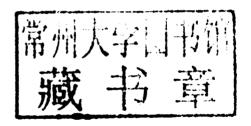


Essential Biochemistry for Medicine

Dr Mitchell Fry

Biological Sciences, University of Leeds



This edition first published 2010 © 2010 John Wiley & Sons Ltd.

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SO, UK

Other Editorial Offices: 9600 Garsington Road, Oxford, OX4 2DO, UK

111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/ wiley-blackwell

The right of the author to be identified as the author of this work has been asserted in accordance with the Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book. This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

Library of Congress Cataloging-in-Publication Data

Fry, Mitchell.
Essential biochemistry for medicine / Mitchell Fry.
p.; cm.
Includes index.
ISBN 978-0-470-74328-7 (cloth)
1. Clinical biochemistry. 2. Biochemistry. I. Title.
[DNLM: 1. Biochemical Phenomena. QU 34 F947e 2011]
RB112.5.F79 2011
616.07-dc22

2010018059

A catalogue record for this book is available from the British Library

ISBN: 978-0-470-74328-7

Typeset in 9/11 Times by Laserwords Private Limited, Chennai, India

Printed in Singapore by Markono Print Media Pte Ltd.

First Impression 2010

Essential Biochemistry for Medicine

Preface

To the uninitiated, biochemistry is a complex and intricate subject, but importantly it is a subject that underpins the biosciences, including medicine. As a university lecturer, and by training a biochemist, I have taught my subject to both 'my own' students, and to those on allied degree schemes and pre-clinical medicine. Of course, the lines so conveniently drawn (for teaching purposes) between the different bio-disciplines are very artificial; there is far more commonality than difference between these subjects. As a biochemist I am pleased to see the subject have such eminence, and rightly so, but at the same time it should not be delivered as a *fate accompli*, but rather as an aid to understand and clarify, a foundation to build upon and allow explanation. When I set out to write this book, it was not my intention to write a 'biochemistry' text, nor a 'medical' text, but rather something that provided a more complete picture. This is not meant to be a reference work, but rather a companion, and hopefully one that accurately reflects the type, depth and amount of biochemistry that is appropriate for medical and biomedical undergraduate students alike.

Essential Biochemistry for Medicine should provide a useful and helpful supplement to lectures and workshops, a biochemical-physiological-medical continuum, full of numerous medical examples, additional factual material and FOCUS sections on some favourite medical topics. I have tried to keep the book simply presented but packed with information, and it contains a full index to aid quick navigation. Indeed, it may be the only biochemistry book you need.

Mitch Fry

Contents

Pr	Preface		
1	Nutri	tional requirements	1
	1.1	Carbohydrates and sugars	1
	1.2	Glycogen	2
	1.3	Glycaemic index	3
	1.4	Lipids	3
	1.5	Proteins and amino acids	6
	1.6	Biological value	7
	1.7	Other energy sources	7
	1.8	Vitamins	8
	1.9	Minerals	11
2	Metal	polism and energy	13
	2.1	A metabolic strategy	13
	2.2	Carbohydrate metabolism (catabolic)	14
	2.3	Glycolysis	15
	2.4	Tricarboxylic acid cycle (TCA cycle – Krebs cycle – citric acid cycle)	17
	2.5	Oxidative phosphorylation	17
	2.6	Brown adipose tissue and heat generation	17
	2.7	Glycogenolysis	18
	2.8	Carbohydrate metabolism (anabolic)	20
	2.9	Gluconeogenesis	20
	2.10	Glycogenesis	20
	2.11	Fatty acid catabolism	22
	2.12	Amino acid catabolism	23
	2.13	Blood glucose homeostasis	24
	2.14	Glucokinase and hexokinase	27
	2.15	Glucose transporters	27

