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Biochemistry and the Central Nervous System

FIFTH EDITION

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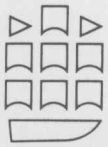

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Biochemistry and the Central Nervous System

Preface to the fifth edition

This new edition again bears witness to the rapid development of biochemical studies of neural systems. It is nearly half as large again as the fourth edition, and new material, plus regrouping of much previously written has given four new chapters: expansion is especially noteworthy in relation to neurotransmitters and the mediation and consequences of their actions. The object of the book remains unchanged, in giving a reasoned exposition of the current status of its subject to students and research workers in medicine and science, especially to those concerned with biochemistry, neurophysiology, neurochemistry, neuropharmacology, neurology and psychiatry.

The present edition comes at a time when its subject is increasingly taught both at undergraduate and at postgraduate level. Neurochemistry is now an important component of the neurosciences which feature as subjects both in biology and medicine. It can thus form part of courses for BSc, as well as for higher degrees and for professional qualifications. The replanning of biochemical teaching for such purposes is one factor which has given stimulus to this new edition. Another is the initiation of an MSc in Neurochemistry in the University of London, in the organization of which biochemical teachers of this Department have collaborated with those of the Institutes of Psychiatry, of Neurology and of Ophthalmology. Increasing also are the calls on members of this Department for neurochemical teaching in first degree courses in science and medicine; in recent years such teaching has been given at several schools of London University, with numerous special lectures elsewhere. This reflects in part the growth of neurology and psychiatry in medical curricula: an associated department of biochemistry is called on to give correspondingly increased time to the biochemistry of neural systems. Courses in biochemistry to meet the needs of students of pharmacology, physiology, neurobiology and other of the neurosciences have also involved much growth of neurochemical teaching.

In this rewriting we have been greatly helped by discussion in this and other schools of the University, and with many workers who have come as students and colleagues and who have added expertise and variety to an already intriguing realm of research. Thanks are also due to the publishers for the care which has been given in producing the book.

H. McI.
London, 1985 H. S. B.

Preface to the first edition

This book has developed from research and from teaching in faculties both of medicine and science. Its subject forms part of teaching in physiology and in psychological medicine, in the University of London. In addition, the story of chemical change and structure in the central nervous system presents to the biochemist a well developed branch of his own subject and one which has often been in the forefront of biochemical discovery. Attention has been paid to each of these aspects in the present book.

Biochemistry and the central nervous system overlaps and adjoins several other subjects, notably pharmacology and endocrinology; each year some 3000 papers appear which concern chemical substances or processes and the central nervous system. It has therefore been a major problem to decide how much to include in the present book. The solution chosen has been to include sufficient reference to neighbouring subjects to illustrate where they are applicable to biochemistry and the central nervous system, and it to the neighbouring subjects. When several aspects of the action of a drug can be seen to be linked by known biochemical mechanisms, these are indicated. When hormonal interactions with the central nervous system have as yet little biochemical logic, mention is brief or absent.

Because the subject of the present book extends beyond the limits of biochemistry itself, I have been most grateful for comments on it from Professor Aubrey Lewis and Professor Alfred Meyer, as well as from Professor F. Dickens and from members of the Department of Biochemistry of this Institute. It also owes much to informal discussion in this and in other departments where I have worked, including the Department of Physiology of the University of Chicago, and the Medical School at Dunedin, New Zealand. The last chapter contains material from the Christian Herter Lecture given at New York University College of Medicine in 1954.

London, 1955 H. McI

Contents

1

Biochemical studies of the brain

When chemical investigation of the organs of the animal body developed about 1800, the gross anatomy of the central nervous system was familiar but little was known of its physiology and pathology. These, and especially the histology of the brain, grew to be major subjects during the nineteenth century. Biochemical and electrophysiological studies of the brain remained rudimentary until after the first quarter of the present century. Berger's discovery of rhythmic potential changes from the brain measurable outside the head was made in 1929; reasonably accurate measurement of respiration of cerebral systems began about 1920 with separated tissue, was obtained in perfused animals in 1939 but in normal human subjects not until 1947. Until relatively recently, therefore, there has been much scope for speculation with respect to these most fundamental aspects of cerebral metabolism: the level of energy utilization in the brain and the manner of its adjustment to functional requirements.

