Hypoxia

K.K. Jain

Abstract

Tissue hypoxia plays an important role in the pathogenesis of many disorders, particularly those of the brain. Correction of hypoxia by hyperbaric oxygenation is, therefore, an important adjunct in the treatment of those disorders. This chapter describes pathophysiology of hypoxia with general impact on the functions of various systems of the body and particularly the brain. Role of HBO in the treatment of hypoxic states is discussed as well as possible adverse effects of HBO.

Keywords

Hypoxia • Tissue hypoxia • Cerebral hypoxia

Introduction

The term "hypoxia" generally means a reduced supply of oxygen in the living organism. Hypoxia may be either generalized, affecting the whole body, or local, affecting a region of the body. It is difficult to define hypoxia precisely, but it may be described as a state in which aerobic metabolism is reduced by a fall of pO_2 within the mitochondria. In this situation, the partial pressure of oxygen, which in dry air is 160 mmHg, drops to about 1 mmHg, by the time it reaches the mitochondria of the cell. Below this value aerobic metabolism is not possible. Hypoxia is not always a pathological condition as variations in arterial oxygen concentrations can be physiological, e.g., during strenuous physical exercise. In contrast, "anoxia" implies a total lack of oxygen, although the word is sometimes used as a synonym for hypoxia.

The subject of hypoxia was dealt with in detail in a book on oxygen (Jain 1989). Recent developments and a few important aspects should be discussed here because relative tissue hypoxia is frequently the common denominator of many diseases that are amenable to HBO therapy.

Pathophysiology of Hypoxia

Within the cell, 80 % of the total oxygen consumption is by mitochondria, and 20 % by a variety of other subcellular organs. The biochemical reactions in these locations serve a variety of biosynthetic, biodegradative, and detoxificatory oxidations. Some of the enzymes involved in the synthesis of neurotransmitters have low affinities for oxygen and are impaired by moderate depletions of oxygen. Some of the manifestations of oxygen depletion are related to "transmitter failure" (decreased availability of transmitter), rather than bioenergetic failure. The disturbances that lead to decreased oxygen supply could operate at any of the three phases mentioned in Chap. 2, i.e.:

- The respiratory phase
- The phase of oxygen transport
- The phase of oxygen use by the tissues

Hypoxia can potentiate injury due to oxidative stress. The proposed sequences are shown in Fig. 5.1.

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Fig. 5.1 Proposed sequence in which hypoxia potentiates injury due to oxidative stress. *ROS* reactive oxygen species, *HIF* hypoxia-inducible factor, *ATP* adenosine triphosphate
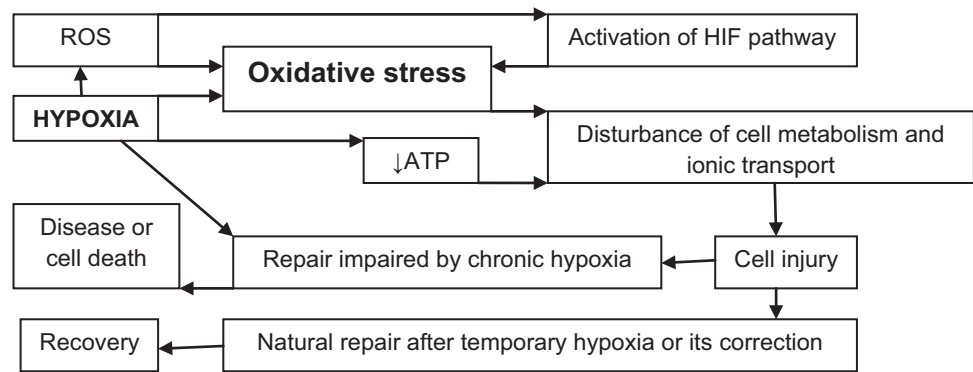
Hypoxia-Inducible Factor

Hypoxia-inducible factor (HIF) senses and coordinates cellular responses to hypoxia. HIFs mediate the ability of the cell to cope with decreased oxygen tension. These transcription factors regulate cellular adaptation to hypoxia and protect cells by responding acutely and inducing production of endogenous metabolites and proteins to promptly regulate metabolic pathways. HIF pathway plays an important role in physiological adaptation, cell survival, pH regulation, and adaptation during exercise (Kumar and Choi 2015). HIF-1α, the most well-established member of the HIF family, is a master regulator for the expression of genes involved in the response to hypoxia in most mammalian cells.

