HANDBOOK OF CLINICAL NEUROLOGY

VOLUME 27

METABOLIC AND DEFICIENCY DISEASES OF THE NERVOUS SYSTEM

PART I

METABOLIC AND DEFICIENCY DISEASES OF THE NERVOUS SYSTEM

PART I

Edited by

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in collaboration with

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NORTH-HOLLAND PUBLISHING COMPANY · AMSTERDAM · OXFORD

AMERICAN ELSEVIER PUBLISHING CO., INC. · NEW YORK

Library of Congress Catalog Card Number: 68-8297

ISBN for the complete set: 0 7204 7200 8
ISBN North-Holland for this volume: 0 7204 7227 ×
ISBN American Elsevier: 0 444 11209 ×

120 illustrations, 43 tables

PUBLISHED BY:

NORTH-HOLLAND PUBLISHING COMPANY · AMSTERDAM
NORTH-HOLLAND PUBLISHING COMPANY, LTD · OXFORD

SOLE DISTRIBUTORS FOR THE U.S.A. AND CANADA:

AMERICAN ELSEVIER PUBLISHING COMPANY, INC.
52 VANDERBILT AVENUE
NEW YORK, N.Y. 10017

PRINTED IN GERMANY

Foreword to volumes 27, 28 and 29

When planning these volumes on Metabolic and Deficiency Diseases, the Editors had to decide what, for their purpose, constitutes a metabolic disorder of the nervous system – the exact boundaries of this subject being difficult to define.

The clinical disorders they wished to bring together were those in which an alteration in metabolism, occurring within or outside the central nervous system, plays a major role in producing clinical dysfunction of the nervous system. Such disorders range from those of heredo-degenerative origin to toxic or systemic diseases.

Nervous system dysfunctions related to toxins have been excluded unless the major effect of the toxin is metabolic or the toxin itself is an important metabolite. Vitamin toxocities, in addition to deficiencies, have been dealt with. The numerous neurological problems associated with alcoholism are the only organic toxicities which have been included. The remaining toxicities will be presented in a future volume of this Handbook: 'Intoxications of the Nervous System'.

The neurological manifestations of systemic diseases have been included if the disease results in a metabolic disorder (whether or not this has been elucidated) leading to some form of nervous system dysfunction. Hence, the effect of uremia, liver failure and electrolyte imbalance are discussed, but problems caused by collagen vascular disorders, hematological disorders, sarcoidosis, etc. will be presented in the volume, 'Neurology of Systemic Disease'.

It will be obvious from the foregoing that these volumes are not limited to the inborn errors of metabolism; in fact, many inborn errors have been absorbed into other volumes – for example, 'Leucodystrophies and Poliodystrophies' (Volume 10). It is, of course, an artefact to define some hereditary disorders as metabolic and others as degenerative, since the latter may well be metabolic disorders awaiting elucidation. In general, we have included only those disorders in which there is some evidence of a known metabolic deficit.

In this Handbook, a major concern of both the Editors and their collaborators is to keep the time between completion of a chapter and its publication as short as possible. The main problem has always been the failure of some contributors to complete their manuscripts within the given deadline. Especially in this rapidly growing field, time is an important factor, as new inborn errors of metabolism are being identified every 4–5 months. In two ways, we have managed to overcome this recurring headache of delayed submission. The first was the editorial decision to restructure the internal

organization so that instead of delaying an entire volume for a single chapter, groups of chapters were moved to facilitate rapid publication. The second was the willingness of new contributors to take over the writing of chapters at short notice when the initial authors were unable to fulfill their obligations. We are indebted to Professor Klaus Kunze who stepped into the breach when the untimely and violent death of Professor Erbslöh prevented him from working with Dr. Leitenmaier on Vitamin B_{12} deficiency. We are also grateful to Drs. Donna Bergen, Stanley Fahn, Oleh Hornykiewicz and Peter Huttenlocher for preparing their contributions within a short space of time.

The Editors feel that these three volumes provide a comprehensive review of biochemical neurology in diseased states, which will be useful as a background to, and a basis for, further developments. The success of biochemical research in this rapidly growing field is clear, and it has become evident that the future of neurological understanding lies largely in the hands of the neurobiochemist and the developmental technologist.