Electrophysiological and biochemical exploration of the brain are akin not only in the time at which they developed but also in the velocity of the processes with which they are concerned. Typical changes in electrical potential seen with the electroencephalogram occupy periods of 1 to 1/50 of a second. Changes observed by ordinary biochemical techniques usually take some minutes, but early in the exact study of cerebral constituents it was found necessary to measure processes lasting a second or less. Now one can estimate that during the 1/10 second occupied by a ripple of potential change at alpha frequency appreciable proportions of many important cerebral metabolites are degraded or synthesized. Here one is dealing, not with the fastest cerebral processes in which voltage change and ion migration occupy only parts of a millisecond, but with processes occurring at speeds commensurate with ordinary impressions of the activities of the brain. Interrelations between biochemical and more overt aspects of cerebral functioning have played a large part in making this book. It remains, nevertheless, within a framework largely biochemical for in this manner can best be expressed the biochemical properties on which cerebral function is based and by which also it is characterized and restricted.

THE GROWTH OF CHEMICAL KNOWLEDGE OF THE BRAIN

Metabolic studies of the brain though of recent development had notable precursors. During most of the past 150 years, investigation of neural systems by chemical methods has attracted a reasonable proportion of the chemical resources of the times. It has passed through many phases, which will now be briefly summarized in a fashion which introduces the literature of the subject.

Fractionation of cerebral constituents

The first satisfactory application of chemical methods to the brain was made in studying its composition. This commenced before chemistry had fully emerged as a science; Hensing's notable account dates from 1719 (see Tower, 1983). Other eighteenth-century writers contributed knowledge of inorganic constituents of the brain, but the realization that it and other organs con-

tained a multiplicity of organic constituents did not come until about 1800. Vauquelin (1811) developed a type of investigation which almost became the standard chemical approach of the nineteenth century. By systematic use of an organic solvent and a heavy metal precipitant (ethanol and lead salts) he separated cerebral constituents to fractions with the intention of accounting for all the brain in terms of materials of definite composition. Of the many workers who developed this theme, Couerbe (1833) is noteworthy in attempting to show differences in the composition of the brain in mental disorder and Thudichum in the comprehensiveness of his study: *The Chemical Constitution of the Brain* (1884; 1901; see McIlwain, 1958c, 1975) lists some 140 constituents and carries a comprehensive bibliography. Because of the large proportion of fatty materials in the brain, much of this study concerned lipids. Although succinic acid and proteins also featured, it was their 'chemical statics' with which, in Thudichum's own phrase, he was concerned. Fractionation of cerebral constituents from this point of view is still in progress; it represents an important route to chemical understanding and features prominently in the *Symposia* (1956a, b; 1957b), *Colloquium* (1958), *Handbook* (Lajtha, 1969–1972; 1983 to date) and *Research Methods* (1972 to date).

Metabolic studies

It is a mark of the distinctiveness of biochemistry as a discipline that chemical fractionation of cerebral constituents gave a body of knowledge which did not in itself afford much understanding of cerebral functioning. To a much greater extent this has come, as in physiology as a whole, by two main routes: by study of energy and of membrane relationships, and by the chemical characterization of substances which perform some specific role as substrate, intermediary metabolite, vitamin, enzyme or messenger substance: hormone or neurotransmitter. In the present account, as much quantitative information as possible has been collated about such substances and processes, specifically in the central nervous system. These aspects first received comprehensive treatment by Winterstein (1929) in his contributions on the *General Physiology of Nerve* and on the *Central Nervous System* to Bethe's *Handbook*. Peripheral nerve had then been studied in isolation, both biochemically and electrophysiologically, and such investigations were beginning also with the central nervous system. Winterstein's account of these investigations, to which his laboratory greatly contributed, is excellent in its description of relations between energy metabolism and functional activity. He could of necessity say little or nothing of intermediary metabolism.

This aspect was as far as possible supplied in Page's (1937) *Chemistry of the Brain* but, it is very significant, largely in terms of investigation with tissues from organs other than the brain. Several aspects of cerebral metabolism came to their own in Himwich's (1951) *Brain Metabolism and Cerebral Disorders*, especially those concerned with carbohydrate metabolism. They were also prominent in a Conference (1952) and in several Symposia (1952, 1955, 1956a, b; 1957b; 1959a, b) and Collected papers (1954, 1955): the subject, it will be noted, was expanding rapidly in the 1950s.