vi		CONTENTS	
	2.16 2.17	Diabetes mellitus Type 1 diabetes	28 29
	2.18	Type 2 diabetes	30
	2.19	Insulin/Glucagon effects on metabolism	32
	2.20	Hyperglycaemia and associated pathology	33
	2.21	Glycation	33
	2.22	The polyol pathway	35
3	Regul	ating body weight	37
	3.1	Obesity	37
	3.2	Weight regulation	37
	3.3	Controlling food intake	38
	3.4	Pre-gastric factors	38
	3.5	Gastrointestinal and post-absorptive factors	39
	3.6	Enteric nervous system	39
	3.7	The central nervous system	40
	3.8	Long-term control	41
	3.9	CNS factors	41
	3.10	Lifestyle changes	42
	3.11	The basics of dieting	44
	3.12	Medical and surgical treatment	45
4	Digest	tion and absorption	47
	4.1	The gastrointestinal tract	47
	4.2	Gastric acid production	48
	4.3	Proton pump inhibitors	50
	4.4	Helicobacter pylori	51
	4.5	The small intestine	52
	4.6	The gastrointestinal barrier	52
	4.7	Paneth cells	53
	4.8	The enteric endocrine system	54
	4.9	The pancreas	55
	4.10	Absorption in the small intestine: general principles	55
	4.11	Crossing the gastrointestinal barrier	57
	4.12	Absorption and secretion of water and electrolytes	58
	4.13	Pathophysiology of diarrhoea	59
	4.14	Rehydration therapy	60
	4.15	Absorption of sugars and amino acids	60
	4.16 4.17	Absorption of amino acids and peptides Absorption of lipids	62
	4.17	Absorption of tipids Absorption of minerals and metals	63
	4.19	Malabsorption syndromes	63 65
	4.13	Matabsorption syndromes	65

		CONTENTS	vii
	4.20	Steatorrhoea	70
	4.21	Lactose intolerance	70
	4.22 Glucose—galactose malabsorption		70
	4.23	Coeliac disease	71
	4.24	Crohn's disease	71
	4.25	The large intestine	71
5	Synthe	esis, mobilisation and transport of lipids and lipoproteins	75
	5.1	Fatty acid synthesis	75
	5.2	Long-term control of fatty acid synthase	77
	5.3	Triacylglycerols	77
	5.4	Mobilisation of lipid stores	78
	5.5	Transport of lipids	78
	5.6	Intestinal uptake of lipids	78
	5.7	Chylomicrons	79
	5.8	Apolipoproteins	79
	5.9	Export of fat from the liver	82
	5.10	Role of HDL in lipid metabolism	82
	5.11	Apoprotein classes	84
	5.12	LDL receptors	84
	5.13	Disorders of lipoprotein metabolism	85
	5.14	Alzheimer's disease	85
	5.15	Pharmacologic intervention	85
6	The liv	ver	91
	6.1	General overview	91
	6.2	Storage diseases	91
	6.3	Glycogen storage diseases	92
	6.4	General liver metabolism	92
	6.5	Production and excretion of bile	93
	6.6	Pattern and control of bile secretion	96
	6.7	Clinical significance of bile secretion	97
	6.8	Cholesterol metabolism	97
	6.9	Regulating cholesterol synthesis	97
	6.10	Regulating sterol synthesis	98
	6.11	Drug metabolism	99
	6.12	Breakdown of haem (Haemoglobin)	102
	6.13	Bilirubin	102
	6.14	Jaundice	104
	6.15	Protein metabolism – albumin	104
	6.16	Protein metabolism – nitrogen metabolism and	
		the urea cycle	105

vii	i	CONTENTS	
	6.17	The urea cycle	109
	6.18	Regulation of the urea cycle	109
	6.19	Urea cycle defects	111
	6.20	Neurotoxicity associated with ammonia	111
7	Alcoho	l metabolism and cirrhosis	113
	7.1	The alcohol dehydrogenase system	113
	7.2	The microsomal cytochrome P450 system	115
	7.3	The peroxisome catalase system	115
	7.4	The consequence of alcohol intake	115
	7.5	Short-term metabolic consequences of alcohol intake	116
	7.6	Long-term consequences of chronic alcohol intake	116
	7.7	Cirrhosis of the liver	118
	7.8	Complications of cirrhosis	118
8	Proteir	structures	121
	8.1	Protein primary structure	121
	8.2	Peptide bonds	121
	8.3	Protein interactions	121
	8.4	Levels of protein structure	123
	8.5	Types of protein structure	123
	8.6	The α -helix	124
	8.7	The β -sheet	124
	8.8	Protein folding	124
	8.9	Carbohydrates and lipid association with protein	125
	8.10	Disruption of the native state	126
	8.11	Incorrect protein folding and neurodegenerative disease	126
	8.12	The study of proteins	126
	8.13	Defects in protein structure and function	127
	8.14	Glycolipid degradation	128
	8.15	Protein receptor defects	129
	8.16	Transformation and carcinogenesis	129
9	Enzyme	es and diagnosis	131
	9.1	Enzyme nomenclature	131
	9.2	Catalytic mechanism	132
	9.3	Lowering the activation energy	132
	9.4	Reactions, rates and equilibria	133
	9.5	Michaelis-menten kinetics	134
	9.6	Lineweaver - burk	134
	9.7	Isoenzymes	135
	9.8	Enzyme inhibitors	136

