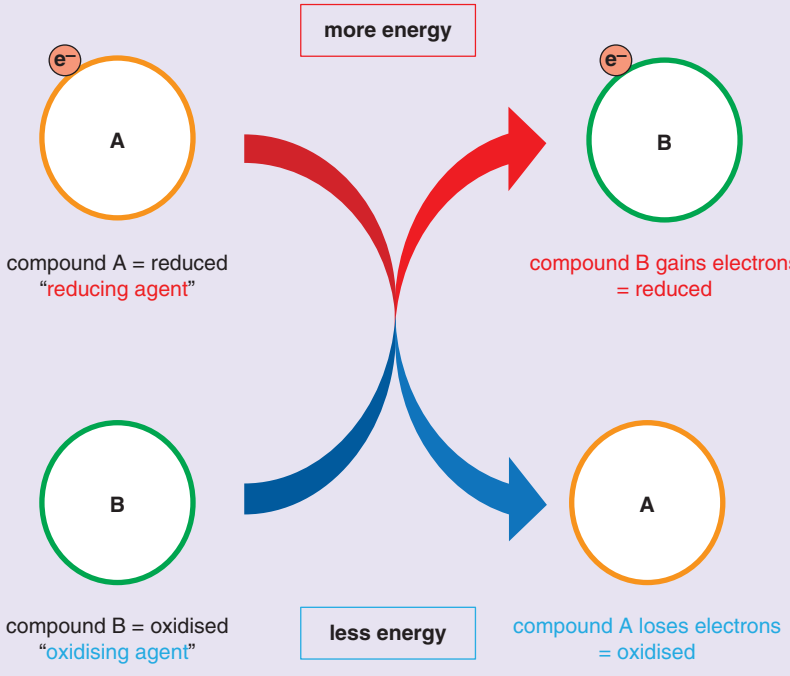
The chemically usable energy in a biomolecule which is a metabolic substrate is therefore present in the form of electrons, and therefore electron-rich molecules will be energy-rich and serve as good energy sources for metabolism. All three major metabolic substrate groups – carbohydrates, lipids, and proteins – contain these electrons in association with carbon-hydrogen (C–H) bonds. They can all be thought of as reduced (electron-rich) carbon (as found in wood, coal, house gas, and heating oil). In energy-yielding metabolism they act as reducing agents, donating these electrons to an electron acceptor, and ultimately themselves getting oxidised (the carbon ending up fully oxidised as CO_2 and the hydrogen as H_2O). The ultimate electron acceptor (oxidising agent) is, of course, oxygen.

e.g.

$$\underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{oxygen}}{6O_2} \rightarrow \underset{\text{carbon dioxide}}{6CO_2} + \underset{\text{water}}{6H_2O}$$

This demonstrates the importance of oxygen in metabolism: a strong electron acceptor is required to permit adequate electron transfer (and energy yield) from energy-rich substrates to occur, the difference in free energy levels between the tendency of the reducing agent to donate electrons and of the oxidising agent to accept electrons representing the energy yield of the overall process. (This may be contrasted with fermentation reactions which do not involve net reduction-oxidation, for example glycolysis of glucose to lactate: the energy yield is too small to sustain mammalian energy requirements and the substrate must be oxidised to maximise energy yield.) It can also be seen that lipids (e.g. fatty acids: $CH_3(CH_2)n{\cdot}COOH$, where n is typically 12–16, Figure 1.4) are far more reduced (C–H bond-rich; electron-rich) than carbohydrates (e.g. glucose $C_6H_{12}O_6$), in which the carbon atoms are already partially oxidised, with fewer

Box 1.2 Redox reactions

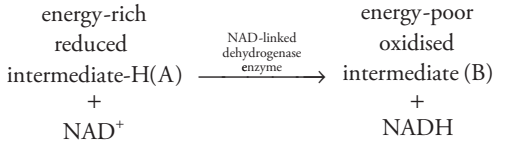


CH_4 (reducing agent) donates 8 electrons, becoming oxidised (to CO_2);
O_2 (oxidising agent) accepts 8 electrons, becoming reduced (to H_2O);

C–H bonds and therefore fewer energy-rich electrons to donate, and hence lipids contain far more energy (per gram) than carbohydrates. Amino acids are comparable to carbohydrates in the state of reduction of their carbon atoms, and hence of their energy content.

