HANDBOOK OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EDITOR-IN-CHIEF A. REMOND

VOLUME 7

Physiological Correlates of EEG

EDITORS: E. K. KILLAM AND K. KILLAM

Department of Pharmacology, School of Medicine, Davis, Calif. (U.S.A.)

PART B

Influence on the EEG of Certain Physiological States and Other Parameters

EDITOR: R. COOPER

Burden Neurological Institute, Bristol (Great Britain)

ELSEVIER

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International Federation of Societies for EEG and Clinical Neurophysiology

A great need has long been felt for a Handbook giving a complete picture of the present-day knowledge on the electrical activity of the nervous system.

The International Federation of Societies for EEG and Clinical Neurophysiology is happy to be able to present such a Handbook, of which this is a small part.

The decision to prepare this work was made formally by the Federation at its VIIth International Congress. Since then nearly two hundred specialists from all over the world have collaborated in writing the Handbook, each part being prepared jointly by a team of writers.

The Handbook begins with an appraisal of 40 years of achievements by pioneers in these fields and an evaluation of the current use and future perspectives of EEG and EMG. The work subsequently progresses through a wide variety of topics – for example, an analysis of the basic principles of the electrogenesis of the nervous system; a critical review of techniques and methods, including data processing; a description of the normal EEG from birth to death, with special consideration of the effect of physiological and metabolic variables and of the changes relative to brain function and the individual's behaviour in his environment. Finally, a large clinical section covering the electrical abnormalities in various diseases is introduced by a study of electrographic semeiology and of the rules of diagnostic interpretation.

The Handbook will be published in 16 volumes comprising 40 parts (about 2500 pages altogether). For speed of publication most of the 40 parts will be published separately and in random order.

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PART B

INFLUENCE ON THE EEG OF CERTAIN PHYSIOLOGICAL STATES AND OTHER PARAMETERS

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Preface

The survival time of only a few min when the brain is deprived of oxygen clearly shows that the availability of this gas is not much more than adequate for normal living. This rapid onset of permanent brain damage implies also that there is but little storage of oxygen in the tissue and that function is thus vitally dependent on a reliable supply of oxygen saturated blood flowing through the brain. An additional complication is that the blood is contained in a separate system and the oxygen must diffuse through the walls of the vessels to reach the tissue.

These physical constraints, together with the high cerebral metabolic demand (20% of the total body) has led to the evolution of a number of regulatory systems that preserve the level of tissue oxygen despite variations of the blood pressure driving the blood through the brain and despite the considerable increase of tissue oxygen consumption that can occur in normal and abnormal brain processes.

The mechanisms of these regulatory processes are discussed in Section II. It will be seen in this section that these processes depend considerably upon the levels of oxygen and carbon dioxide in the cerebral tissue. Because of this dependence, much of Section III is concerned with the effects on the EEG of changes of these gas tensions provoked by *external* manipulations of the respiratory gases.

Section IV describes the relationships between the EEG, oxygen tension and cerebral blood flow to *internal* cerebral events both normal, during sleep, mentation etc., and abnormal, during epileptic seizures for example.

But before all of this there is a description in Section I of the basic processes of the biochemical events that transform the cerebral nutrients, oxygen etc., into energy that is available for the metabolising tissue.

Perhaps the most astonishing conclusion after study of all these systems is not that they occasionally malfunction but that they function at all.

Section I. Cerebral Metabolism

A. INTRODUCTION

During the past 20 years a considerable amount of knowledge has been accumulated on the biochemical functions of the brain.

In this Section a general picture of today's knowledge of cerebral metabolism will be given using data obtained from *in vitro* experiments (with all the limitations that they present when they are correlated with physiological activities) as well as data obtained on the isolated perfused brain, and from experiments *in vivo*.

The energy required by the brain (and other tissue) to maintain function is derived from the oxidation of constituents of food by molecular oxygen yielding carbon dioxide and water. The oxygen and other components for the reactions are carried to the tissue and the metabolic products taken away by the flow of blood. The most important source of energy is the oxidation of carbohydrates.