		CONTENTS	ix
	9.9	The control of enzyme activity	137
	9.10	Allosteric enzymes	138
	9.11	Covalent modification of enzymes	138
	9.12	Control proteins	139
	9.13	Enzymes in medicine	140
	9.14	Biomarkers and enzymes in diagnosis	142
	9.15	Enzymes in the diagnosis of pathology	143
	9.16	Liver-function tests	144
10	The ki	dney	147
	10.1	Nephron structure	147
	10.2	Kidney function	147
	10.3	Diuretics	150
	10.4	Anti-diuretic hormone	151
	10.5	Aquaporins	151
11	Haemo	stasis	153
	11.1	Blood vessel trauma	153
	11.2	Blood coagulation	154
	11.3	The coagulation cascade	154
	11.4	The tissue factor (TF) pathway	154
	11.5	The contact activation pathway	155
	11.6	The common pathway	156
	11.7	Amplification of the clotting process	156
	11.8	Co-factors in coagulation	156
	11.9	Regulators of coagulation	157
	11.10	Breaking down the clot	158
	11.11	Disorders of haemostasis	159
		11.11.1 Platelet disorders	159
		11.11.2 Disorders of coagulation	159
	11.12	Pharmacology of haemostasis	160
12	Bone n	netabolism and calcium homeostasis	167
	12.1	Mineral density test	167
	12.2	Osteoblasts	
	12.2 12.3	Osteoblasts Osteoclasts	167
	12.2 12.3 12.4	Osteoblasts Osteoclasts Bone structure	167 168
	12.2 12.3 12.4 12.5	Osteoblasts Osteoclasts Bone structure Composition of bone	167 168 168 169
	12.2 12.3 12.4 12.5 12.6	Osteoblasts Osteoclasts Bone structure Composition of bone Collagen	167 168 168
	12.2 12.3 12.4 12.5 12.6 12.7	Osteoblasts Osteoclasts Bone structure Composition of bone Collagen Bone disorders	167 168 168 169
	12.2 12.3 12.4 12.5 12.6	Osteoblasts Osteoclasts Bone structure Composition of bone Collagen	167 168 168 169

X		CONTENTS	
	12.10 12.11 12.12 12.13	Calcium homeostasis Endocrine regulation of [Ca ²⁺] _{ECF} Parathyroid hormone Vitamin D	172 172 173 174
13	Intrace	ellular signalling	175
	13.1 13.2 13.3 13.4 13.5 13.6 13.7	Hormones The hierarchical nature of hormonal control Hormone synthesis and secretion Hormonal control Types of chemical messenger Intracellular signalling and signal transduction Cell-surface and intracellular receptors 13.7.1 Cell-surface receptors 13.7.2 Intracellular receptors Second messengers The glucagon receptor The gastrin receptor	175 176 178 179 181 182 182 182 185 187 190
14	Inflammation		
	14.1 14.2 14.3 14.4 14.5 14.6 14.7	The acute inflammatory response Leukocyte transmigration Chronic inflammation Mediators of inflammation Acute-phase proteins Patterns of acute and chronic inflammation Inflammatory disorders	193 194 196 197 197 199
15	The im	mune response	209
	15.1 15.2	Leukocytes Innate immunity 15.2.1 The complement system 15.2.2 Complement deficiency 15.2.3 Natural killer cells	209 209 210 211 213
	15.3 15.4	Passive immunity Acquired immunity 15.4.1 The humoral immune response 15.4.2 The clonality of B-cells 15.4.3 Antibodies 15.4.4 The Cell-mediated immune response	213 213 213 214 214 216
		15.4.5 Antigen-presenting cells	219

			CONTENTS	xi	
		15.4.6	Interaction of APCs with T-cells	219	
		15.4.7	Major histocompatibility complex (MHC)	219	
		15.4.8	Autoimmunity	221	
		15.4.9	Tolerance	222	
		15.4.10	Overcoming tolerance	223	
		15.4.11	Treating autoimmune disease	224	
16	Mitoch	Mitochondrial dysfunction			
	16.1	l Mitochondrial DNA			
	16.2	Non-Men	delian inheritance	231	
	16.3	Mitochon	drial cytopathies	232	
	16.4		symptoms of mitochondrial dysfunction	234	
	16.5		dria and ageing	234	
	16.6	Diagnosis	s of mitochondrial myopathies	235	
17	Nerve a	and muscl	e systems	237	
	17.1	Nerves		237	
	17.2	The nerve	e message	237	
	17.3		of the nervous system	240	
	17.4	Specific r	241		
	17.5				
	17.6				
	17.7		scular disease	248	
	17.8		es and focal adhesions	249	
	17.9	Dystroph		250	
	17.10		cardiomyopathy	251	
	17.11	Metabolio	c diseases of muscle	252	
18	The cyt	oskeletor	1	255	
	18.1	Actin fila	ments/microfilaments	255	
	18.2	Intermed	iate filaments	255	
	18.3	Microtub	ules	256	
	18.4	Spectrin		256	
	18.5		r's disease	257	
	18.6		hic lateral sclerosis	258	
	18.7	Synapsins	5	258	
19	Genes a	and medic	rine	259	
	19.1	Chromoso		259	
	19.2	Chromoso	ome banding	259	