Study of substances acting on the brain

Chemical factors were first recognized as capable of a major role in cerebral activities not by the metabolic studies just described, but rather by the spectacular way in which defined substances modified the activities of the brain. Lack of oxygen or the administration of alcohol or morphine were among the earliest examples, followed around 1850 by synthetic drugs developed specifically for their central effects, as has been recounted in *Chemotherapy and the Central Nervous System* (McIlwain, 1957). Chemical induction of changed mental states by such substances gave important data to those who, in the past century, invoked chemical factors in normal mental functioning and in its derangement in disease (see McIlwain, 1955, 1958a, b). The subjects often termed neuropharmacology and psychopharmacology have for some time formed a notable part of pharmacological texts, and have recently developed the specialized literature indicated in Chapters 15 to 17 and to which the book of Cooper et al (1982) gives a valuable biochemical introduction.

Neurochemistry

These various applications of chemistry and biochemistry to the study of the brain have formed a large part of the now well-established subject of neurochemistry. The term *Nervenchemie* in the 1850s meant, more literally, the chemistry of the nervous system (see Schlossberger, 1856). To judge by present literature, for example, the *Handbook of Neurochemistry* (1969–83) and the *Journal of Neurochemistry* (1956 to date), the term is now envisaged to include a much wider application of chemical concepts, techniques and reagents in the many sciences which are concerned with neural structures. To these publications have now been added *Neurochemical Research* (1976 to date) and *Neurochemistry International* (1980 to date). Collected papers entitled *Neurochemistry* appeared in 1955, 1956 (*Symposium*, 1956b), 1958 (*Colloquium*, 1958) and 1962. International symposia in neurochemistry commenced in 1954 and their first meetings concerned the development of the nervous system, its metabolism, chemical pathology and also comparative and regional aspects of its chemistry, physiology and pharmacology. The structural units to which these sciences are applied are primarily the neurons and their assemblies. In biochemical as in biological characteristics, neurons are highly complex and versatile cell-types with a long history of development as part of the organs and organisms to which they contribute. Among the most interesting aspects of current neurochemistry are the quantitative comparisons now being established between chemical concomitants of excitation in neural components as diverse as the giant axons of marine invertebrates and the finely-ramifying dendrites of the mammalian brain.

Reviews of neurochemistry first appeared in the *Annual Review of Biochemistry* in 1959, in the Annual Reports of the Chemical Society for 1960 and now contribute to the *Annual Review of Neuroscience* (1978 to date). *Practical Neurochemistry* (edited by McIlwain, 1975b) and the *Research Methods* (1972 to date) are more immediately connected with laboratory work. The International Society for Neurochemistry held its first meetings in 1967 and 1969 and neurochemical societies or cognate associations have been formed in several countries (Bulletin, 1967). In Britain a Neurochemical Group of the Biochemical Society (1967 to date) has held meetings since 1967 while the American Society for Neurochemistry has published *Transactions* since 1970. The International Brain Research Organization (*IBRO Bulletin*, 1962 and *Monograph Series*, 1975 to date) includes a neurochemical panel, and national Brain Research associations have also been formed in several localities, often with major neurochemical representation. The *Journal of Neurobiology* commenced in 1969 and includes neurochemical subjects. The Neurosciences Research Program (1969) has published a Bulletin since 1964 and subsequently *Study Programs* (1966 to date), and also includes biochemical subjects. The UCLA Brain Information Service issues bibliographies and a guide to neuroenzyme literature (Hoijer, 1969).

Neurobiology

The present account of biochemistry and the central nervous system has a sphere of interest which includes the neurochemistry of the brain but extends beyond it to involve many phenomena of the living animal interacting with its environment. It is then part of neurobiology and of general biology. Input at the special senses is itself primarily chemical, as is indicated in brief accounts of taste, smell and vision in later chapters. An important aspect of subsequent events in the brain itself is the fashion in which incoming signals affect future responses of an animal to repetition of the same or of concomitant signals: phenomena which form part of the study of conditioning, learning and memory. Several recent approaches to these subjects have invoked chemical mechanisms, in which the change representing learning occurs primarily in nucleic acids, at special polypeptide messengers, or by growth of cell-contacts (John, 1967; Kandel & Spencer, 1968; Eccles, 1966; Rosenzweig & Bennett, 1976; Brazier, 1979).