B. CARBOHYDRATE METABOLISM

1. *Energy release*

The oxidation of carbohydrate can be represented by the equation.

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + 685.5\,\text{Kcal.}$$

This reaction proceeds in stages and about half of the energy released is dissipated as heat. The other half is stored temporarily in an energy pool as high energy phosphates (adenosine triphosphate, ATP).

Another energy storage compound is creatine phosphate which is involved in the reconversion of ADP into ATP.

The energy available from the conversion of glucose to lactate (see later) is only 56 Kcals, that is, only about 8% of the total energy available. The remainder is produced when the pyruvic acid is oxidised to carbon dioxide and water.

2. *Oxygen consumption and CO_2 productiom*

The brain is the organ which shows highest speed of utilisation of oxygen and thus is most vulnerable to its depletion (Section III.B). The cerebral consumption of oxygen in man in normal conditions is about 100 μ moles/g of tissue/h, about 1/5th of the total amount of oxygen needed by the human body.

Studies made on human subjects both in physiological and pathological conditions

have shown that a decrease in oxygen consumption is always associated with some disturbance of cerebral function but alterations in intermediate metabolism of the central nervous system that disturbs function may coexist with normal consumption of oxygen. Brain cortex slices incubated in a medium containing glucose show an oxygen consumption that is inferior to that observed *in vivo*. It may be brought back to the same values observed *in vivo* in two ways: (a) subjecting the tissue to electrical impulses; (b) increasing the concentration of potassium ions in the incubation medium. This effect of potassium is unique to the nervous system and is not observed in tissue homogenates, which means that it is somehow connected with cellular membrane functions (McIlwain 1966).

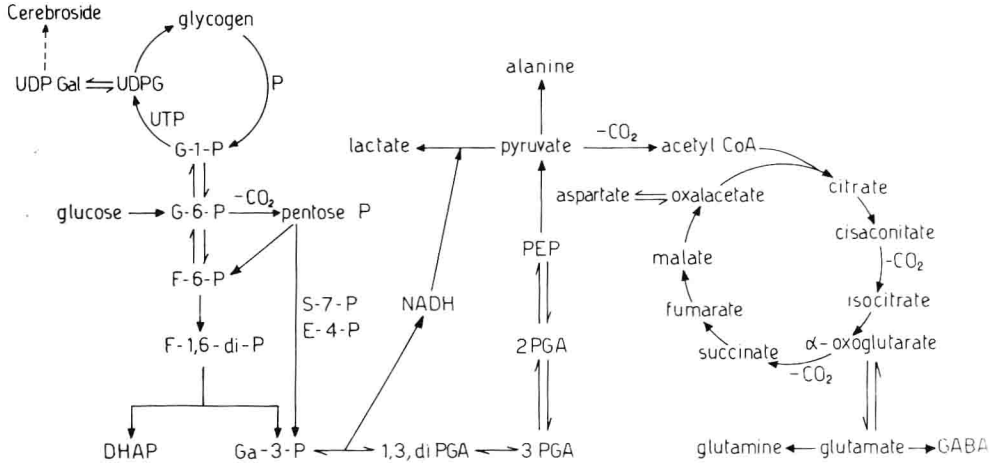

Fig. 1. Schematic representation of carbohydrate metabolism. DHAP is dihydroxyacetone phosphate. E-4-P is erythrose-4-phosphate, F-6-P is fructose-6-phosphate, F-1-6-di-P is fructose 1,6-diphosphate. GABA is γ-aminobutyrrate, G-1-P is glucose-1-phosphate, G-6-P is glucose-6-phosphate, Ga-3-P is glyceraldehyde-3-phosphate, NADH is nicotinamide-adenine-dinucleotide, PEP is phosphoenolpyruvate, 1-3, di-PGA is 1,3 diphosphoglycerate, 2PGA is 2-phosphoglycerate, 3PGA is 3-phosphoglycerate, S-7-P is sedoheptulose-7-phosphate, UDPG is uridindiphosphate-glucose, UDPGal is uridindiphosphate-galactose, UTP is uridin-triphosphate.