HIF-1α plays a role in the pathogenesis of several diseases and can be modulated by HBO. Interaction of HBO with HIF is variable according to whether the disease is characterized by upregulation or downregulation of HIF-1α. For example, the ability to downregulate the expression of HIF-1α may partially explain the therapeutic effect of HBO on taurocholate-induced acute pancreatitis in Wistar rats (Bai et al. 2009). Another study has shown that induction of fibroblast proliferation in HBO disappears when HIF-1α is knocked down (Sunkari et al. 2015). Furthermore, the local transfer of stable HIF-1α-expressing adenovirus into experimental wounds in diabetic animals has an additive effect on HBO-mediated improvements in wound healing. In conclusion, HBO stabilizes and activates HIF-1, which contributes to increased cellular proliferation. In diabetic animals, the local transfer of active HIF further improves the effects of HBO on wound healing.

Hypoxia and Heat Shock Proteins

Heat shock proteins (Hsps) is the term used for a family of proteins that are produced by cells in response to exposure to stressful conditions. Originally described as a response to heat shock or rise in temperature, they are now known to be induced by other stressful situations such as hypoxia. Hsps are named according to their molecular weight, e.g., Hsp60, Hsp70, and Hsp90. A study on healthy volunteers subjected to transient normobaric hypoxia has shown that hypoxic conditions can trigger the release of Hsp70 (Lichtenauer et al. 2014).

A study has shown that HBO treatment prevents nitric oxide (NO)-induced apoptosis in articular cartilage injury via enhancement of the expression of Hsp70 (Ueng et al. 2013). The histological scores showed that HBO markedly enhanced cartilage repair. Immunostaining showed that HBO enhanced HSP70 expression and suppressed iNOS and caspase 3 expressions in chondrocytes.

Effect of Hypoxia on Cellular Metabolism

Hypoxia depresses mitochondrial oxidative phosphorylation. Creatine phosphorylase is released, as evidenced by sarcolemmal damage during hypoxia. This process is considered to be calcium mediated, because calcium channel blockers protect the cell from hypoxic damage.

A rapid decline in ATP levels under hypoxic conditions may cause an increase in calcium flux into the cytosol because of inhibition of the calcium pump in the plasma membrane, mitochondria, and endoplasmic reticulum. Alternatively, ATP may be metabolized to hypoxanthine, a substrate for superoxide anion formation. Barcroft's classification of hypoxia is as follows (Barcroft 1920):

- Hypoxic: includes all types of hypoxia in which not enough oxygen reaches the alveoli.
- Anemic: caused by inadequate hemoglobin or abnormal hemoglobin, so that not enough oxygen can be transported to the tissues.
- Stagnant or circulatory: blood flow is inadequate to carry the oxygen to the tissues.
- Histotoxic: the tissues cannot use the oxygen even though it reaches the tissues in adequate quantities.

Table 5.1 Causes of hypoxia

I.   Inadequate oxygenation in the lungs
1. Deficient oxygen in the atmosphere: high altitudes (mountain sickness), closed spaces
2. Hypoventilation
(a) Respiratory muscle paralysis or weakness due to neuromuscular or neurological diseases
(b) Extreme obesity
(c) Central depression of respiration due to the effect of sedatives, narcotics, or anesthetics
3. Pulmonary disorders
(a) Chronic obstructive pulmonary disease, such as chronic bronchitis and emphysema, hypoxic cor pulmonale
(b) Restrictive lung disease: adult respiratory distress syndrome, chest injuries, deformities of the chest and the thoracic spine
(c) Pulmonary infections: pneumonia, diphtheria, whooping cough
4. Sleep-disordered breathing: sleep apnea, snoring, nocturnal hypoxia
II. Inadequate transport and delivery of oxygen
1. Carriage of oxygen combined with hemoglobin
(a) Anemia, reduced RBC
(b) Reduced effective hemoglobin concentration: COHb, MetHb, etc.
2. Increased affinity of hemoglobin for oxygen
(a) Reduced DPG in RBC
(b) Reduced temperature
(c) Increased pH of blood
3. Circulatory disorders
(a) Global decrease of cardiac output
(b) Systemic arteriovenous shunts, right to left cardiac shunts
(c) Maldistribution of cardiac output, regional circulatory disturbances
4. Disturbances of hemorheology and microcirculation
(a) Increased viscosity
(b) RBC disease: decreased surface, stiff cell membrane, etc.
III. Increased demand of tissues beyond normal supply (relative hypoxia)
1. Inflammation
2. Hyperthermia
3. Strenuous physical exercise
IV. Capability of the tissue to use oxygen is inadequate
1. Cellular enzyme poisoning: cytochrome P-450 and a3 cytochrome oxidase
2. Reduced cellular enzymes because of vitamin deficiency

The causes of hypoxia are shown in Table 5.1.

