Metabolic Pathways in Medicine

Howard G.J. Worth
David H. Curnow

Metabolic Pathways in Medicine

Howard G.J. Worth
Principal Biochemist, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex

David H. Curnow
Professor of Clinical Biochemistry and Head of the Department of Clinical Biochemistry, The University of Western Australia; Head of the Clinical Biochemistry Service, The Queen Elizabeth II Medical Centre; Formerly, Head of the Department of Clinical Biochemistry, Royal Perth Hospital

Edward Arnold

First published 1980
by Edward Arnold (Publishers) Ltd
41 Bedford Square, London WC1B 3DQ

British Library Cataloguing in Publication Data

Worth, H G J
Metabolic pathways in medicine.
1. Biological chemistry 2. Metabolism.
I. Title II. Curnow, D H
612'.39 QP514.2

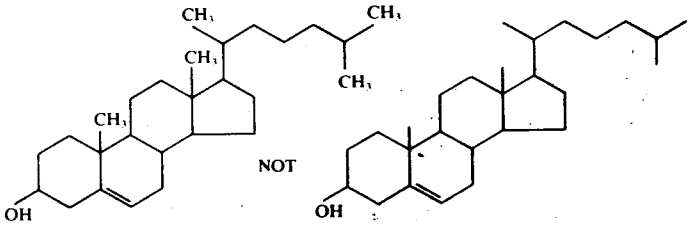
ISBN 0-7131-4336-3

Phototypeset in V.I.P. Plantin by
Western Printing Services Ltd, Bristol
Printed in Great Britain by
The Pitman Press, Bath

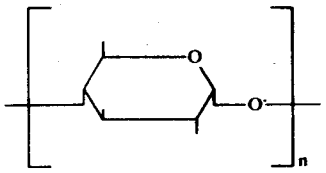
Preface

A few years ago the number of good books available to students of medical biology was very limited. This is no longer true and the potential author now has to be sure that he has something real to offer and is not just writing another book to add to the number already available. We feel that with *Metabolic Pathways in Medicine* we are offering something that is different and will be useful to many students of metabolic medicine.

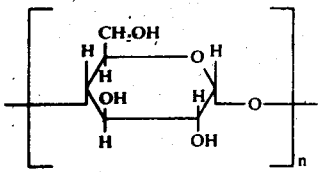
This area of medicine has expanded more rapidly than most over the last fifteen to twenty years and with this expansion has come a diversity of interested specialists including clinicians, biochemists, physiologists and chemists. Despite their differences in background these specialists need to have a common grasp of the basic principles of each others' discipline. We hope that *Metabolic Pathways in Medicine* will make a contribution to the basic principles of biochemistry for the non biochemist. Neither of us is a specialist in biochemistry and because of this we feel we may be more aware of the problems encountered by the non-specialist in getting to grips with the basic principles. Each pathway is accompanied by comprehensive formulae depicting each step. We have attempted to make these as unambiguous as possible. For example we have clearly stated the position of methyl side groups in steroid molecules although these are frequently omitted, thus the formula for cholesterol is given as:



Undesignated bonds are not used to denote carbon-hydrogen links. It may always be assumed where a carbon appears to be less than tetravelent that it has sufficient hydrogen atoms linked to it to make it tetravalent. For example C-1 in cholesterol has two carbon/hydrogen linkages. The only place where the first of these two rules has been disregarded is in the metabolism of glycogen in Chapter 1. Here in some places the glucose moiety has been represented thus:-



The position of the side group (-OH or -CH_2OH) has been indicated, but the group itself omitted for the sake of the clarity of the diagram. As before, carbon centres which appear to be less than tetravalent become so by the addition of hydrogen/carbon linkages, the stereo chemistry of the hydrogen atom being opposite to that indicated for the groups in the diagram above. Thus the full formula for the glucose moiety becomes:



To have used this nomenclature in full each time we feel would be confusing and detract from the main points of the metabolic pathway.
We have used the Recommendations (1972) of the International Union of Pure and Applied Chemistry and the International Union of Biochemistry for enzyme nomenclature, but have also included trivial names where appropriate. The Enzyme Commission classification (E.C. designation) is also included. This is useful in that it gives an indication of the function of the enzyme, for example the first number indicates to which of the six main groups the enzyme belongs, viz:

1 oxidoreductase
2 transferase
3 hydrolase
4 lyase (cleaving)
5 isomerase
6 ligase (synthesizing)

A more detailed analyses of classification may be found in the Commission's publication on Enzyme Nomenclature. Some enzymes that are discussed have not yet been designated; this is made clear at the appropriate points in the text.
We believe that the usefulness of this book is dependent on keeping text and relevant diagrams on opposite pages. In order to do this some tailoring has been necessary, and so, although the student may feel that more detail would have been useful in places, it would have been at the expense of clarity. As a result little detail of control mechanisms has been included. Where a pathway is commonly known by more than one name, for example the glycolytic pathway, the common names have been included. The non specialist student is often confused by a plethora of names, and his confusion is only alleviated if he sees them all stated in the same place.