Such approaches see the brain as the main organ of adaptation in higher animals and to seek in cerebral systems the enzyme induction or metabolic adaptation which operates in other organs

and organisms. The occurrence of such adaptation in the brain has long been evident: most of the substance of the brain is first synthesized or assembled while the animal concerned is receiving sensory signals. Synthesis and degradation of structural materials and metabolic machinery of the brain continues throughout life, and is open to the influence of hormones, substrates, activators and inhibitors which modify enzymes and other specific proteins in biological systems generally. An attractive presentation of neurochemistry within a physiological and neurobiological setting is given by McGeer et al (1978). The journal *Neuroscience* (1976 to date) also places neurochemical studies in a wider setting and its *Commentaries* (1980) have been published separately.

Changes which show features in common with metabolic adaptation can also occur to purely electrical input to the brain. Displacement of the normal standing potential at the mammalian neocortex by surface-positive polarization, increases cell-firing, and the resultant increase persists when after a few minutes the polarizing current is discontinued. The persistent change in cell-firing is inhibited by prior application to the cortex, of inhibitors of protein synthesis in concentrations which do not affect the increase in cell-firing during application of the polarizing current. Adaptation to input, sensory and chemical, contributes to individual experience in fashions which have received interpretation from electrophysiological (Popper & Eccles, 1977) but not yet from biochemical viewpoints; this matter is discussed further in Chapter 20.

Biochemistry and psychiatry

Problems of mental illness have given important stimuli to chemical as to other studies of the brain. As psychiatry is much concerned with adaptation and interactions among individuals and groups, metabolic adaptive processes can represent an important approach of which exploration is just commencing. Current methods employ analysis or enzyme assay of the brain and of other parts of the body and an increasing variety of non-invasive in situ measurements based on isotope techniques (Ch. 2). An impressive number of genetically-conditioned errors of metabolism have mental disorder or defect as prominent symptoms (Chs 8, 11). Orthodox chemotherapeutic processes also constitute a major application of chemistry to diseases of the central nervous system (McIlwain, 1957; Gordon, 1967; Bradley & Brimblecombe, 1972; Lickey & Gordon, 1983). Programmed synthesis of organic compounds, guided by assays which include behavioural tests have afforded compounds which disturb normal cerebral functioning as well as others which restore such function when it is abnormal.

Comments on psychoactive compounds of these various categories will be found widely distributed among the chapters of the present book; for the substances or processes which may afford starting-points for future therapeutic applications are of diverse chemical types. Journals of neurology and psychiatry have in recent years contained up to 40% of papers with pronounced chemical or pharmacological interests. The bibliographies of the present book will be noted to contain many references to such journals, and year books in these subjects which also carry chemical aspects include *Recent Progress in Psychiatry*, *Progress in Neurology and Psychiatry* and the Research Publications of the *Association for Research in Nervous and Mental Disease*. Literature quoted in the present book is necessarily selected but is intended to cover or to lead to information on the greater part of the subject especially in its quantitative aspects. It has also been considered important to indicate clearly the type of neural system and preparation which afforded the information recorded. The following references include a few general publications related to biochemistry and the nervous system as well as those which received specific mention above.

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2

Metabolism of the brain in situ

The brain is continually active, as is evident from ordinary experience and from the continuously fluctuating electrical potentials which can be detected in the head. No means are available for supporting such activity other than a continuous supply of substances to the brain by the bloodstream. The nature of these substances can be determined by analysing the blood which enters the brain from the heart. The substances taken from or added to the blood by the brain can be determined by comparing the composition of the blood entering the brain with the composition of that leaving it. These propositions give the basis for the first major experimental method described here, that of measuring cerebral metabolism by determining arteriovenous differences. This method has had wide clinical application in man, for the necessary measurements and sampling can be made outside the head. Even less investigative interference is possible in some instances by using radioactive isotopes of which the cerebral content can be measured outside the head, so that the taking of blood samples can be minimized or avoided; these latter methods are especially applicable to localized aspects of cerebral metabolism, as described separately towards the end of this chapter.