P.J.V.
G.W.B.
H.L.K.

Acknowledgement

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

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Contents

CHAPTER 1

Carbohydrate and energy metabolism of the central nervous system: biochemical approach

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Normal brain function requires a continuous supply of nutrients from the blood stream; of these, by far the most critical are glucose and oxygen. The absolute dependence of the brain on these two nutrients has long been recognised from the seizures, coma and ultimate death which result relatively quickly from their lack. The endogenous stores of glucose, glycogen and high energy phosphate compounds (Table 1) are so low as to support brain function for minutes only; continued function requires a constant supply of glucose and oxygen from the blood stream. The normal rates of glucose and oxygen consumption by the human brain, and indeed the brains of mammals in general, account for 20 to 25% of the total bodily consumption, although the brain is only 3% of the total adult body weight (Himwich 1951; Kety 1957). The interest in this area of brain metabolism stems also from the apparent lack of obvious work carried out by the brain, in comparison to the mechanical work performed by heart and other muscles, the biosynthetic work carried out by 'exporting organs' such as liver and pancreas, or the osmotic work of the kidneys. It is to the physiological function of the brain that we must turn in terms of the electrical energy produced by the functioning brain: perhaps as much as 40% of the energy produced from the oxidative metabolism in the brain (Whittam, 1962) is used to support the active transport of sodium (Na^+) and potassium (K^+) ions described by Pappius in Volume 28. The high rate of energy utilization is supported by the highest rates of energy production in the body – as much as 20 times the average for the whole body. Indeed the brain is unique amongst mammalian organs, not only in its electrical excitability but also in these quantitative aspects of its intermediary metabolism. It is characterised by exhibiting a respiratory quotient (i.e. the ratio of CO_2 produced to the O_2 consumed) of 0.99 (Gibbs et al. 1942). The brain is very sensitive to any interference in its energy metabolism and the effects of vitamin deficiency in causing convulsions, mental abnormality or retardation are a reflection of this; relevant metabolic pathways in which the vitamins function as coenzymes are common to all organs of the body and the peculiar lability of cerebral function is quantitative rather than qualitative.

Interest in energy metabolism of the brain has received much impetus from observations that the basal metabolic rates can be increased rapidly, transiently and reversibly, by techniques which cause generalised membrane depolarization. Thus, in vivo, electric shock has been shown to cause 10- or 20-fold increases in the rate of carbohydrate metabolism, which may last only seconds, until endogenous supplies of nutrients are exhausted; use of these far outstrips the rate of supply from the bloodstream. In vitro also, electrical stimulation

References, p. 23

TABLE 1

Concentrations of intermediates of energy metabolism in the brain.

Metabolite	Content
Glucose	1.0–1.5
Glycogen	1.5–2.0
ATP	2.5–3.0
ADP	0.3–0.5
AMP	0.05–0.1
3′,5′-Cyclic AMP	0.001–0.002
Creatine phosphate	3.0–4.5
Phosphoenolpyruvate	0.8
Acetylcoenzyme A	0.006
NAD^+	0.3
NADH	0.1

Values are μmol/g of whole brain, rapidly frozen without anaesthesia. (From McIlwain and Bachelard 1971; Heinrich et al. 1973; Bachelard and Strang 1974.)

of slices causes vastly increased metabolic rates. These studies indicate an enormous reserve capacity of the metabolic machinery and pose questions on the underlying mechanisms of metabolic regulation. Given this excessive capacity, what mechanisms operate to control rates at normal levels and how are these control mechanisms overcome or reversed in the stimulated tissue? While all of the answers are not yet available, some insight can be gained from the results of investigations described below.

In this chapter the pathways of intermediary metabolism are described and the mechanisms which are concerned with their regulation are discussed. The known metabolic effects of adverse conditions (ischaemia, hypoglycaemia, hypoxia) are noted; the clinical aspects and implications of these are discussed in Chapters 2, 3 and 4 of this volume).