XII	CONTENTS

		2011121112	
19.3	Karvotypes		260
		5 5.	260
19.5	•		262
19.6	Genetic dis	sorders	262
19.7	Gene testir	ng	263
	19.7.1 A	Advantages and disadvantages of	
		-	264
19.8	The human	genome project	264
	19.8.1 H	How do we compare to other organisms?	265
19.9	Gene thera	ру	265
	19.9.1	Current status	266
	19.9.2	Some ethical questions	267
19.10	The next st	tep: functional genomics	267
19.11	Pharmacog	enomics	268
19.12	Genetic en	gineering: recombinant DNA technology	270
	19.12.1	The tools and terminology of the	
	g	genetic engineer	270
			271
			272
19.13	The polyme	erase chain reaction (PCR)	272
19.14	Complemen	ntary DNA (cDNA)	273
19.15	DNA probes	S	273
19.16			274
19.17	Genetic en	gineering applications	276
			276
			278
			278
			280
			281
19.23		The state of the s	281
		, , , , , ,	282
			283
2 =			283
		cancer	284
			285
19.26	Caspases		285
Antiba	terial drug	resistance	291
20.1	Horizontal	gene transfer	291
20.2			292
	19.7 19.8 19.9 19.10 19.11 19.12 19.13 19.14 19.15 19.16 19.17 19.18 19.19 19.20 19.21 19.22 19.23 19.24 19.25 19.26 Antibac 20.1	19.4 The spectra hybridisati 19.5 Gene muta 19.6 Genetic dis 19.7 Gene testir 19.7.1 / 19.8 The human 19.8.1 I 19.9 Gene thera 19.9.1 Genetic en 19.12.1 The next st 19.11 Pharmacog 19.12 Genetic en 19.12.1 The polymer 19.15 DNA probes 19.16 DNA seque 19.17 Genetic en 19.18 Commercia 19.19 Gene thera 19.19 Gene thera 19.20 Controlling 19.21 Transcription 19.22 Response en 19.23 Genes and 19.23.1 Genes and 19.23.1 Genes and 19.23.2 I 19.23.3 Genes and 19.23.1 Genes and 19.23.2 I 19.23.3 Genes and 19.24 Viruses and 19.25 Apoptosis 19.26 Caspases Antibacterial drug 20.1 Horizontal	19.4 The spectral karyotype: fluorescence in situ hybridisation (FISH) 19.5 Gene mutations 19.6 Genetic disorders 19.7 Gene testing 19.7.1 Advantages and disadvantages of gene testing 19.8 The human genome project 19.8.1 How do we compare to other organisms? 19.9 Gene therapy 19.9.1 Current status 19.9.2 Some ethical questions 19.10 The next step: functional genomics 19.11 Pharmacogenomics 19.12 Genetic engineering: recombinant DNA technology 19.12.1 The tools and terminology of the genetic engineer 19.12.2 Transferring genes 19.12.3 Genetic markers 19.13 The polymerase chain reaction (PCR) 19.14 Complementary DNA (cDNA) 19.15 DNA probes 19.16 DNA sequencing 19.17 Genetic engineering applications 19.18 Commercial gene products 19.19 Gene therapy 19.20 Controlling gene expression 19.21 Transcription factors 19.22 Response element 19.23 Genes and cancer: the cell cycle 19.23.1 Checkpoints and cell-cycle regulation 19.23.2 Initiation of cell division and differentiation 19.23.3 Genes controlling the cell cycle 19.24 Viruses and cancer 19.25 Apoptosis 19.26 Caspases Antibacterial drug resistance 20.1 Horizontal gene transfer

	CONTENTS	xiii
20.3	Sulphonamide resistance	294
20.4	Bacterial efflux pumps	296
20.5	Pseudomonas aeruginosa	297
20.6 Vancomycin		297
20.7	Staphylococcus aureus	298
20.8	Clostridium difficile	298
Index	299	

CHAPTER 1 Nutritional requirements

Food consists of water, macronutrients (carbohydrates, fats and proteins) and micronutrients (vitamins, minerals).

