NEUROLOGICAL SURGERY

THIRD EDITION

VOL
2

VOLUME TWO

NEUROLOGICAL SURGERY

A Comprehensive Reference Guide to the Diagnosis and Management of Neurosurgical Problems

THIRD EDITION

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Cerebral Blood Flow in Clinical Neurosurgery

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chapter 21

Cerebral metabolism

This chapter discusses those parts of cerebral metabolism that are of direct interest to neurosurgeons. The presentation is focused on the aspects that are relevant to an understanding of the pathophysiology of disease, primarily cerebrovascular, as well as to neurosurgical intensive care. Two comprehensive textbooks on brain metabolism and various review articles on cerebral hypoxia/ischemia and on hypoglycemia* are recommended for further information.

Utilization and Production of Energy at the Cellular Level

Directly or indirectly, all cellular work occurs at the expense of energy contained in the adenosine triphosphate (ATP) molecule. When work is performed ATP is degraded to adenosine diphosphate (ADP) and orthophosphate (P_i). Thus, cellular energy metabolism may simply be described as the balance between the utilization of ATP during the performance of work and its resynthesis through rephosphorylation of ADP.

When production of ATP is impeded by lack of oxygen or during intense neuronal activity, three reactions may retard the depletion of ATP. First, the reaction catalyzed by creatine kinase forms ATP at the expense of its storage form, phosphocreatine (PCr). Second, the reaction catalyzed by adenylate kinase retards both the depletion of ATP and the increase in ADP, and causes adenosine monophosphate (AMP) to accumulate. Third, during anaerobic conditions the glycolytic degradation of glycogen and glucose results in the accumulation of lactate and H^+ ions. Since the anaerobic metabolism of glucose to two molecules of lactate has a small energy yield (only two molecules of ATP), the brain relies on oxidative metabolism for its normal function. Even if glycolytic rate is maximally increased (to about five times control), the anaerobic production of ATP covers less than 50 per cent of the normal energy requirements.

Under normal circumstances glucose is the sole substrate for brain metabolism. Conditions with high blood concentrations of ketone bodies (beta-hydroxybutyrate, acetoacetate) such as starvation, diabetes, and ethanol ingestion are the only important exceptions. The brain is exclusively dependent on glucose or ketone bodies because only these substrates are transported from blood to brain tissue at sufficient velocity. This reflects the presence of a blood-brain barrier and of relatively specific mechanisms for transport of a variety of substances between blood and cerebral tissues. These carrier mechanisms constitute one important feature of cerebral metabolism.[15a]

Normally, the glycolytic degradation of glucose to pyruvate is coupled to its further metabolism by the mitochondria. Within the

*See references: cerebral hypoxia/ischemia and hypoglycemia, 4, 31, 60, 73, 74, 86, 87, 146, 172, 173, 181, 184, 185, 200, 214, 216; brain metabolism, 169, 171.

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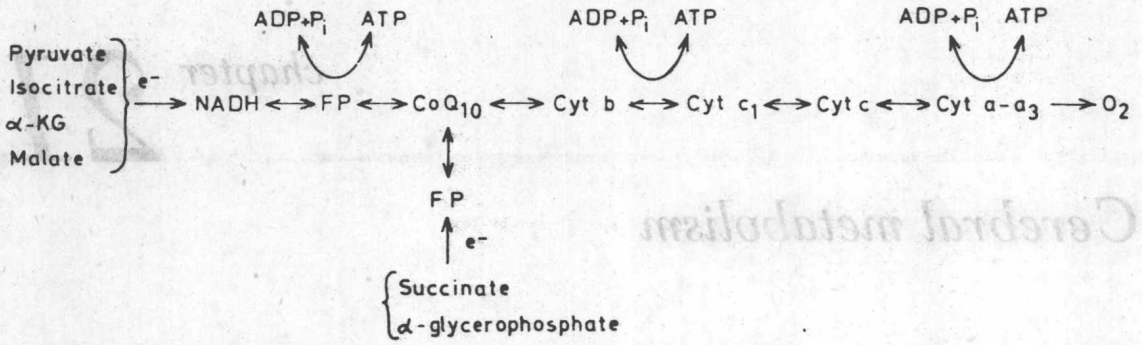

Figure 21–1. Diagram illustrating electron flow and coupled ATP production in the respiratory chain. Some substrates deliver electrons to NADH, others at a more distal step. (From Siesjö, B. K.: Brain Energy Metabolism. New York, John Wiley & Sons, 1978. Copyright 1978, John Wiley & Sons. Reprinted by permission.)

mitochondria, pyruvate is degraded in a cyclic series of reactions resulting in various citric acid cycle intermediates. As schematically illustrated in Figure 21–1, when some of these intermediates are oxidized their electrons enter a series of reactions constituting the respiratory chain. Ultimately the electrons are accepted by oxygen with the formation of water. At three steps in this reaction sequence, the free energy change during electron transfer is sufficient to allow the phosphorylation of ADP to ATP.