Many determinations of cerebral metabolism by analysis of arterial and of cerebral venous blood have now been carried out, especially in man, so that information is available on cerebral metabolism in a variety of circumstances. Blood from the heart can be sampled at any convenient artery, for example in man at the arm or the thigh; but there are relatively few points which afford a representative sample of venous blood from the brain when, as in the present account, it is being considered as a single organ. Among the most suitable in man is the internal jugular vein, especially at its superior bulb. When arterial and cerebral venous blood are analysed it is found that the greatest differences between them are in substances concerned in carbohydrate metabolism (Table 2.1). Blood constituents such as water, protein, total base or inorganic phosphate, show little change. The change in oxygen content is outstanding. It falls by about 6.7 ml/100 ml of blood, which is a somewhat greater fall than is found to take place in oxygen when the blood traverses most of the other organs of the body. This is reflected in the relatively low value of 62% for the oxygen saturation level of the cerebral venous blood.

SUBSTANCES EXCHANGED BETWEEN BLOOD AND BRAIN

The briskness of normal cerebral respiration leads to enquiry as to the substrate oxidized. Its nature in the normal subjects who afforded the data of Table 2.1 is indicated by the concomitant change in carbon dioxide which at 6.6 ml/100 ml of blood is almost exactly equivalent to the oxygen absorbed; that is, the normal cerebral respiratory quotient is almost unity. This leads to the conclusion that, of blood constituents, glucose is most likely to be the main substance oxidized, and indeed the arteriovenous difference in glucose is found to be large. At 9.8 mg/100 ml it is somewhat larger than is required to account for the oxygen used in respiration, so that even if all the respiratory carbon dioxide is derived from glucose, other substances requiring less oxygen for

Table 2.1 Changes in blood on its passing through the brain. The blood content of the brain is relatively low at about 3–3.5% of the total volume compared with a CSF content of some 9% (Ponten, 1963; Everett, Simmons & Lasher, 1956; Rosomoff, 1961) and is renewed rapidly. In the adult human, with a total-body blood-volume of 5500 ml, the blood flows through the 1300-g brain at a mean rate of 750 ml/min (Dobbing, 1961)

Constituent	*Blood levels*		*Venous—arterial levels*	
	arterial	*venous*	(±*standard deviation*)	
Oxygen:				
content (ml/100 ml)	19.6	12.9	− 6.7	±0.8
capacity (ml/100 ml)	20.9	20.8	− 0.1	—
saturation (%)	93.9	61.8	−31.7	±3.9
Carbon dioxide:				
content (ml/100 ml)	48.2	54.8	+ 6.6	±0.8
tension (mm Hg)	39.9	49.9	+10.0	±1.2
Glucose (mg/100 ml)	92.0	82.0	− 9.8	±1.7
Lactic acid (mg/100 ml)	9.9	11.5	+ 1.6	±0.9
Free amino acids* (mg α-amino-N/100 ml plasma)	6.16	6.02	− 0.14	—
pH at 38°C	7.42	7.37	− 0.05	—
Inorganic phosphate (mg/100 ml)	3.4	3.4	0	
Total base (meq/l serum)	152.9	154.1	+ 1.2	±1.2

The values are the mean results obtained by Gibbs et al (1942) for 50 healthy men of 18–29 years of age, at rest. Blood was sampled at the internal jugular vein and femoral artery. The respiratory quotient was 0.99 ± 0.03

* Sacks (1969)

their formation must also be produced. One likely product is the lactic acid of Table 2.1, and a further product is pyruvic acid.

These three substances, carbon dioxide, lactic acid and pyruvic acid, account remarkably completely for the glucose utilized by the human brain under normal conditions. In an instance (Himwich & Himwich, 1946) in which the arteriovenous difference in glucose was 10.2 mg/100 ml of blood the carbon dioxide found was equivalent to 8.9 mg of glucose/100 ml; the lactic acid to 1.2 and the pyruvic acid to 0.2, a total 10.3 mg/100 ml. Several subsequent studies have confirmed such equivalence (see Sokoloff, 1960) though the change in lactate and pyruvate can be variable. Thus, immediately after a carbohydrate-rich meal when blood concentrations of lactate and pyruvate were above average, they diminished on passing the brain (Rowe et al, 1959). The brain, also, can display new properties towards ketone bodies when these are present at high levels during starvation (see below).