From the basic metabolic equation given above it will be seen that the theoretical value for the ratio oxygen uptake/glucose utilisation is 6. The value measured is 5.5 showing that the oxygen consumption is less than expected. Such a difference could be explained by the formation of lactic acid which prevents entry into the citric acid cycle, Fig. 1. On the other hand experiments using uniformly labelled ^{14}C (carbon isotope) glucose indicate that the carbon in the end product carbon dioxide is not all derived from the glucose as is expected from the reactions. Sacks (1957) showed that after 1 h injection of uniformly labelled ^{14}C glucose in normal human subjects, the specific radio-activity of CO_2 produced after 90 min was 0.5, that is only half the carbon appears to come from the glucose. Similar data have been obtained using rat cortex slices: after one h incubation, the specific activity of the CO_2 produced was 0.5 (DiPietro and Weinhouse 1959) and after two h 0.7 (Chain *et al.* 1962).

This can be explained by the fact that intermediate products deriving from the catabolism of glucose enter small metabolic pools, which are in equilibrium with relatively larger pools (like those of amino acids) connected with the tricarboxylic acid cycle. This can cause an isotopic dilution of the CO_2 (Balàzs 1970).

3. *Glycolysis*

In man, the uptake of glucose from the blood by the brain is about 18 μmoles/g of tissue/h and more than 90% is metabolised through the glycolytic pathway (Sacks 1965).

The first *irreversible* step in the glycolytic pathway, Fig. 1, is the conversion of fructose-6-phosphate (F-6-P) into fructose-1, 6-diphosphate (F-1, 6-di-P), catalysed by phosphofructokinase. This is a highly elaborated regulatory enzyme which possesses a variety of internal mechanisms (Lowry and Passoneau 1966) making possible extremely fine adjustments of activity according to the metabolic demands of the cells. To go from fructose-1, 6-diphosphate to phosphoenolpyruvate (PEP) in glycolysis involves the activity of six enzymes, most of them reversible. The transformation of phosphoenolpyruvate (PEP) into pyruvate is irreversible and is an additional point of regulation. Determination of the concentration and activity of the enzymes involved, and of the levels of various intermediates clearly show that glucose metabolism in brain via glycolysis is very rapid.

As already explained in Section I.1 the free energy production in the brain is associated with the formation of ATP. In aerobic glycolysis of one mole of glucose followed by complete oxidation of the pyruvate through the tricarboxylic acid cycle 40 moles of ATP are formed with the release of free energy of 320,000 calories. This represents about 40% or the total energy available in the combustion of glucose. In contrast, only 2 moles of ATP are formed for each mole of glucose by anaerobic glycolysis to lactate. The brain utilises 18 μmoles of glucose/g tissue/h, of which 3 μmoles are converted into lactate with irrelevant formation of ATP. The remaining 15 μmoles give rise to 600 μmoles of ATP/g tissue/h. As the level of ATP measured in the intact tissue is about 2 μmoles/g tissue, the turnover of ATP reaches the imposing figure of 300 changes/h. The rapidity of the glycolytic reactions are necessary to preserve this great turnover rate.

4. *Citric acid cycle*

In normal aerobic conditions the pyruvate formed from glucose by glycolysis is converted to carbon dioxide and water by the citric acid or tricarboxylic cycle first described by Krebs. The process is shown in Fig. 1 but it is unnecessary for the detail of all the steps to be considered here. As already mentioned, this is the main energy source in the metabolic pathways.

5. *Pentose phosphate cycle*

An alternate means of glucose oxidation is provided by the pentose phosphate

pathway. By comparing the quantity of $^{14}CO_2$ produced from glucose ^{14}C labelled in position 1 with that produced from glucose labelled in position 6, one can approximately determine whether the pentose shunt is operating (Katz and Wood 1960). When the C_6/C_1 is equal to 1 the pentose pathway is practically non-existent. This is the case in brain slices of various animals (Bloom 1955; Tower 1958; Hoskin 1960) and also with human brain *in situ* (Sacks 1957).