Theoretically, the complete intramitochondrial oxidation of one molecule of pyruvate to carbon dioxide and water has an energy yield of 18 molecules of ATP. The rate of electron transfer, and thus ultimately the rate of oxygen consumption, is regulated by the levels of ADP, P_i, and ATP.[23a, 38a] At the mitochondrial level, therefore, there is normally a strict coupling between cellular energy consumption (which leads to formation of ADP and P_i) and ATP production.

This oversimplified illustration of mitochondrial respiration necessitates some further comments.[42] First, electron transport can be dissociated from ATP formation. This phenomenon, called "uncoupling" or "loose coupling" of oxidative phosphorylation, occurs when ion transport across the mitochondrial membrane takes preference over ATP formation. Uncoupling of phosphorylation probably contributes to energy failure in some pathological conditions. Second, within the respiratory chain, reactions occur that result in univalent reduction of oxygen. Hereby a formation of superoxide radicals ($\cdot O_2^-$) and hydrogen peroxide (H_2O_2) takes place. One site of such radical formation is known to exist at the coenzyme Q_{10} step of the respiratory chain.[46a] In pathological conditions, enhanced production or dislocation of free radicals constitutes a possible mechanism contributing to cellular damage.

Overall Cerebral Metabolic Rates

During physiological conditions, the rate at which ATP is degraded and resynthesized is proportional to the rates of consumption of glucose and oxygen. Utilizing conventional techniques for measurements of overall cerebral blood flow and arteriovenous differences for oxygen, carbon dioxide, glucose, and lactate, the following data have been obtained in man.[24, 53a] Cerebral blood flow is about 50 ml × 100 gm^{-1} × min^{-1}, the rate of cerebral oxygen utilization ($CMRO_2$) is about 1.5 μmole × gm^{-1} × min^{-1} (about 3 ml × 100 gm^{-1} × min^{-1}), carbon dioxide production ($CMRCO_2$) is similar (e.g., the respiratory quotient is close to unity), glucose consumption (CMRgl) is 0.25 to 0.29 μmol × gm^{-1} × min^{-1}, and very little lactate or pyruvate is produced.

Metabolic rates reflect the intensities whereby cellular work is performed. Below we discuss in some detail the work tasks of the cerebral cells. Conventionally, cellular work is divided into "osmotic" and "biosynthetic." Osmotic work includes the transmembrane transport of ions as well as axonal transport of macromolecules and packing of transmitter compounds.

Osmotic Work

Active transport of ions has been estimated to account for about 50 per cent of the total cerebral energy consumption. Although the

actual figure is not even approximately known, there is no doubt that an appreciable amount of this energy is consumed in reactions leading to "uphill" transport of ions.

During cellular activity, potassium passively leaks out of the cell, and sodium enters (Fig. 21–2). This stimulates the sodium-potassium–dependent adenosine triphosphatase (ATPase), resulting in a coupled accumulation of potassium and efflux of sodium. Thus, hydrolysis of adenosine triphosphate (ATP) provides the energy for restoration of the ionic gradients. The ensuing increase in adenosine diphosphate (ADP) and inorganic phosphate (P_i) as indicated in Figure 21–1, should promote electron flow and ATP resynthesis in the mitochondrial respiratory chain.

Transmembrane fluxes and intracellular concentrations of calcium have attracted much attention during recent years. Normally, calcium is distributed across the cell membrane far away from its electrochemical equilibrium. Thus, its extracellular concentration (about 10^{-3} moles $\times$ l^{-1}) is very much higher than its intracellular concentration (about 10^{-7} moles $\times$ l^{-1}), and the negative potential in the cell interior also tends to drag Ca^{2+} into the cell.[13,18] Figure 21–2 illustrates such passive influx of calcium and also one likely mechanism for calcium extrusion, i.e., that occurring by Na^+/Ca^{2+} exchange. In this mechanism, energy required for calcium transport originates in the large Na^+ gradient, created by the $Na^+ - K^+$–dependent ATPase.