The prompt oxidation of glucose to carbon dioxide at the brain has been shown also by isotopically-labelled glucose, administered systemically to man (Fig. 2.1B). Cerebral venous blood consistently contained less of the isotope as glucose, and more as CO_2, than did arterial blood. In these experiments the organs of the body competed for the labelled glucose, and values indicated that between 7 and 20% of the glucose injected was oxidized to CO_2 at the brain. Although under normal conditions glucose forms the main oxidizable substrate for other organs of the body as well as for the brain, the brain is unusual among the larger organs in its dependence on glucose. When blood glucose is caused to fall within a few minutes, muscle, liver, or kidney oxidize other substrates and their level of functioning does not immediately change. The

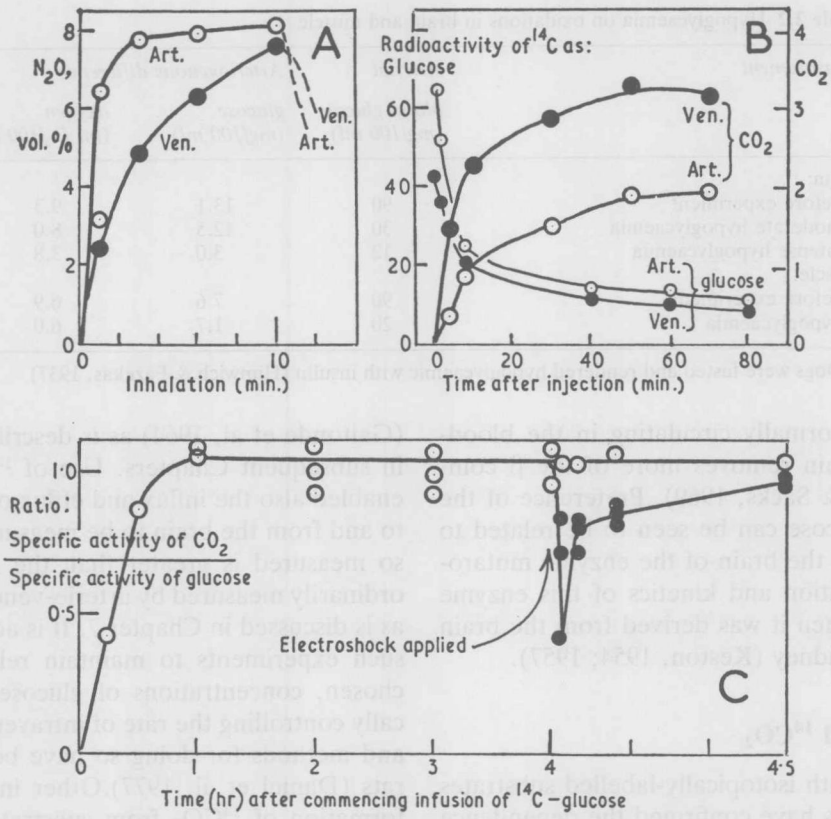

Fig. 2.1 Interchange of substances at the brain, as measured by analysis of arterial and cerebral venous blood.

A. *Redistribution without metabolic change:* nitrous oxide is not altered chemically in the brain but diffuses from the arterial blood to cerebral tissues. The data come from its use in man to measure the rate of blood flow. The gas is inhaled for 10 min., at which time its concentrations in arterial and venous blood have become nearly equal. The dotted lines show the loss of N_2O from the brain during subsequent inhalation of air only.

B. *Metabolic change:* using ^{14}C and reflecting a process operating at steady rate. ^{14}C-Glucose, after a single injection is yielding $^{14}CO_2$ in human subjects. The ^{14}C-glucose of cerebral venous blood is throughout lower than that of arterial samples, while $^{14}CO_2$ shows the reverse relationship.

C. *Metabolic change*, with alteration in the rate of metabolism. The processes measured in **B** are here observed in anaesthetized dogs during a constant infusion of ^{14}C-glucose. Some animals were subjected to electroshock at the time indicated; note the change in time-scale at this point. The data in this case are expressed as the ratio of the specific activities of glucose utilized and CO_2 produced, calculated from analyses of arterial and cerebral venous blood.