At variance with what happens during the oxidation of glucose through the tricarboxylic acid cycle, no ATP is produced in the pentose cycle. In this pathway two important products are formed: pentose phosphates, which are precursors of nucleotides and NADPH, which participates as coenzyme in several synthetic reactions like that of fatty acids. For these reasons the pentose cycle plays a major role in the brain of the developing animal (Burt and Wenger 1961).

6. *Storage and supply of glucose*

The reactions already described were all concerned with the breakdown of glucose to yield energy. If no storage system of glucose were available the tissues would be flooded with excess glucose immediately after a meal and starved of it all other times. The storage of large quantities of such a small molecule is not possible and the glucose is converted to glycogen which can be stored to be called upon in particular physiological or pathological conditions, and it may even participate in nervous activity (Coxon 1970).

The synthesis and the breakdown of glycogen follow two different patterns, Fig 1. UDPG pyrophosphorylase and glycogen synthetase are responsible for the transfer of glucose units from glucose-1-phosphate into glycogen; phosphorylase catalyses the breakdown of glycogen (Greville 1962). The amount of glycogen found in the adult brain is about 1 mg/g fresh tissue. Studies with ^{14}C labelled precursors show a rapid turnover, pointing to a dynamic role of glycogen in nervous tissue.

In hypoglycaemic conditions the addition of glucose to the blood can restore impaired nervous function: mannose, lactose, and glycerol can substitute for glucose. On the other hand, fructose cannot restore cerebral function even in high concentrations. As this sugar is utilised almost as easily as glucose by rat cortex slices (Chain *et al.* 1969), this incapacity is presumably due to the fact that it does not cross the blood–brain barrier. The same was thought to be true of lactic, pyruvic, succinic, and glutamic acids, all well metabolised by the cerebral cortex *in vitro*, but said to be incapable of restoring nervous activity impaired by hypoglycaemia (McIlwain 1966). Other evidence indicates that lactic, pyruvic and glutamic acids cross the blood–brain barrier and may be metabolised by brain (Gomez *et al.* 1961: Oldendorf 1970). In glycolysis the concentration of the first enzyme, hexokinase, responsible for the phosphorilation of glucose, is by far higher than that needed to sustain the observed reaction velocity in normal conditions and might represent a mechanism of control of the flux of glucose through the organ.

7. Fate of ^{14}C glucose

In rat (Beloff-Chain *et al.* 1955) or cat (Tower 1958) cortex slices incubated with ^{14}C glucose contain about 60% of the radioactivity in lactic acid, 20% in CO_2, and the remaining 20% is incorporated into amino acids, connected with the tricarboxylic acid cycle, namely glutamic acid, glutamine, γ-amino-butyric acid, aspartic acid, and alanine. Qualitatively comparable results were obtained *in vitro* with mannose, fructose (Chain *et al.* 1969), and pyruvate (Beloff-Chain *et al.* 1959). Mannose behaves like glucose even in a quantitative sense. Fructose on the other hand is utilised similarly to glucose only when present in high concentrations. Under these conditions, the activity incorporated into lactate is lower while that incorporated into aspartate is higher.

These *in vitro* differences observed between the metabolism of glucose and that of fructose may be due to a lower affinity of fructose for the soluble hexokinase present in nervous tissue (Sols and Crane 1954). This would result in a lower amount of fructose entering the glycolytic cycle with consequent lower amounts of NADH being formed during the oxidation of phosphogliceraldehyde, and therefore a reduced production of lactic acid from pyruvate. This mechanism does not explain the increased incorporation of radio-activity into aspartic acid. This point is still obscure, even though Kini and Quastel (1959) put forth the hypothesis that by decreasing the availability of pyruvic acid, there may be an increase in the level of oxalacetic acid and therefore, by transamination, of the aspartic acid.