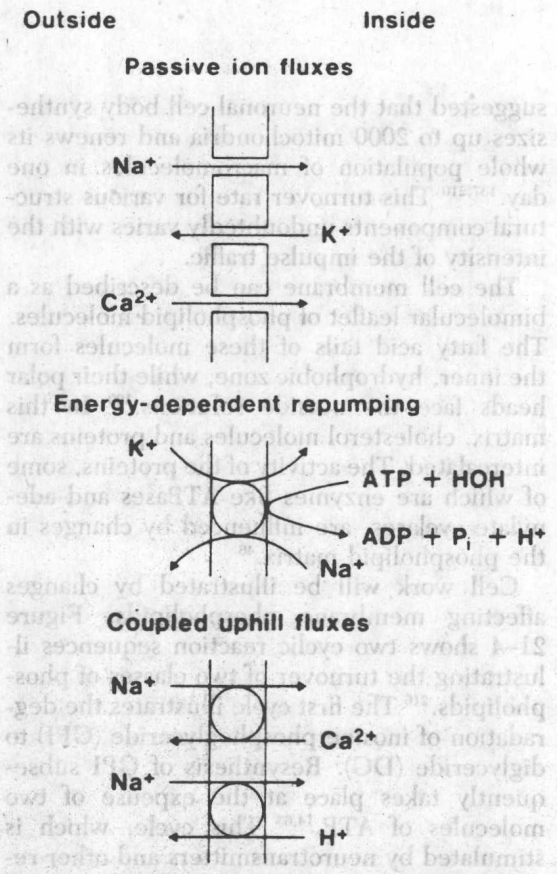

Figure 21–2. Passive and energy-dependent ion fluxes across plasma membranes. Neuronal depolarization leads to cellular influx of Na^+ and Ca^{2+}, and efflux of K^+. Restoration of the electrochemical gradients occurs at the expense of ATP. It is hypothesized that Ca^{2+} efflux occurs by Na^+/Ca^{2+} exchange. The Na^+ gradient is also believed to transport H^+ from the cells to extracellular fluid. (From Siesjö, B. K.: Cerebral energy metabolism. J. Neurosurg., *60*:883–908, 1984. Reprinted by permission.)

Figure 21–3 gives a more detailed account of mechanisms for calcium influx/efflux, and its intracellular sequestration. Presynaptic influx of Ca^{2+} causes the release of transmitters. Postsynaptically, calcium influx constitutes an important mechanism of cell excitation, e.g., in the pyramidal cells of the cerebral cortex and the hippocampus and in the Purkinje cells of the cerebellum (see below). Such influx occurs via voltage- and agonist-dependent channels.

As Figure 21–3 shows, efflux of calcium across the cell membrane probably occurs both by Na^+/Ca^{2+} exchange and by the mediation of a calcium-dependent ATPase. However, regulation of intracellular calcium also involves intracellular sequestration, as well as its binding to intracellular proteins such as calmodulin and calcium-binding protein.

It has been widely assumed that mitochondria play an important role in the regulation of intracellular calcium concentration.[3,112] The energy released in the electron transport chain (see Fig. 21–1), according to the chemiosmotic theory, is used to split water in such a way that H^+ is accumulated at the outside of the mitochondrial membrane and OH^- at the inside.[116] The large electrochemical gradient for H^+ thus created is utilized to reverse a mitochondrial ATPase reaction ($ADP + P_i + H^+ \rightarrow ATP + H_2O$; see Fig. 21–1), and ATP is thus produced. However, this transmitochondrial electrical gradient may also be used to drag Ca^{2+} into the mitochondria or to transport other ions.[42] ATP production and sequestration of Ca^{2+} are thus alternative ways of utilizing the energy from the electron transport chain.

Other workers have challenged the proposal that mitochondria normally sequester calcium when its concentration rises during physiolog-