EXPERIMENTAL APPROACHES

In vivo techniques

Some of the earliest evidence for rates of consumption of glucose and oxygen by adult human brain emerged from 'arterio-venous difference studies'. This technique, which has been applied to measurement of rates of utilization of normal substrates in the brain, involves comparison of the concentration of a particular chemical in the blood entering the brain with the concentration of the same chemical in the blood leaving the brain. In order to calculate metabolic rates, either of consumption or of production, a measure of the rate of blood flow through the brain is also required. Arterial blood has usually been sampled from the brachial or femoral artery and venous blood from the jugular vein.

The cerebral blood flow (CBF) rate is determined by measuring the arterial and venous concentrations of a metabolically-inert molecule (e.g. nitrous oxide or krypton), at precise time intervals after injection or inhalation. The blood flow rate is calculated from the formula:

$$Vt/\left[\int_0^t (A-V)\,dt\right]$$

where A and V are the arterial and venous concentrations (in vol.%), and t is the time interval in minutes. The value obtained, which should become constant within 8–10 min after administration, represents the CBF rate in ml/min/g of brain.

Measurement of the arterio-venous difference in concentrations of selected metabolites, together with the CBF rate, have been used by many workers (Gibbs et al. 1942; Kety 1957) to calculate rates of utilization of glucose and oxygen and rates of production of lactate and carbon dioxide in the brains of men, women and children under a variety of conditions. The metabolic rate is calculated from the formula:

$$\text{blood flow rate} \times \frac{(A-V)}{100}$$

Adults were found to have a CBF rate of 0.5–0.6 ml/g min: the lower rates came from erect subjects and the higher from supine subjects. The rate of oxygen consumption was between 0.03 and 0.04 ml O_2/min g and of glucose consumption, 0.05–0.06 mg/min g, equivalent to between 0.28 and 0.33 μmoles/min g (Table 2). In young children the rates of CBF and of metabolism may be as much as double those observed in adults and very young children seem also to be more resistant to hypoxia (below). The rates of energy metabolism so measured in adults were not significantly different in schizophrenia, during natural sleep or intense mental activity, but were shown

References, p. 23

TABLE 2

Rates of cerebral metabolism calculated from arterio-venous differences.

Constituent	Blood level		Difference (venous–arterial)		Rate of consumption (−) or of formation (+)	
	arterial	venous		(μmol/g)	(μmol/min g)	(μmol/hr g)
Glucose (mg/100 ml)	92.0	82.0	−10.0	−0.56	−0.28	−17
Lactate (mg/100 ml)	9.9	11.5	+1.6	+0.178	+0.089	+5.4
Oxygen (ml/100 ml)	19.6	12.9	−6.7	−3.0	−1.50	−90
Carbon dioxide (ml/100 ml)	48.2	54.8	+6.6	+2.95	+1.475	+89

The calculations are based on a CBF rate of 0.5 ml/min/g for adult human brain. (From Gibbs et al. 1942; Kety 1948.)

to be lower during deep anaesthesia, in insulin coma or in diabetic coma.

The rates of consumption of glucose and oxygen can be quantitatively accounted for by rates of production of CO_2, lactate and pyruvate, from studies of the type described above on the normal brain. Many similar experiments have been performed on a variety of animals and, in general, these quantitative results are almost identical to those observed in man. With relatively small laboratory animals (rat and mouse), determinations of rates of CBF and metabolism are less easy, due to the small size of blood vessels; in general the results indicate higher rates of metabolism.

Use of the arterio-venous technique is as useful now as it was 30 years ago: examples of its application are given below in recent studies on glucose transport, hypoglycemia and hypoxia, and of the utilization of ketone bodies under unusual conditions of prolonged starvation. This has been about the only feasible way of exploring cerebral metabolism in man but a variety of alternative techniques are used on experimental animals: whole-head perfusion techniques were used by Geiger and his co-workers (Geiger 1958) to study intermediary metabolism in the brain, and have recently been applied to research into hypoxia. Some of the difficulties inherent in studying the effects of chemicals, drugs and hormones which do not readily enter the brain from the bloodstream (see Chapter 15, Volume 28) have been circumvented by direct intracerebral injections into the cisterna magna (Feldberg 1963; Strang and Bachelard 1971).