The metabolic picture observed for glucose in the cerebral cortex is qualitatively similar in other regions of the brain such as the hypothalamus and the cerebellar cortex. On the other hand, the quantitative picture is different. The amount of ^{14}C incorporated into amino acids is lower than that observed in the cerebral cortex except that of γ-aminobutyric in the hypothalamus, which is higher (Chain *et al.* 1960b).

The origin of nitrogen in the amino acids formed from glucose was studied by incubating rat cortex slices with ^{14}C glucose and ^{15}N labelled ammonium ion. By calculating ratios of specific activities for each amino acid, it was possible to demonstrate (Chain *et al.* 1960a) that the ^{15}N is readily incorporated into aspartic and glutamic acids and glutamine. Alanine on the other hand contains only a small amount of ^{15}N which means that its nitrogen is derived from other sources. This is also true for glycine and, contrary to all expectations, for γ-aminobutyric acid.

It has been proven beyond doubt that γ-aminobutyric acid is formed in brain by decarboxylation of glutamic acid (Awapara *et al.* 1950; Roberts and Frankel 1950), so it would be natural to think that its production from glucose would follow the same pathway. However, its remarkably low incorporation of ^{15}N points to the possibility that another mechanism for its production might be operative in the brain. Another possibility to keep in mind is that the existence of several pools of glutamic acid which have been demonstrated (see below) might apply also to γ-aminobutyric acid.

One must consider that in brain 2-oxoglutaric acid can be transformed into succinic acid not only via the usual tricarboxylic acid cycle, but also by means of the following

shunt: (Roberts 1960)

2-oxoglutaric + γ-aminobutyric = 1-glutamic + succinic semi-aldehyde + CO_2

succinic semi-aldehyde + NAD = succinic acid + NADH

8. *Pyruvate metabolism*

In the brain as in the other organs, the pyruvate is oxidised completely via the tricarboxylic acid cycle, Fig. 1. The first oxidative step involves acetylcoenzyme A, which requires the simultaneous presence of oxaloacetic acid. Normally there is a regular supply of this metabolite due to the cyclic nature of the process. Under certain conditions, however, some intermediate products of the cycle are withdrawn for different metabolic purposes and in these cases, oxaloacetic acid is no longer available. The tissue fulfils this lack by producing oxaloacetic acid through carboxylation of pyruvic acid. This can occur either directly by an action of ATP-dependent pyruvic carbohylase (Utter and Keech 1960) or through the intermediate formation of malic acid (Ochoa *et al.* 1948). Minced brain from day old mice (Moldave *et al.* 1953) can incorporate $^{14}CO_2$ in pyruvate to give as final products labelled aspartic and glutamic acids. This means that the brain has the capacity of synthesising these amino acids. The amount of pyruvic carboxylase in the brain is very low if compared to that of other organs such as liver and kidney, while the concentration of the malic enzyme is comparable to that found in other organs and even higher than that in muscle. It is therefore quite possible that the second sequence is that used by the brain for the carboxylation of the pyruvate (Greville 1962).

Another metabolic sequence for pyruvate in the brain is the following dismutation (Krebs and Johnson 1937).

2 pyruvate $\rightarrow$ lactate + acetate + CO_2

This step becomes very important under anaerobic conditions (Section III.B); in fact, in the absence of oxygen, the brain, at variance with other organs, utilises pyruvate almost at the same rate as it would aerobically. Rat brain preparations utilise pyruvate at the rate of about 20 μmoles/g tissue/h aerobically and 16 μmoles/g tissue/h anaerobically.

9. *Anaerobic metabolism*

The formation of amino acids from glucose or from other carbohydrates via the citric acid cycle is a strictly aerobic process. Under anaerobic conditions the production of lactic acid is greatly increased, and as a consequence the consumption of glucose increases. The NADH oxidised by pyruvate is reduced by glyceraldehyde-3-phosphate which permits the production of large quantities of lactic acid. The mechanism of this reaction, called the Pasteur effect, is still unknown. Several hypotheses have been formulated (Greville 1962).