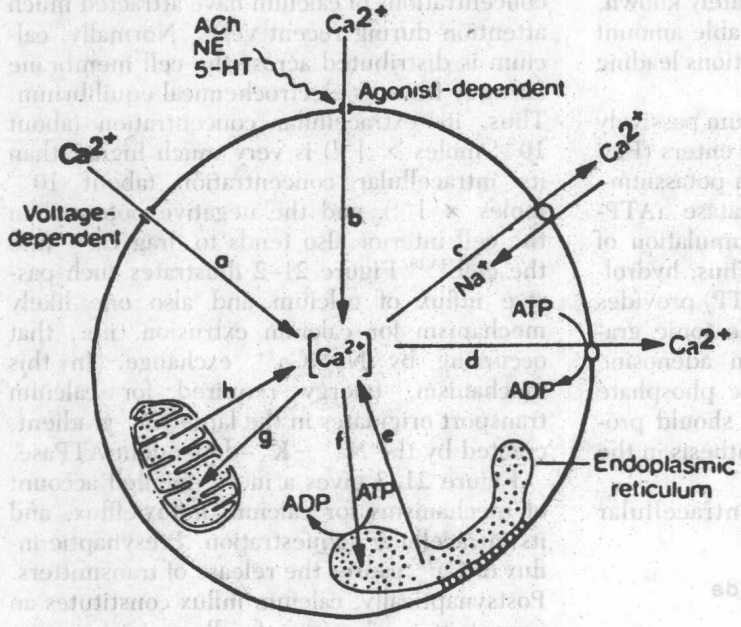

Figure 21–3. Influx of Ca^{2+} into neurons via (a) voltage- and (b) agonist-dependent channels. Extrusion of Ca^{2+} can occur by Na^+/Ca^{2+} exchange (c) and by ATP-driven translocation (d). Sequestration/release occurs between cytosol and endoplasmic reticulum (e,f) or mitochondria (g,h). (From Berridge, M. J.: Modulation of nervous activity by cyclic nucleotides and calcium. *In* Schmitt, F. O., and Worden, F. G., eds.: The Neurosciences: Fourth Study Program. Cambridge, MA, MIT Press, 1979, pp. 873–889. Reprinted by permission.)

ical activity.[61,193] These authors emphasize that since intramitochondrial calcium regulates the activity of several citric acid cycle enzymes, sequestration of calcium by mitochondria would upset this regulation. They suggest, therefore, that the mitochondrial membrane transport of calcium regulates intramitochondrial rather than cytoplasmic calcium, and that any real sequestration of calcium in the mitochondria is pathological.

Finally, a comment on the intracellular concentration of H^+ is justified. From measured transmembrane electrical potentials of -60 to -80 mV an intracellular pH (pH_i) of less than 6.4 and a bicarbonate concentration of below 2.5 μmol per ml can be calculated supposing a passive transmembrane distribution of H^+ and HCO_3^-. Since the actual pH_i is about 7.0 and the bicarbonate concentration about 12 μmol per ml, active transport must be involved.[156,179] Probably Na^+/H^+ exchange utilizing the energy from the Na^+ gradient is involved (Fig. 21–3).[157,202]

In summary, the transmembrane Na^+ gradient created by the $Na^+ - K^+ -$ ATPase does not only form the basis for the neuronal action potential. The energy is also utilized for coupled efflux of Ca^{2+} and H^+ and other kinds of osmotic work, such as the reaccumulation of transmitter molecules.

Biosynthetic Work

Synthetic tasks must consume a large share of the energy expended by cells. It has been suggested that the neuronal cell body synthesizes up to 2000 mitochondria and renews its whole population of macromolecules in one day.[137,210] This turnover rate for various structural components undoubtedly varies with the intensity of the impulse traffic.

The cell membrane can be described as a bimolecular leaflet of phospholipid molecules. The fatty acid tails of these molecules form the inner, hydrophobic zone, while their polar heads face the outside solutions.[190] In this matrix, cholesterol molecules and proteins are intercalated. The activity of the proteins, some of which are enzymes like ATPases and adenylate cyclases, are influenced by changes in the phospholipid matrix.[46]

Cell work will be illustrated by changes affecting membrane phospholipids. Figure 21–4 shows two cyclic reaction sequences illustrating the turnover of two classes of phospholipids.[216] The first cycle illustrates the degradation of inosine phosphoglyceride (GPI) to diglyceride (DG). Resynthesis of GPI subsequently takes place at the expense of two molecules of ATP.[14,65] This cycle, which is stimulated by neurotransmitters and other receptor agonists, seems involved in the regulation of Na^+/H^+ exchange across the plasma membrane, and of intracellular calcium concentration.[14]

The second cycle describes the degradation of other phospholipids to lysophospholipids and free fatty acids. In this turnover cycle the free fatty acids are subsequently activated by coenzyme A to the corresponding acyl-coen-