(Kety, 1948; Sacks, 1957; Coxon & Robinson, 1959; Gainer et al, 1963.)

contrast in this respect between cerebral and muscular tissues is shown well in the experiment with dogs, fasted and rendered hypoglycaemic with insulin, which is quoted in Table 2.2. It is instructive to see that in the brain the fall in arteriovenous difference in oxygen paralleled that in glucose as blood glucose was lowered. Reduction of arterial glucose to 30 mg/100 ml was associated with a small fall in each arteriovenous difference, while at 12 mg/100 ml both had fallen considerably. Changes in blood on its passing through skeletal muscle reacted differently to hypoglycaemia: at 20 mg glucose/100 ml arterial blood, the arteriovenous difference in glucose was less than one-quarter of its normal value while oxygen uptake was little changed. Muscle therefore oxidizes substances other than glucose when glucose is lacking; the brain has only a limited ability to do so. This makes it understandable that it is cerebral function which fails in hypoglycaemia rather than, for example, muscular function: coma ensues with the heart still beating. These matters are examined more fully below.

Of the two isomeric forms of glucose, α and

Table 2.2 Hypoglycaemia on oxidations in brain and muscle

Measurement	*Arterial*	*Arteriovenous difference*	
	blood glucose (mg/100 ml)	*glucose (mg/100 ml)*	*oxygen (ml O_2/100 ml)*
Brain:			
before experiment	90	13.1	9.3
moderate hypoglycaemia	30	12.5	8.0
intense hypoglycaemia	12	3.0	3.8
Muscle:			
before experiment	90	7.6	6.9
hypoglycaemia	20	1.7	6.0

Dogs were fasted and rendered hypoglycaemic with insulin (Himwich & Fazekas, 1937)

β, which are normally circulating in the bloodstream, the brain removes more of the β compound (Sacks & Sacks, 1969). Preference of the brain for β-glucose can be seen to be related to the presence in the brain of the enzyme mutarotase; the activation and kinetics of this enzyme were similar when it was derived from the brain and from the kidney (Keston, 1954; 1957).

^{14}C-Glucose and $^{14}CO_2$

Experiments with isotopically-labelled substrates in dogs and rats have confirmed the dependence of the brain on glucose. Infusing ^{14}C-glucose intravenously to the anaesthetized animals and measuring the $^{14}CO_2$ in blood from the brain, it was found to reach a specific activity equal to that of the glucose within an hour (Fig. 2.1C). The accuracy of the data was sufficient to indicate that 90–100% of the CO_2 was derived from glucose and substances which equilibrated relatively quickly with glucose; after displacement by electrical stimulation (see below) equilibrium was re-established in some 30 min.

The output of CO_2 from the brain, which has been described above, is a net process and can be accompanied by processes which lead to uptake of CO_2. Inhaled $^{14}CO_2$, or ^{14}C-bicarbonate by intracarotid injection, yields a number of ^{14}C-metabolites in the brain, and associated evidence indicates that they are formed in the brain itself (Waelsch et al, 1964). Such processes of CO_2-fixation in cat brain yielded in greatest abundance ^{14}C-aspartate and glutamine (q.v.). Understandably, these compounds are among the cerebral metabolites found after administering ^{14}C-glucose (Gaitonde et al, 1964) as is described more fully in subsequent Chapters. Use of ^{14}C-glucose has enabled also the influx and efflux of glucose itself to and from the brain to be measured. The influx so measured is greater than the net entry rate ordinarily measured by arterio-venous difference, as is discussed in Chapter 7. It is advantageous in such experiments to maintain relatively stable, chosen, concentrations of glucose by automatically controlling the rate of intravenous injection, and methods for doing so have been applied to rats (Daniel et al, 1977).Other instances of the formation of $^{14}CO_2$ from substrates supplied to the brain in situ are described later in this chapter.

MEASUREMENT OF CEREBRAL METABOLIC RATES, WHOLE BRAIN

The level of metabolic activity exhibited by an organ or by a tissue with respect to a particular substance is often best expressed as a metabolic rate. This gives the quantity of substance caused to react in unit time by unit weight of the organ or tissue. Measurements of metabolic rates of the brain in situ have usually been expressed in ml or mg of substance caused to react, per 100 g fresh weight of brain per minute. Determination of change in concentration of a substance in the blood as it passes through the brain, gives one part of the data needed to express its activity as a metabolic rate. The other part of the data needed is the rate of flow of blood through the brain. Thus, when arterial blood loses 6.6 ml of oxygen per 100 ml on passing through the brain