In areas of the brain distant from the capillaries, the oxygen tension might be

extremely low (Rémond *et al.* 1946; Thews 1963) and therefore a slight decrease in blood flow or an increased demand due to functional reasons (Section IV) might bring about anaerobic conditions with a consequent increase in glycolysis, a decrease in pH and a dilation of cerebral vessels bringing a larger flow of blood to counteract the anoxic state (Sections II and III). Furthermore, Himwich *et al.* (1942) are of the opinion that anaerobic glycolysis is an important source of energy in brains of new born animals.

C. AMINO ACID AND PROTEIN METABOLISM

1. *Amino acids*

The relation between the metabolism of the amino acids and their functions in the central nervous system has not been finally elucidated. However, the physiological importance of γ-aminobutyric (GABA) as inhibitory transmitter substance in the peripheric nervous system of crustacea is generally accepted and there are experimental results suggesting a similar function in mammalian nervous system (Baxter 1970). The formation of glutamine, the other product of glutamate, is the major mechanism used by the central nervous system for binding free ammonia (Takagaki *et al.* 1961). Glutamine synthetase, an ATP dependent enzyme is very active in the brain and seems to be concentrated in microsomal and mitochondrial fractions (Waelsch 1962).

In the brain there is a considerable concentration of glutamic (0.01 M), γ-aminobutyric (0.002 M) and acetyl aspartic (0.006 M) acids. The carbon skeleton of non-essential amino acids in the brain derives from glucose through the tricarboxylic acid cycle.

There has been much discussion on whether amino acids may pass the blood–brain barrier. Schwerin *et al.* (1950) clearly demonstrated that glutamine circulating in the blood can be utilised by the brain. However, no increase of glutamic acid in the brain can be obtained by increasing its concentration in the blood; the same is true for lysine (Lajtha 1958) and leucine (Lajtha and Toth 1961). Using ^{14}C labelled amino acids several workers (Lajtha *et al.* 1957; Waelsch 1958) have shown some exchange at the level of the blood–brain barrier. This exchange is very important because it suggests that the amino acid pool of the brain may be replenished (even at a very slow rate) from the blood amino acids in spite of the presence of the blood–brain barrier. If it were not so, it would be difficult to explain how the essential amino acids reach the brain pool.

l-glutamic acid is the only one of the 13 amino acids tried by Weil-Malherbe (1936) that is capable of sustaining nervous tissue respiration. Glutamic acid oxidation (contrary to glucose) does not support oxidative phosphorylation (Woodman and McIlwain 1961). Weil-Malherbe (1938) showed that glutamic acid causes a gradual inhibition of the anaerobic and a stimulation of the aerobic glycolysis. Glutamic acid *in vitro* is metabolised into CO_2, aspartic, γ-aminobutyric acids and glutamine (Sellinger *et al.* 1962). Aspartic acid whether *in vitro* or *in vivo* is transformed into the same metabolites as the glutamic.

The study of glutamate metabolism in the brain has shown that in short-time

experiments the glutamine isolated from tissue showed a specific activity higher than that of glutamic acid (Berl *et al.* 1961; Berl 1965). Other experiments on brain slices (Berl *et al.* 1968) and on sympathetic ganglia *in vitro* (Masi *et al.* 1969) showed the existence of at least 2 pools of glutamate, a small one responsible for the synthesis of glutamine and a larger one connected via oxoglutarate with the oxidative sequence of Krebs' cycle. It is to be noted that two oxoglutarate pools have been indicated (Waelsch *et al.* 1964; Gaitonde 1965) and quite recently the existence of two separate pools of Krebs' cycle components has been postulated in cerebral tissue (O'Neal and Koeppe 1966; Van den Berg *et al.* 1966) as well as in sympathetic ganglia.

2. *Protein synthesis*

At variance with most other organs, brain function is not affected by changes in protein concentration. Even in case of protracted fasting or high protein losses, the cerebral protein content remains unchanged. Since proteins do not pass the blood–brain barrier, they must be synthesised and broken down topically. The relation between protein synthesis and cerebral function was reviewed recently (Richter 1970) and four main areas were pointed out:

1. Memory: it has been suggested that protein synthesis is involved in storage of information and in learning processes.

2. Membranes: a particularly active turnover of specific proteins is required in brain to maintain membrane structure, which indergoes rapid functional changes in connection with nervous activity.