Since the advent of radioisotopes, the use of ^{14}C- and ^{3}H-labelled precursors have shown that only a proportion of the glucose taken up to the brain from the blood stream is oxidised *directly* to form CO_2: some is rapidly incorporated into amino acids such as glutamate, glutamine, aspartate and γ-aminobutyrate (Vrba 1962) due to rapid isotopic exchange between intermediates of the tricarboxylic acid cycle (Bachelard 1965; Lindsay and Bachelard 1966) and the amino acids (below). These techniques, involving measurement of the rates of labelling of these and other intermediates such as lactate have proved useful in studying the effects on regulation of centrally-active drugs (Bachelard et al. 1966; Strang and Bachelard 1971, 1973).

The rapidity of cerebral anaerobic glycolysis continues post mortem so precautions must be taken to prevent the changes in concentrations of intermediates which can occur within seconds. The most common method used for small animals is rapidly freezing the whole animal by total immersion in liquid nitrogen. This is based on the original method described by Kerr (1936) who froze the brains of animals by pouring liquid nitrogen over their exposed skulls, and has been used in recent studies (Granholm et al. 1968); a plastic funnel is placed directly over the skull of the anaesthetized animal and liquid nitrogen is poured in. The whole-body freezing technique requires no anaesthetic but has the disadvantage that the animal convulses briefly. The funnel technique has the disadvantage that anaesthesia is involved.

A further method has been devised for rapid freezing without the use of anaesthetics and with-

References, p. 23

out convulsions (Veech et al. 1973). In this, the brains of conscious small animals are expelled by air-pressure directly into a freezing chamber.

In vitro techniques

Various problems and limitations are experienced in the application of the in vivo techniques noted above; these include:

– difficulties in access of many chemicals from the blood stream to the brain: intracerebral injection may not be an adequate alternative since the penetration of the injected substance throughout the brain substance has proved in many cases to be limited (see Chapter 15, Volume 28).
– the heterogeneity of cell types in the central nervous system (CNS) and the limitations in distinguishing between various aspects of metabolism in them.
– limitations in opportunities to vary the immediate environment of the cells.

The in vitro techniques which have evolved have largely been developed with the object of overcoming these problems but it should be emphasized that such techniques have their own inherent limitations:

– many cerebral functions depend on the architectural and structural relationships between cells and their processes in various regions of the brain, some of which are certain to be disrupted.
– the tissue to medium ratio in incubated preparations is much lower than the ratio of intracellular to extracellular space in situ. Thus, for example, the lactate produced by cerebral metabolism (below) is normally carried away in the venous blood in situ (Table 2) whereas it remains in the immediate environment of the cells in vitro. The recent development of in vitro superfusion methods has overcome this problem to a great extent (Pull et al. 1972).

Much caution should therefore be exercised in extrapolating from results obtained with in vitro preparations to what might be likely to occur in vivo. Nevertheless these in vitro techniques have contributed significantly to our knowledge of cerebral function, particularly those involving the use of carefully prepared cerebral cortex slices. These, preferably hand-cut, are usually taken from the surface of the cerebral cortex of small laboratory animals and are optimally 0.3–0.35 mm thick, to ensure adequate penetration of nutrients. Relatively little damage to cell bodies or their processes is considered to have occurred during their preparation, so the slices are regarded as whole-cell containing samples in which much of the original architectural and structural relationships between constituent cells have been preserved. They maintain resting membrane potentials, and share the unique features of nervous tissues in situ in their electrical excitability. Immediately after their preparation, key metabolic constituents are found to be present in abnormal concentrations, but a

TABLE 3

Changes in concentrations of cerebral constituents during incubation of slices in vitro.

Constituent	Concentration (μmol/g)				
	In vivo		Incubated (min) in vitro		
	total	internal*	total (0)	total (30)	internal (30)**
K^+	100	97	55	85	80
Na^+	60	35	140	110–120	35–40
ATP	2.5		2.0	2.3	
Creatine phosphate	3.0		0.5	2.0	
Inorganic phosphate	3.5		10.0	2.8	

* Calculated intracellular concentration based on an extracellular space of 20%.
** Calculated 'intracellular' concentration based on thenon-inulin space of incubated tissues (McIlwain and Bachelard 1971).