However, if electrons were transferred directly from substrate (e.g. glucose, fatty acid) to oxygen, the large energy yield would be uncontrollable. Therefore, a long series of intermediary electron transfer (redox) reactions occur in which energy-rich e^- is transferred sequentially and incrementally down a gradually decreasing (free) energy gradient. This explains why metabolic pathways are relatively long with many steps: small amounts only of energy are given off at each step. The energy (electron) extracted is then conveyed by electron carriers. Examples of electron carriers are NAD^+, $NADP^+$, and FAD. These are of course redox compounds themselves, accepting electrons (in the form of hydride ions H^-, i.e. a hydrogen atom with the extra, energy-carrying electron) from the metabolic pathway (becoming reduced – e.g. NADH; NADPH; $FADH_2$) and passing them on (becoming re-oxidised) to

further carriers at sequentially lower energy levels (electron transport chain redox proteins) until ultimately oxygen accepts the electrons, becoming itself reduced to water. It is for this reason that many key energy-yielding reactions in metabolic pathways are catalysed by *dehydrogenase* enzymes linked to transfer of a hydride ion H^- to the hydride acceptor NAD^+:



The *redox state* of a cell refers to the proportion of these intermediary electron carriers that are in the reduced (high energy) state compared to those in the oxidised (low energy) form: the NAD^+:NADH ratio for example provides an estimate of the energetic 'charge' (potential) contained within the cell (in an analogous fashion to the phosphorylation potential denoting the amount of adenine nucleotide in the form of ATP) – it is for this reason that many metabolic pathways are regulated not only by the phosphorylation potential ([ATP]:[ADP] and [AMP]) but, as we are increasingly recognising, also by the redox potential (NAD^+:NADH; $NADP^+$:NADPH).

1.2.2 The chemical characteristics of macronutrients

1.2.2.1 Carbohydrates

Simple carbohydrates have the empirical formula $C_n(H_2O)_n$; complex carbohydrates have an empirical formula which is similar to this (e.g. $C_n(H_2O)_{0.8n}$). The name carbohydrate reflects the idea, based on this empirical formula, that these compounds are hydrates of carbon. It is not strictly correct but illustrates an important point about this group of compounds – the relative abundance of hydrogen and oxygen, in proportions similar to those in water, in their molecules. From the discussion above, it will be apparent that carbohydrates are mostly relatively polar molecules, miscible with, or soluble in, water. Carbohydrates in nature include the plant products starch and cellulose and the mammalian storage carbohydrate glycogen ('animal starch'), as well as various simple sugars, of which glucose is the most important from the point of view of human metabolism. The main source of carbohydrate we eat is the starch in vegetables such as potatoes, rice, and grains.

The chemical definition of a sugar is that its molecules consist of carbon atoms, each bearing one hydroxyl group (–OH), except that one carbon bears a carbonyl group (=O) rather than a hydroxyl. In solution, the molecule exists in equilibrium between a 'straight-chain' form and a ring structure, but as the ring structure predominates sugars are usually shown in this form (Figure 1.7). Nevertheless, some of the chemical properties of sugars can only be understood by remembering that the straight-chain form exists. The basic carbohydrate unit is known as a monosaccharide. Monosaccharides may have different numbers of carbon atoms, and the terminology reflects this: thus, a hexose has six carbon atoms in its molecule, a pentose five, and so on. Pentoses and hexoses are the most important in terms of mammalian metabolism. These sugars also have 'common names' which often reflect their natural occurrence. The most abundant in our diet and in our bodies are the hexoses *glucose* (grape sugar, named from the Greek γλυκύς [*glykys*] sweet), *fructose* (fruit sugar, from the Latin *fructus* for fruit), and *galactose* (derived from lactose, milk sugar; from the Greek γαλακτος [*galaktos*], milk), and the pentose *ribose*, a constituent of nucleic acids (the name comes from the related sugar arabinose, named from *Gum arabic*).