1979

HGJW
DHC

Abbreviations

ACP	Acyl carrier protein
ACTH	Adrenocorticotrophic hormone
ADP	Adenosine-5′-diphosphate
AMP	Adenosine-5′-monophosphate
Arg	Arginine
Asp	Aspartate
ATP	Adenosine-5′-triphosphate
cAMP	Cyclic adenosine-5′-phosphate
CDP	Cytidine-5′-diphosphate
CMP	Cytidine-5′-monophosphate
CoA	Coenzyme A derivative (used in text)
CTP	Cytidine-5′-triphosphate
DNA	Deoxyribonucleic acid
DOPA	3,4-Dihydroxyphenylalanine
$FADH_2$	Flavin adenine dinucleotide (reduced form)
$FMNH_2$	Flavin mononucleotide (reduced form)
GDP	Guanosine-5′-diphosphate
GMP	Guanosine-5′-monophosphate
GTP	Guanosine-5′-triphosphate
HbO_2	Oxyhaemoglobin
HHb	Reduced haemoglobin
$HHbCO_2$	Carbaminohaemoglobin
His	Histidine
HMGCoA	Hydroxymethylglutaryl coenzyme A
HMMA	4-Hydroxy-3-methoxy mandelic acid
HSCoA	Coenzyme A (used in formulae)
IDP	Inosine-5′-diphosphate
Ile	Isoleucine
IMP	Inosine-5′-monophosphate
IUPAC	International Union of Pure and Applied Chemistry
ITP	Inosine-5′-triphosphate
K	Equilibrium constant
Km	Michaelis constant
Leu	Leucine
NADH	Nicotinamide adenine dinucleotide (reduced form)
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
Ⓟ and Pi	Phosphate or pyrophosphate
Phe	Phenylalanine
PKU	Phenylketonuria

Pro	Proline
RNA	Ribonucleic acid
SCoA	Coenzyme A derivative (used in formulae)
Ser	Serine
Tyr	Tyrosine
UDP	Uridine-5′-diphosphate
UMP	Uridine-5′-monophosphate
UTP	Uridine-5′-triphosphate
Val	Valine
VMA	Vanilmandelic acid

Contents

Preface iii

Abbreviations viii

1. Carbohydrates 1
Introduction 1
Glycolytic pathway 4
Pentose phosphate pathway 10
Glucuronate-xylulose cycle 16
Glycogenesis (α-1,4-glucan formation) 20
Glycogenesis (branching) 22
Glycogenolysis 22
Control of glycogenesis and glycogenolysis 26
Fructose metabolism 28
Galactose metabolism 30
Mannose metabolism 32
Pyruvate 34

2. Lipids 36
Degradation of triglycerides 36
β-Oxidation of fatty acids 38
β-Oxidation of palmitic acid 40
Oxidation of fatty acid containing an odd number of carbon atoms 42
Oxidation of unsaturated fatty acids 42
Fatty acid synthesis 44
Mitochondrial fatty acid synthesis and chain desaturation 46
Synthesis of triglycerides 48
Acetyl coenzyme A 50
Ketone bodies 52
Cholesterol synthesis 54
Lecithin synthesis 58
Synthesis and degradation of sphingomyelin cerebrosides and gangliosides 62

3. Amino Acids 64
Tyrosine 64
Phenylalanine metabolism 66
Methionine metabolism 70
Histidine metabolism 72
Leucine metabolism 74
Isoleucine and valine metabolism 76
Tryptophan metabolism 78
Alternative tryptophan metabolism 80
Formation of 5-hydroxyindolacetate 82
Proline and hydroxyproline metabolism 84
Urea synthesis 86

4. Nucleic Acids 90
Purine synthesis 90
Purine degradation 92
Pyrimidine synthesis 94
Pyrimidine degradation 98

5. Haem 100
Haem synthesis 100
Haem degradation 106

6. Vitamins B 110
Thiamine 110
Biotin 112
Pantothenate 114
Pyridoxal 116
Niacin 118
Folate 120

7. Steroid Hormones 122
Introduction 122
Cortisol synthesis 126
Aldosterone synthesis 130
Testosterone synthesis 132
Oestrogen synthesis 134
Feto-placental synthesis 138