References, p. 23

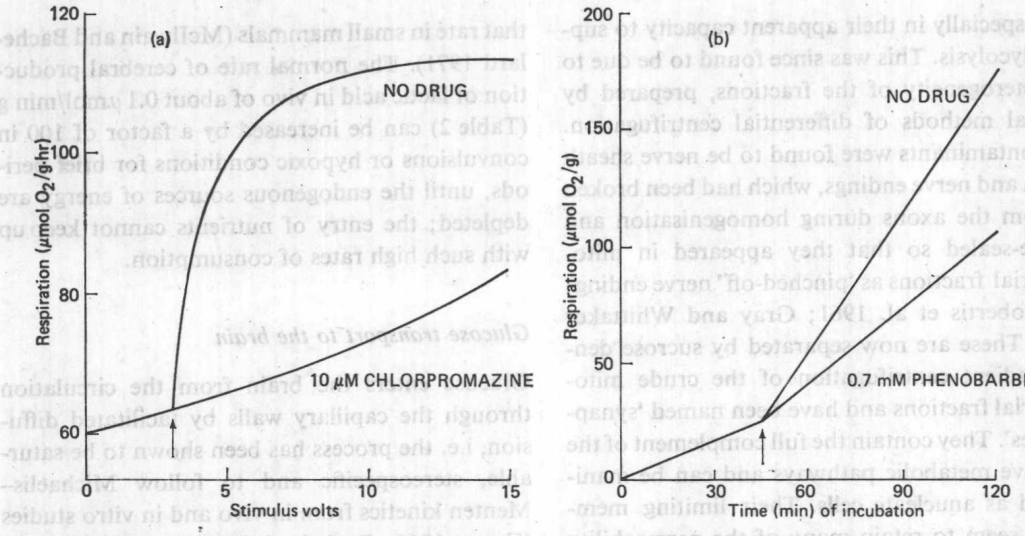

Fig. 1. Inhibition by chlorpromazine and phenobarbitone of the metabolic response to electrical stimulation in vitro. The normal rates of respiration of cerebral cortex preparations incubated in vitro are doubled by electrical stimulation, applied at the arrows. The respiratory responses are prevented by minute concentrations of chlorpromazine (A) and of phenobarbitone (B). (McIlwain 1953; McIlwain and Greengard 1957.)

30 min incubation period in warm, oxygenated, glucose-containing media restores these to close to their original levels (Table 3). In practice, the most sensitive (and most easily monitored) criterion of the metabolic integrity of the incubated tissue is the concentration of K^+. Active pumping of K^+ into the cells, and of Na^+ out from the cells, has been shown to occur during this 'recovery' incubation period (Bachelard et al. 1962).

Such in vitro preparations have been applied to studies on the effects of membrane depolarisation (using electrical stimulation or high extracellular K^+) on cerebral metabolic rates (Winterstein 1929; McIlwain 1953) and to provide some of the first indications (Fig. 1) of the effects of centrally active drugs, such as chlorpromazine and the barbiturates, on cerebral membrane permeability phenomena. Action potentials can now be evoked from brain slices, particularly those prepared from the pre-piriform cortex of the guinea pig (Fig. 2) in which the exposed optic nerve can be stimulated. This preparation offers opportunities to study metabolic and neurophysiological phenomena simultaneously (Richards and McIlwain 1967; Richards and Sercombe 1968).

Investigations using homogenates and cell free preparations of the brain were originally based on those developed for other mammalian tissues, and it seemed from such studies that cerebral mitochondria exhibited unique metabolic abil-

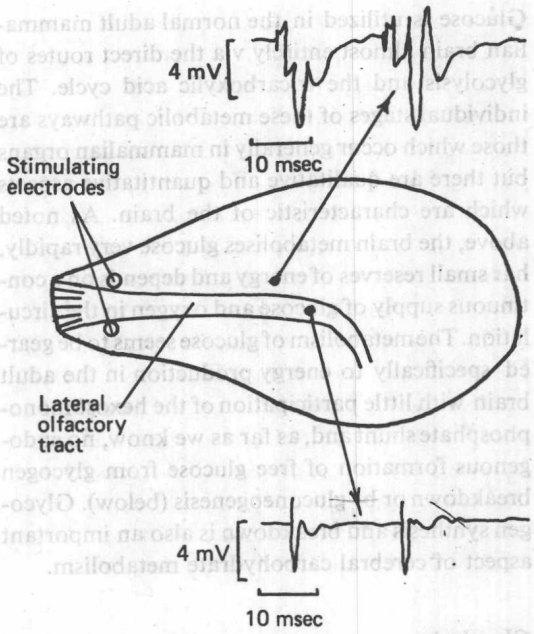

Fig. 2. Action potentials evoked in vitro from the prepiriform cortex of the guinea pig. The stimulus was two identical 10 V pulses of 50 μsec duration, applied 20 msec apart. (Richards and Sercombe 1968.)