Complex carbohydrates are built up from the monosaccharides by covalent links between sugar molecules. The term *disaccharide* is used for a molecule composed of two monosaccharides (which may or may not be the same), *oligosaccharide* for a short chain of sugar units, and *polysaccharide* for longer chains (>10 units), as found in starch and glycogen. Disaccharides are abundant in the diet, and again their common names often denote their origin: *sucrose* (table sugar, named from the French, *sucre*), which contains glucose and fructose (Figure 1.7); *maltose* (two glucose molecules) from malt; *lactose* (galactose and glucose) from milk. The bonds between individual sugar units are relatively strong at normal hydrogen ion

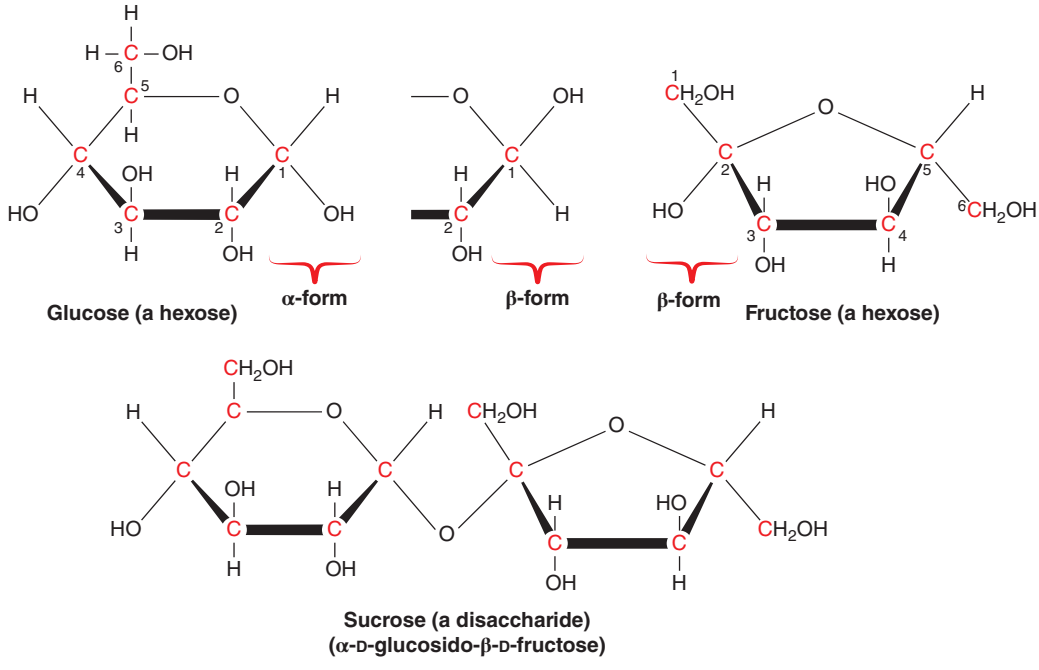


Figure 1.7 Some simple sugars and disaccharides. Glucose and fructose are shown in their 'ring' form. Even this representation ignores the true three-dimensional structure, which is 'chair' shaped: if the middle part of the glucose ring is imagined flat, the left-hand end slopes down and the right-hand end up. Glucose forms a six-membered ring and is described as a pyranose; fructose forms a five-membered ring and is described as a furanose. In solution the α- and β- forms are in equilibrium with each other and with a smaller amount of the straight-chain form. The orientation of the oxygen on carbon atom 1 becomes fixed when glucose forms links via this carbon to another sugar, as in sucrose; α- and β-links then have quite different properties (e.g. cellulose vs starch or glycogen).

concentrations, and sucrose (for instance) does not break down when it is boiled, although it is steadily broken down in acidic solutions such as cola drinks; but there are specific enzymes in the intestine (described in Chapter 4) which hydrolyse these bonds to liberate the individual monosaccharides.

Polysaccharides differ from one another in a number of respects: their chain length, and the nature (α- or β-) and position (e.g. ring carbons 1–4, 1–6) of the links between individual sugar units. Cellulose consists mostly of β-1,4 linked glucosyl units; these links give the compound a close-packed structure which is not attacked by mammalian enzymes. In humans, therefore, cellulose largely passes intact through the small intestine where other carbohydrates are digested and absorbed. It is broken down by some bacterial enzymes. Ruminants have complex alimentary tracts in which large quantities of bacteria reside, enabling the host to obtain energy from cellulose, the main constituent of their diet of grass. In humans there is some bacterial digestion in the large intestine (Chapter 4, Box 4.3). Starch and the small amount of glycogen in the diet are readily digested (Chapter 4).

The structure of glycogen is illustrated in Figure 1.8. It is a branched polysaccharide. Most of the links between sugar units are of the α-1,4 variety but after every 9–10 residues there is an α-1,6 link, creating a branch. Branching makes the molecules more soluble, and also creates more 'ends' where the enzymes of glycogen synthesis and breakdown operate. Glycogen is stored within