8. Vitamin D 142

9. Bile Acids 144

10. Catecholamines 148
Adrenaline and noradrenaline 148

11. Thyroxine 152

12. Oxidation Processes 154
Tricarboxylic acid cycle 154
Oxidative phosphorylation 158

13. Transport Mechanisms 160
Fatty acid transfer across mitochondrial membrane 160
Acetyl coenzyme A transfer across mitochondrial membrane 162
Renal transport 164
Oxygen and carbon dioxide transport 166

14. Angiotensin 168

15. Coagulation and Fibrinolysis 170
Coagulation 170
Fibrinolysis 172

Index 174

1
Carbohydrates

Introduction

Glucose is at the centre of mammalian carbohydrate metabolism, and the homeostasis of blood glucose concentration is affected by many factors.

Blood glucose concentration is increased by:

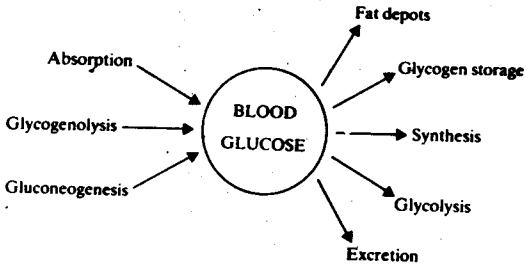
Absorption. Temporary increases in blood glucose may result from the absorption from the gut of ingested glucose, glucose-containing oligosaccharides (sucrose, lactose, raffinose series of saccharides etc) and glucose-containing polysaccharides (starch, glycogen).
Glycogenolysis. Formation of glucose by the degradation of liver glycogen.
Gluconeogenesis. Gluconeogenesis is the hepatic synthesis of glucose from certain amino acids derived from protein, and from lactate derived, for example, from muscle glycogen.

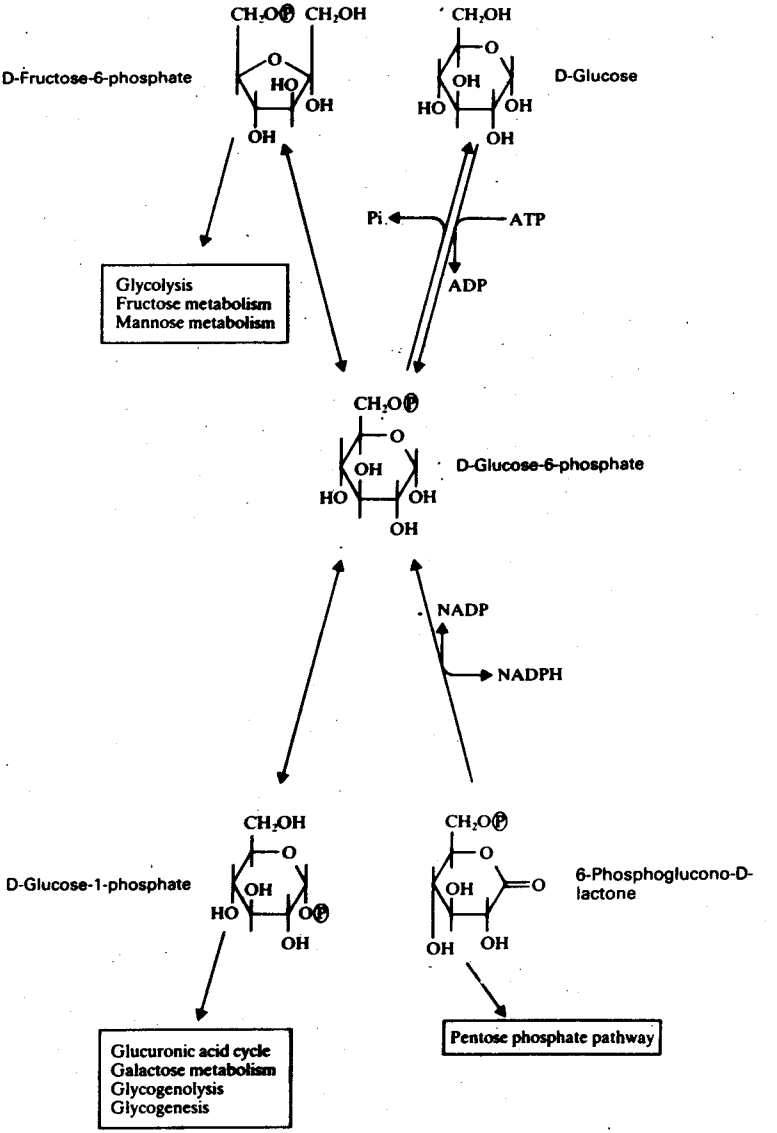
Blood glucose concentration is decreased by:

Triglyceride synthesis. Glucose may be converted to glycerol and fatty acids and stored as triglycerides in fat depots. This is a means of storing energy.
Glycogenesis. Glycogen is the main form of carbohydrate store in man, but is of limited capacity.
Synthesis. Conversion to other monosaccharides, e.g. fructose and galactose. Synthesis of disaccharides (lactose), mucopolysaccharides, glycolipids, glycoproteins and nucleic acids. Formation of glucuronic acid for the conjugation of steroids, bilirubin etc.
Glycolysis and oxidation. Degradation of glucose via pyruvate and finally to carbon dioxide and water under aerobic conditions with energy release.
Excretion. Glucose is virtually completely reabsorbed by the renal tubules unless the renal threshold is exceeded, in which case glycosuria is observed.

These processes, coupled with the effect of many hormones, control glucose homeostasis. Insulin is the main hypoglycaemic hormone, but many others are antagonistic to its action, e.g. growth hormone, glucagon, cortisol and adrenaline.

Because of the importance of glucose in carbohydrate metabolism and the need for its homeostatic control, the measurement of its blood concentration is of considerable importance. Glucose-6-phosphate, however, may be regarded as the central metabolite in carbohydrate metabolism.


Fat depots
Absorption
Glycogen storage
BLOOD
GLUCOSE
Glycogenolysis
Synthesis
Gluconeogenesis
Glycolysis
Excretion


D-Fructose-6-phosphate
D-Glucose
Pi
ATP
ADP
Glycolysis
Fructose metabolism
Mannose metabolism
D-Glucose-6-phosphate
NADP
NADPH
D-Glucose-1-phosphate
6-Phosphoglucono-D-lactone
Glucuronic acid cycle
Galactose metabolism
Glycogenolysis
Glycogenesis
Pentose phosphate pathway

Glycolytic pathway
(Glycolysis, Embden-Meyerhof Pathway)

D–Glucose → D–Glucose–6–phosphate

ATP: D—hexose 6–phosphotransferase (E.C.2.7.1.1). More commonly known as hexokinase Like all kinases this enzyme nees the presence of ATP as substrate and Mg^{++} as cofactor. K at pH 7·4 = 6300 and the reverse reaction is very slow. Some tissues contain glucokinase which specifically catalyses glucose phosphorylation, while hexokinase will enable phosphorylation of other hexoses also. This reaction is an important rate-determining step in glucose utilization.

D–Glucose–6–phosphate → D–Glucose

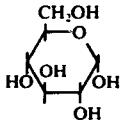
D—Glucose–6–phosphate phosphohydrolase (E.C.3.1.3.9). More commonly known as glucose–6–phosphatase Mg^{++} is a cofactor. The reaction is irreversible and is not the reverse of the hexokinase reaction. The energetics are different and neither ATP nor ADP is involved in the reaction. The enzyme is absent in glycogen storage disease Type I, Von Gierke's disease, a serious condition causing hepatomegaly and also involving the kidneys. Hypoglycaemia, hyperlipidaemia, lactic acidosis, hyperuricaemia and aminoaciduria may occur.

D–Glucose–6–phosphate ↔ D–Fructose–6–phosphate

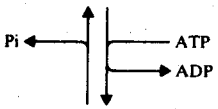
D–Glucose–6–phosphate ketol–isomerase (E.C.5.3.1.9). More commonly known as glucose phosphate isomerase This is an easily reversible reaction with K at pH 7·4 = 2·3 (fructose–6–phosphate → glucose–6–phosphate), thus favouring the formation of glucose–6–phosphate. No cofactors are required.

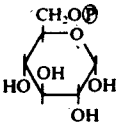
D–Fructose–6–phosphate → D–Fructose–1,6–diphosphate

ATP: D—fructose–6–phosphate 1–phosphotransferase (E.C.2.7.1.11). More commonly known as 6–phosphofructokinase In this reaction Mg^{++} is a cofactor, ADP and AMP are activators and citrate and ATP are inhibitors; ATP is also a substrate. The enzyme is highly specific and the reaction not easily reversible. It provides an important rate determining step in glycolysis and gluconeogenesis. The muscle enzyme is absent in Type VII glycogen storage disease, clinically similar to Type V disease, neither being seriously incapacitating.