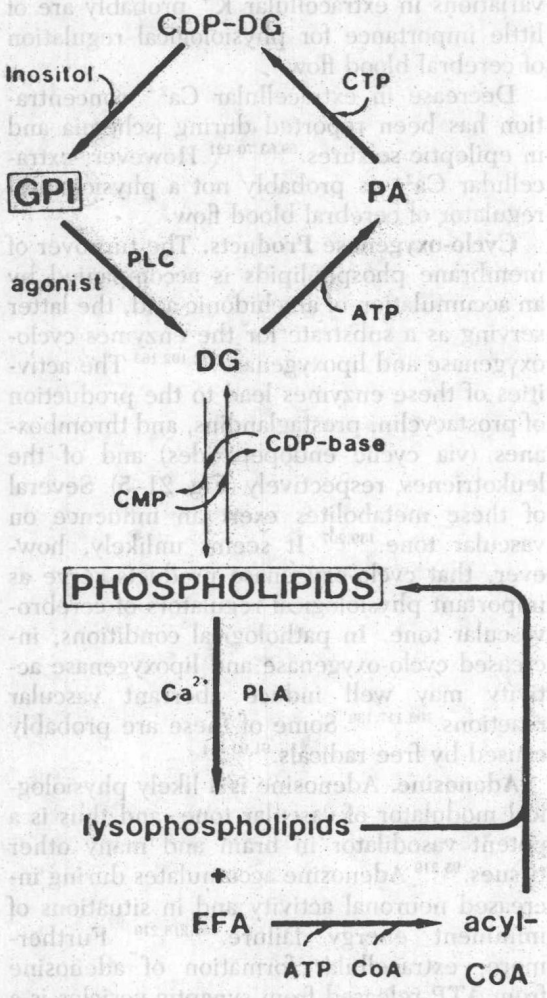

Figure 21–4. Schematic illustration of reactions involved in turnover of neuronal phospholipids, showing the interaction between inositol phosphoglyceride (GPI) turnover and general phosphoglyceride turnover. The two phospholipid cycles are interconnected by a reaction allowing base exchange. (From Wieloch, T., and Siesjö, B. K.: Ischemic brain injury: The importance of calcium, lipolytic activities, and free fatty acids. Pathol. Biol., *30*:269–277, 1982. Reprinted by permission.)

zyme A, and the cycle is completed through reacylation of the lysophospholipid.[198] It has been suggested that this cycle is involved in the activation of membrane-bound enzymes and/or the opening of gates for Ca^{2+}.[72,216] It is also proposed that the activation of phospholipase through the opening of Ca^{2+} gates leads to a release of arachidonic acid.[72] This accumulation may serve as a stimulus for the production of prostaglandins and leucotrienes (see below).

The two cyclic phospholipid cycles are obviously related to transmembrane ionic fluxes and thereby to cellular activity. For this reason, it does not seem justified to discuss osmotic and biosynthetic work as strictly separate entities.

Metabolism of Glial Cells

Opinions differ regarding the energy demands of glial cells as compared with those of neurons. It has been suggested that the work tasks of the glial cell cause a metabolic rate at least as high as in neurons, but this is a controversial issue.[67,69] Several facts indicate a lower metabolic turnover in glial cells. Thus, the mitochondrial density is less in glial cells, and cellular protein synthesis has been shown to be more intense in cerebral areas with a high density of neurons.[82] Finally, it is well established that in situations with a shortage of substrate and/or oxygen, resulting in energy failure, neurons succumb while glial cells may survive and even multiply.

The three kinds of glial cells—astrocytes, oligodendrocytes, and microglia—have been estimated to occupy about one half of the cerebral volume. Astrocytes separate neurons from each (except at synapses) and from the capillaries. The glial cells not only provide structural support and contribute to electrical isolation of the neurons, but also help to regulate perineuronal fluid composition and form part of the diffusion pathways for neuronal nutrients and waste products. The three main metabolic activities of the astrocytes are as follows: (1) the glial cells behave as almost perfect potassium electrodes, (2) they take part in the absorption and degradation of neurotransmitters such as gamma-aminobutyric acid (GABA), and (3) they may influence the energy metabolism of the neurons.[68,197] Thus, glial cells store glycogen, allowing rapid delivery of glucose to neighboring neurons in emergency situations.[27,67,69]

Cerebral Metabolism and Regulation of Blood Flow

It is usually assumed that blood flow is purposefully adjusted to the metabolic needs by signals reflecting an altered metabolism.[58,98,182,203] Consider events occurring as a result of an increased neuronal activity, with depolarization of membranes and downhill fluxes of ions. Stimulation of ATPases leads to ATP hydrolysis, the latter being accompanied by a rise of AMP concentration and by for-

mation of adenosine. As a result of increased respiratory activity, CO_2 accumulates and, if activity is intense, some lactic acid may be formed as well. These events reduce intra- and extracellular pH. Furthermore, apart from releasing K^+ from cells, increased activity causes influx of calcium and/or its release from intracellular stores. This enhances lipolysis and causes arachidonic acid to accumulate, with an ensuing production of cyclo-oxygenase and lipoxygenase products. The following three factors have been considered as contributing to the control of blood flow.