The amount of energy contained in food is typically measured in calories; a dietary calorie (C) is actually a thousand calories (kcal) (a calorie is defined as the amount of heat energy that is required to increase the temperature of 1 gram of water by 1 degree Celsius). Carbohydrates (a hydrated energy source) and proteins produce about 4 kcal per gram, while fat (an anhydrous energy source) produces about 9 kcal of heat per gram.

1.1 Carbohydrates and sugars

Carbohydrates are mostly used for energy; limited amounts can be stored in the liver and muscles in the form of glycogen. They vary widely in their complexity, and in the speed with which they are digested and metabolised. Sugars are a class of carbohydrates. Sugar monosaccharides include glucose, fructose and galactose. Disaccharides, composed of two monosaccharide units, include sucrose (common table sugar, glucose and fructose), lactose (found mostly in milk), glucose and galactose (Figure 1.1).

Polysaccharides are polymers of monosaccharides. Starch is a polysaccharide composed of amylose, an essentially linear polysaccharide, and amylopectin, a highly branched polysaccharide; both are polymers of D-Glucose.

Amylose (Figure 1.2) consists typically of 200–20 000 glucose units, which form a helix as a result of the bond angles between the units; the linkages between glucose molecules are referred to as 1–4 (between carbon 1 and carbon 4 of adjacent glucose molecules; see Figure 1.1 for numbering of ring structure).

Amylopectin differs from amylose in being highly branched. Short side chains of about 30 glucose units are attached with 1-6 linkages approximately every 20-30 glucose units along the chain.

Figure 1.1 Simple sugar structures.

Figure 1.2 Amylose.

1.2 Glycogen

Glycogen is similar in structure to amylopectin, but branches more frequently (Figure 1.3). Starch and glycogen polysaccharides provide structures that are used for energy storage, in plants and animals respectively.

Fibre is a polymer carbohydrate. Most fibre is derived from the cell walls of plants and is indigestible, for example cellulose.

Figure 1.3 Glycogen.

Classification	GI range	Common examples
Low GI	55 or less	Most fruit and vegetables (except potatoes, watermelon), grainy breads, pasta, legumes/pulses, milk, products that are low in carbohydrates (e.g. fish, eggs, meat, nuts, oils), apples.
Medium GI	56-69	Whole wheat products, brown rice, basmati rice, sweet potato, table sugar, ice cream.
High GI	70-99	Corn flakes, baked potato, watermelon, boiled white rice, croissant, white bread.
	100	Pure glucose.

Table 1.1 Glycaemic indices of some common foods.

1.3 Glycaemic index

The ability of the body to digest different carbohydrates can be described by the glycaemic index (GI) (Table 1.1).

Low GI foods release glucose more slowly and steadily; high GI foods cause a more rapid rise in blood glucose levels. The latter are suitable for energy recovery after endurance exercise or for a person with diabetes experiencing hypoglycaemia. Only foods containing carbohydrates have a glycaemic index. Fats and proteins have little or no direct effect on blood sugar.

1.4 Lipids

Lipids (fats) provide energy and constitute a major energy store, as well as being an important body mass builder. Up to 20% of a healthy male's total weight comprises fat; this can be as much as 25% in females. Fat is a normal and healthy constituent of the body, cushioning internal organs from shock and providing heat insulation. As an energy source, fat contains over twice the energy per gram as does carbohydrate. Carbohydrates (in the form of glucose) are typically used to provide rapid energy, while fat is burned during sustained exercise. Fat is the primary fuel of choice during slow aerobic exercise, while glucose is used during fast aerobic or anaerobic exercise.

Lipids include fats and oils; oils tend to be liquid at room temperature, fats tend to be solid. A fat molecule consists of one molecule of glycerol, bonded by dehydration synthesis (the loss of water) to three fatty acid molecules (this is a triacylglycerol, Figure 1.4). Fatty acids are

$$\begin{array}{c|c} & O \\ & \parallel \\ CH_2-O-C-R_1 \\ & O \\ CH-O-C-R_2 \\ & O \\ & \parallel \\ CH_2-O-C-R_3 \end{array}$$

Figure 1.4 A triacylglycerol molecule. The glycerol backbone is bonded to three fatty acids $(R_1, R_2 \text{ and } R_3)$.