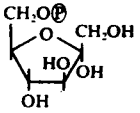


D-Glucose

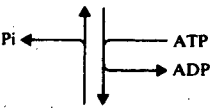


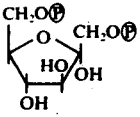


D-Glucose-6-phosphate



D-Fructose-6-phosphate





D-Fructose-1,6-diphosphate

D–Fructose–1,6–diphosphate → D–Fructose–6–phosphate

D–Fructose–1,6–diphosphate 1–phosphohydrolase (E.C.3.1.3.11). More commonly known as hexose or fructose diphosphatase This enzyme is inhibited by a high substrate concentration, AMP, fluoride and citrate. Mg^{++} is a cofactor. The reaction is irreversible and should not be considered as the reverse reaction of phosphofructokinase (cf. glucose–6–phosphatase and hexokinase). Fructose–1, 6–diphosphatase deficiency is a rare congenital abnormality resulting in hepatomegaly and hypoglycaemia.

D–Fructose–1,6–diphosphate ↔ Dihydroxyacetone phosphate + D–Glyceraldehyde–3–phosphate

D–Fructose–1,6–diphosphate D–glyceraldehyde–3–phosphate–lyase (E.C. 4.1.2.13). More commonly known as fructose diphosphate aldolase The reaction favours the formation of the hexose; K at pH 7·4 = 10^{-5}. For the reaction to proceed towards the right, one of the products (trioses) must be removed rapidly. The enzyme is specific for dihydroxyacetone phosphate but less specific towards aldehydes. The enzyme is deficient in hereditary fructose intolerance, which causes serious hypoglycaemia.

Dihydroxyacetone phosphate ↔ D–Glyceraldehyde–3–phosphate

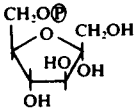
D–Glyceraldehyde–3–phosphate ketol–isomerase (E.C.5.3.1.1). Commonly known as triosephosphate isomerase These trioses are biologically interconvertible with K at pH 7·4 = 25 (glyceraldehyde-3-phosphate → dihydroxyacetone phosphate). Dihydroxyacetone phosphate is involved in triglyceride synthesis.

D–Glyceraldehyde–3–phosphate ↔ 1,3–Diphospho–D–glycerate

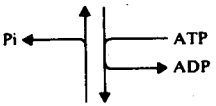
D–Glyceraldehyde-3-phosphate: NAD oxidoreductase (E.C.1.2.1.12). Commonly known as glyceraldehyde phosphate dehydrogenase or triosephosphate dehydrogenase. The forward reaction requires inorganic phosphate and NAD. K at pH 7·4 = 1. Iodoacetate is an inhibitor. Reactions from this point on in the pathway have been illustrated as two molecules at each stage, i.e. conversion of two molecules of 1,3–diphosphoglycerate to two molecules of 3–phosphoglycerate. This follows from the aldolase reaction producing two triose molecules from one hexose and by following this convention the energetics for the overall pathway may be calculated more easily.

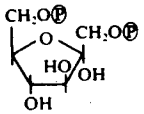
1,3–Diphospho–D–glycerate ↔ 3–Phospho–D–glycerate

ATP: 3–phospho–D–glycerate 1–phosphotransferase (E.C.2.7.2.3). More commonly known as phosphoglycerate kinase The mechanism of reaction is similar to that of glucokinase, but is biologically reversible, K at pH 7·4 = 3000. Mg^{++}, Mn^{++} or Ca^{++} is needed as cofactor.

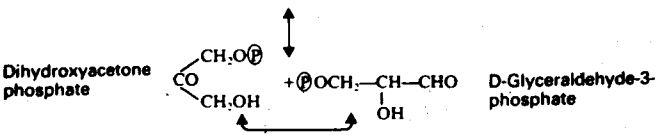


D-Fructose-6-phosphate



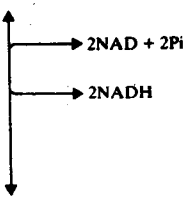


D-Fructose-1,6-diphosphate

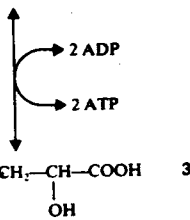


Dihydroxyacetone phosphate

D-Glyceraldehyde-3-phosphate



1,3-Diphospho-D-glycerate



3-Phospho-D-glycerate