Extracellular Ion Concentrations. The extracellular concentration of H^+ was for a long period considered to be a major physiological regulator of cerebral blood flow. Although extracellular H^+ undoubtedly exerts an influence on cerebrovascular tone, it is nowadays hardly recognized as a major physiological regulator. Evidence against the pH hypothesis was obtained in experiments showing a dissociation between extracellular pH and cerebral blood flow. Examples are the initial events during hypoxia and epileptic seizures, during induction of anesthesia, and during hypoglycemia.*

Increases in extracellular K^+ concentration induce vasodilation, while higher concentrations may cause vasoconstriction.[93] However, variations in extracellular K^+ probably are of little importance for physiological regulation of cerebral blood flow.

Decrease in extracellular Ca^{2+} concentration has been reported during ischemia and in epileptic seizures.[59,63,70,121] However, extracellular Ca^{2+} is probably not a physiological regulator of cerebral blood flow.

Cyclo-oxygenase Products. The turnover of membrane phospholipids is accompanied by an accumulation of arachidonic acid, the latter serving as a substrate for the enzymes cyclo-oxygenase and lipoxygenase.[72,102,163] The activities of these enzymes lead to the production of prostacyclin, prostaglandins, and thromboxanes (via cyclic endoperoxides) and of the leukotrienes, respectively (Fig. 21–5). Several of these metabolites exert an influence on vascular tone.[139,207] It seems unlikely, however, that cyclo-oxygenase products serve as important physiological regulators of cerebrovascular tone. In pathological conditions, increased cyclo-oxygenase and lipoxygenase activity may well induce aberrant vascular reactions.[102,117,139] Some of these are probably caused by free radicals.[91,93,164]

Adenosine. Adenosine is a likely physiological modulator of vascular tone, and thus is a potent vasodilator in brain and many other tissues.[95,219] Adenosine accumulates during increased neuronal activity and in situations of imminent energy failure.[164,218,219] Furthermore, extracellular formation of adenosine from ATP released from synaptic vesicles is a

*See references: hypoxia and epileptic seizures, 6, 122, 123; induction of anesthesia, 106; during hypoglycemia, 6, 127.

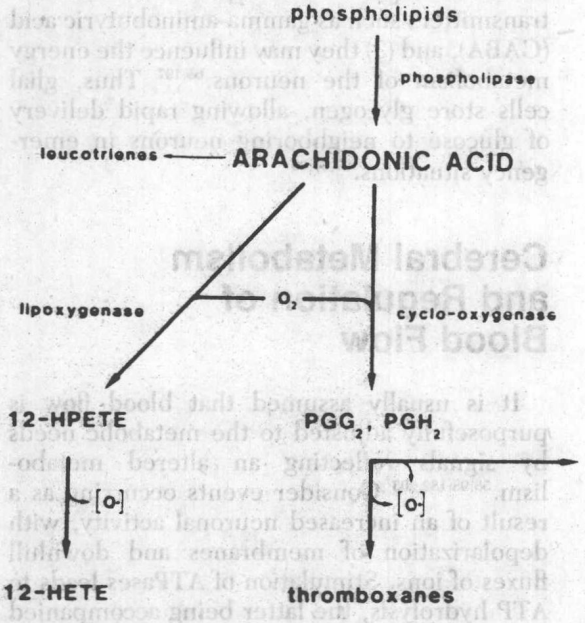

Figure 21–5. Current concepts of oxidative metabolism of arachidonic acid in the brain. 12-HPETE, Hydroperoxy-eicosatetraenoic acid; 12-HETE, 12-hydroxy-eicosatetraenoic acid; PGG_2 and PGH_2, prostaglandin endoperoxides; Q, free radical. (From Siesjö, B. K., and Wieloch, T.: Fatty acid metabolism and the mechanisms of ischemic brain damage. *In* Reivich, M., and Hurtig, H. J., eds.: Cerebrovascular Diseases. New York, Raven Press, 1983, pp. 231–268. Reprinted by permission.)

likely coupling factor adjusting blood flow to physiological demands.

Balance Between Production and Utilization of Energy

Before cerebral metabolic changes in pathophysiological conditions are discussed, the exceedingly efficient circulatory and metabolic adjustments that compensate for variations in brain energy utilization will be reviewed.