References, p. 23

ities, especially in their apparent capacity to support glycolysis. This was since found to be due to the heterogeneity of the fractions, prepared by classical methods of differential centrifugation. The contaminants were found to be nerve sheath myelin and nerve endings, which had been broken off from the axons during homogenisation and had re-sealed so that they appeared in mitochondrial fractions as 'pinched-off' nerve endings (De Robertis et al. 1961; Gray and Whittaker 1962). These are now separated by sucrose density-gradient centrifugation of the crude mitochondrial fractions and have been named 'synaptosomes'. They contain the full complement of the oxidative metabolic pathways and can be manipulated as anucleate cells. Their limiting membranes seem to retain many of the permeability characteristics present in vivo (Johnson and Whittaker 1963; Marchbanks 1967) and have been used to study energy metabolism (Bradford 1969) and transport phenomena (Marchbanks 1968; Heaton and Bachelard 1973).

ROUTES OF CARBOHYDRATE METABOLISM IN THE BRAIN

Glucose is utilized in the normal adult mammalian brain almost entirely via the direct routes of glycolysis and the tricarboxylic acid cycle. The individual stages of these metabolic pathways are those which occur generally in mammalian organs but there are qualitative and quantitative aspects which are characteristic of the brain. As noted above, the brain metabolises glucose very rapidly, has small reserves of energy and depends on a continuous supply of glucose and oxygen in the circulation. The metabolism of glucose seems to be geared specifically to energy production in the adult brain with little participation of the hexose monophosphate shunt and, as far as we know, no endogenous formation of free glucose from glycogen breakdown or by gluconeogenesis (below). Glycogen synthesis and breakdown is also an important aspect of cerebral carbohydrate metabolism.

Glycolysis

The brain uses glucose at rates which vary from 0.3 μmol/min g in man (Table 2) to perhaps twice that rate in small mammals (McIlwain and Bachelard 1971). The normal rate of cerebral production of lactic acid in vivo of about 0.1 μmol/min g (Table 2) can be increased by a factor of 100 in convulsions or hypoxic conditions for brief periods, until the endogenous sources of energy are depleted; the entry of nutrients cannot keep up with such high rates of consumption.

Glucose transport to the brain

Glucose enters the brain from the circulation through the capillary walls by facilitated diffusion, i.e. the process has been shown to be saturable, stereospecific and to follow Michaelis–Menten kinetics from in vivo and in vitro studies (Crone 1965; Bachelard 1971; Bachelard et al. 1973). The maximum capacity of the uptake process under normal conditions is quite low in relation to the overall rates of glucose consumption and to the capacities of subsequent enzymic reactions (Table 4). In whole tissue preparations the maximum velocity (V) is 0.6–0.7 μmol/min g and half-maximum velocity is reached at glucose concentrations of 5–8 mM (the Michaelis constant, K_m). Thus the maximum theoretical capacity of the glucose transport process is only some 2–3 times the normal rate of glucose consumption and at the K_m value, is only slightly higher. It is of interest that the K_m value is of the same order of the glucose concentration in the plasma reaching the brain. This indicates that the initial stage (transport) in the utilization of glucose is important in regulation: Table 5 shows that the rate at which glucose can enter the brain becomes limiting when the plasma glucose concentration falls relatively slightly, to about 2 mM (or 30 mg/100 ml). This is the glucose concentration below which respiratory rates begin to fall and clinical symptoms of hypoglycaemia begin to appear (discussed subsequently).

Enzymic stages in glycolysis

These are summarised in Fig. 3 and Table 4. A comparison of the endogenous intracellular substrate concentrations with the K_m values for the individual enzymes show that the K_m values are generally lower than the relevant substrate concen-

References, p. 23