3. Synaptic transmission: hydrolytic enzymes might participate in the release from protein of γ-aminobutyric acid (GABA) and glycine, which may play a role in the central nervous system as inhibitory transmitters of modulators of synaptic transmission (Aprison *et al.* 1970).

4. Energy storage: brain, which lacks a specific carbohydrate storage system may utilise proteins as energy source in case of glucose deficiency.

The metabolic pathway of protein synthesis in the brain is similar to that of other organs. The amino acid is first "activated" by ATP to form an amino-acyl adenilate, which is transferred into the ribosomes and the peptide linkage is formed. The protein metabolic rate in the brain is rather high and is comparable to that observed in the liver.

In particular areas of the brain, specific peptides with hormonal activity are formed but there is no information as to whether they are products of synthetic or degenerative metabolism.

Another problem concerning the origin of the nervous axon proteins is whether they are synthesised locally along the axon or originate in the perikaryon and are then transported along the axon by the axonic flow. There is some experimental evidence that at least in part they might derive from the perikaryon (Droz and Koenig 1970).

D. LIPID METABOLISM

Lipids are a heterogeneous group of substances and are involved in normal function, maintenance of membrane structure and transport and storage of energy.

1. *Cholesterol*

The normal adult brain contains about 25 g of cholesterol which represents 1/5th of the entire body cholesterol. At birth, the cholesterol content in the brain is 2 g, and the major synthesis occurs during the first year of life. Using ^{14}C labelled precursors it has been shown that the greater part of this cholesterol is synthesised in the brain. It is believed that this biosynthesis follows the same pathways as in liver although all the enzymatic steps and control mechanisms have not yet been elucidated (Davison 1970).

Once formed, brain cholesterol is not further metabolised in appreciable amounts. By isotope labelling, one can observe that cholesterol radioactivity rapidly disappears from heart and liver indicating a high turnover but remains for more than a year in the brain.

2. *Phospholipids*

Phospholipids are a very important class of complex lipids because they play a relevant role in the structure and function of the nerve cell. The metabolic sequences for phospholipid biosynthesis have been summarised by Kennedy (1961) and are reported in Fig. 2. There are good reasons to assume that they are operative in the brain and nerves. Phosphatidylinositol is phosphorilated by ATP and a specific kinase to di- and tri-phosphoinositide. Phosphatidylinositol is involved in post-synaptic events accompanying impulse transmission in sympathetic ganglia. Poly-phosphoinositides appear to play a role in connection with the structure of axonic

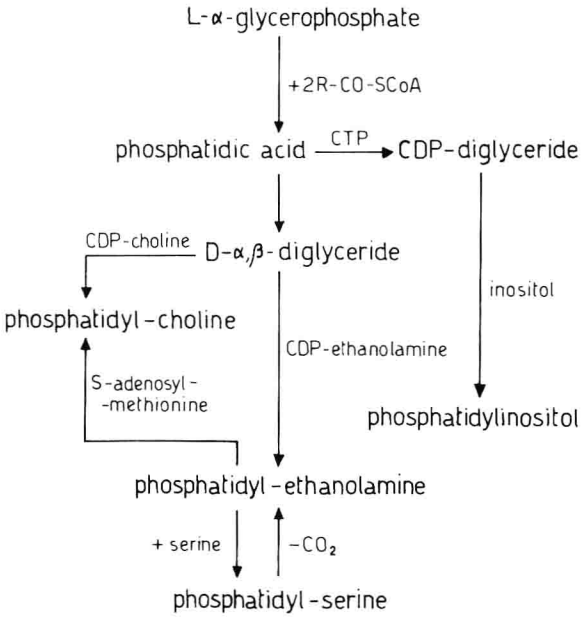

Fig. 2. Biosynthetic pathways for formation of phosphatides.