It is well known that the overall metabolic rate of the brain, e.g., its oxygen consumption, is extraordinarily constant even when there are overt signs of changes in mental activity or behavior such as those occurring during sleep, wakefulness, or performance of mental work. It is also known that the rate of cerebral oxygen consumption is decreased in coma, general anesthesia, and hypothermia, but increased in hyperthermia and during epileptic seizures.[171,192]

The quantitative relationships have been explored in some detail in animal experiments. When body temperature is reduced by 5°, 10°, or 15° C, cerebral oxygen consumption is reduced by 25, 50, and 75 per cent, respectively.[56,113] The 50 per cent reduction in oxygen metabolism observed with a 10° C reduction in body temperature is similar to that obtained during deep anesthesia with, for example, barbiturates. In general, the reduction in metabolic rate due to anesthesia is grossly proportional to the degree of reduction in consciousness, but there are important exceptions.[179,190] In hyperthermia there is an approximately 5 per cent increase in oxygen consumption for each degree of rise in temperature. An increase in rate of energy utilization has also been documented during epileptic seizures and during immobilization stress.[20,112] The latter finding is in line with previous investigations in man, showing that infusion of epinephrine leads to a feeling of anxiety and to increases in cerebral oxygen metabolism and blood flow.[83]

The extraordinarily tight coupling between neuronal energy consumption and production is accomplished through the metabolic mechanisms and the regulation of cerebral blood flow discussed above. The sufficiency of this coupling is schematically depicted in Figure 21–6. As illustrated, the rate of cerebral oxygen metabolism may vary almost tenfold without detectable changes in energy charge. Only

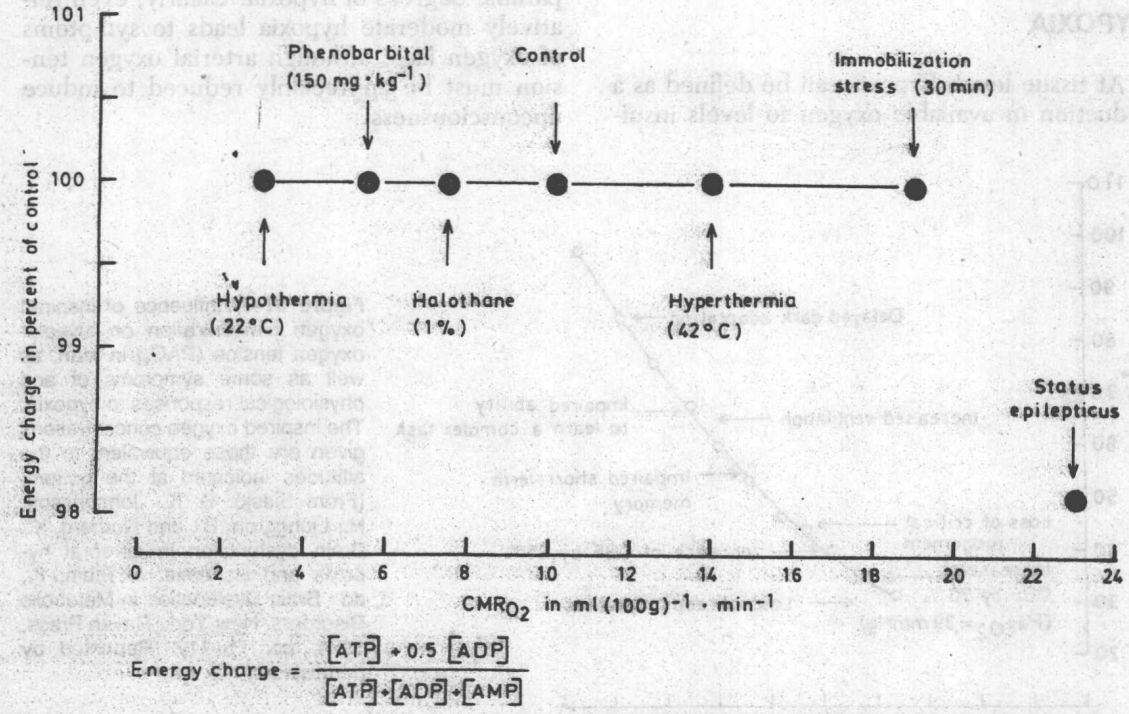

Figure 21–6. Relationship between adenylate energy charge and cerebral metabolic rate for oxygen ($CMRO_2$) of rat cerebral cortex in different conditions. (From Siesjö, B. K., Carlsson, C., Hägerdal, M., and Nordström, C.-H.: Brain metabolism in the critically ill. Crit. Care Med., 4:283–294, 1976. Reprinted by permission.)

during sustained epileptic seizures and their tremendously increased energy demands is it possible to recognize a reduction in energy charge. Consequently, as long as the supply of oxygen and substrate is sufficient, the energy-producing pathways adjust to the functional demands. As a corollary, the conclusion must be drawn that it is not possible to improve the energy state of the normal brain by pharmacological means or by changing body temperature. In pathological situations that encroach upon normal energy production, the situation may be very different.

Pathophysiology of Brain Damage

Three major pathophysiological conditions will be considered: hypoxia, ischemia, and hypoglycemia. When considered in conjunction, they provide an opportunity to discuss most of the pathophysiological conditions and neurochemical events underlying brain damage in energy-deficient states. For additional discussion and further references, the reader should consult articles quoted in the text.

HYPOXIA

At tissue level, hypoxia can be defined as a reduction in available oxygen to levels insufficient for maintenance of function, metabolism, or structure.[171,186] The oxygen availability, i.e., the amount of oxygen carried to the tissue at any given moment, is expressed as

$$\text{Oxygen availability} = \text{CBF} \times \text{Sa}_{O_2} \times \text{Hb} \times 1.39 \quad (1)$$

where Sa_{O_2} is the percentage saturation of hemoglobin, Hb is the hemoglobin concentration, and 1.39 is the amount of oxygen (in milliliters) bound to 1 gm of hemoglobin at full saturation. The term "arterial hypoxia" can be used to describe a reduction in available oxygen in the tissue due to a decrease in either oxygen tension (hypoxic hypoxia) or hemoglobin concentration (anemic hypoxia). Uncomplicated arterial hypoxia is invariably associated with an increase in cerebral blood flow, which serves as an important homeostatic mechanism, allowing the tissue to sustain relatively pronounced hypoxia without energy failure.[171,203]

The functional effects of hypoxic hypoxia, as observed in man, are summarized in Figure 21–7. Most of the results were obtained in simulated high-altitude experiments. In order to facilitate comparisons with animal experiments, the figure also shows the inspired oxygen concentrations that would give comparable degrees of hypoxia. Clearly, even relatively moderate hypoxia leads to symptoms of oxygen lack, although arterial oxygen tension must be appreciably reduced to induce unconsciousness.

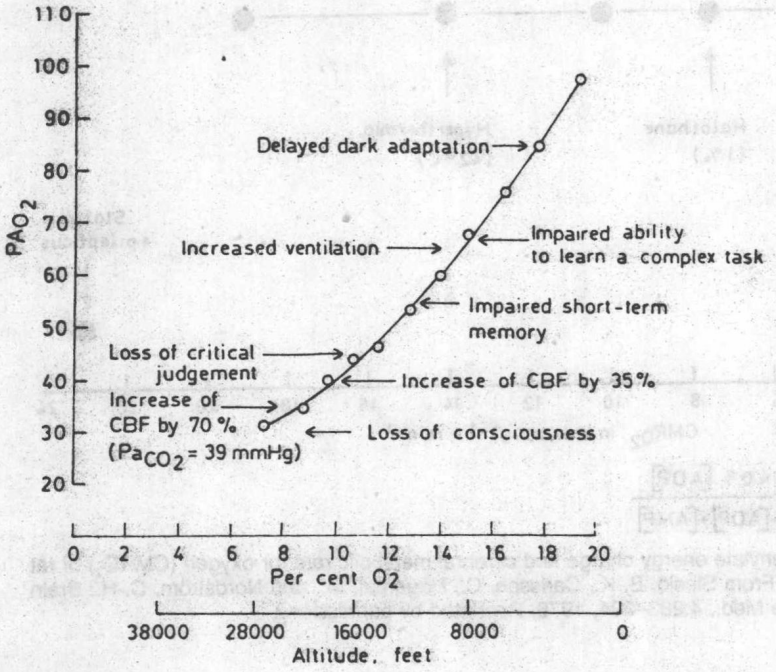

Figure 21–7. Influence of inspired oxygen concentration on alveolar oxygen tension (PAO_2) in man, as well as some symptoms of and physiological responses to hypoxia. The inspired oxygen concentrations given are those equivalent to the altitudes indicated at the bottom. (From Siesjö, B. K., Jóhannsson, H., Ljunggren, B., and Norberg, K.: Brain dysfunction in cerebral hypoxia and ischemia. *In* Plum, F., ed.: Brain Dysfunction in Metabolic Disorders. New York, Raven Press, 1974, pp. 75–112. Reprinted by permission.)