Impact of Hypoxia on Various Body Systems

The effects of hypoxia vary in accordance with its cause, whether the situation is acute or chronic, and also with the overall state of health of the individual in question.

Cellular hypoxia may develop in multiple organ failure syndrome because of the increased oxygen demand at the tissue level and/or because the ability to extract oxygen at the cellular level is decreased. Restoration of oxygen transport and metabolic support are important components of treatment.

Respiratory Function

Hypoxia initially leads to an increase in the respiratory rate, but later the rate is decreased. It remains controversial whether there is depression of the respiratory center, decreased central chemoreceptor pCO_2, or both. Respiratory depression is likely due to a fall in tissue pCO_2 resulting from an increase in blood flow caused by hypoxia.

In hypoxia caused by hypoventilation, CO_2 transfer between alveoli and the atmosphere is affected as much as oxygen transfer, and hypercapnia results, i.e., excess CO_2 accumulates in the body fluids. When alveolar pCO_2 rises above 60–75 mmHg, dyspnea becomes severe, and at 80–100 mmHg stupor results. Death can result if pCO_2 rises to 100–150 mmHg.

Cardiovascular System

Circulatory responses to hypoxia have been studied mainly in the laboratory animals and a few conclusions that can be drawn are as follows:

- The local vascular effect of hypoxic vasodilation is probably common to all but the pulmonary vessels. It is strongest in active tissues (heart, brain, working skeletal muscle) that are dependent on oxygen for their metabolism.
- A chemoreceptor reflex produces an increase in cardiac contractility and selective vasoconstriction that support arterial pressure and some redistribution of cardiac output.
- The overall response to hypoxia involves an increase in cardiac output and selective vasodilation and vasoconstriction in an attempt to maintain oxygen delivery and perfusion pressure to all organs.

General Metabolic Effects

The following disturbances have been observed as a result of experimental hypoxia produced in animals:

- Appearance of excess lactate in the blood
- Appearance of 2,3-DPG in the blood of animals exposed to hypoxia of high altitudes

- Higher plasma levels of corticosterone, leading to neo-glucogenesis
- Decrease of long-chain unsaturated fatty acids in the blood sera of rats adapted to hypoxia

Effects of Hypoxia on the Brain

Although any part of the body can be affected by hypoxia, the effects are most marked on the cells of the central nervous system, for the following key reasons:

- The brain has unusually high resting energy requirements, which can only be met by oxidative breakdown of the exogenous substrate. Anaerobic production of energy by glycolysis is not adequate to maintain normal brain function.
- The brain cannot store oxygen. Its energy reserves are low and usually it cannot tolerate anoxia (due to lack of circulation) for more than 3 min.
- The brain, unlike muscle tissue, is incapable of increasing the number of capillaries per unit of volume.
- Neurons have a poor capacity to recover or regenerate after dysoxia.
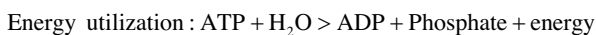
Cerebral Metabolism

Cerebral metabolism, particularly that of oxygen, is closely tied in with cerebral blood flow (CBF). The brain, although it makes up only 2 % of the body weight, consumes 20 % of the oxygen taken in by the body and receives 15 % of the cardiac output. This is remarkably high oxygen consumption, considering that the brain, unlike the heart muscle, does not perform any physical work. Cerebral metabolism is depicted by another term, glucose oxidation quotient (GOQ). It denotes the ratio

$$\text{AVD of Glucose} - \text{AVD of Lactate}\left(\text{in mg / dL}\right):$$
$$\text{AVD Oxygen}\left(\text{in vol\%}\right)$$

where AVD is the arteriovenous difference. Normally this value is 1.34, because 1.0 mL of oxygen oxidizes 1.34 mg of glucose.

Cell energy metabolism is simply a balance between use of adenosine triphosphate (ATP) during the performance of work and its resynthesis in anabolic sequence, which provides the energy required to rephosphorylate adenosine diphosphate (ADP). The resulting energy metabolism is depicted by the following equations:
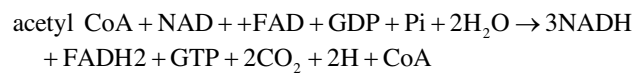
$$\text{Energy utilization}: \text{ATP} + H_2O > \text{ADP} + \text{Phosphate} + \text{energy}$$

$$\text{Energy production}: \text{ADP} + \text{Phosphate} + \text{energy} \rightarrow \text{ATP} + H_2O$$

The brain produces about as much CO_2 as it consumes in oxygen; i.e., the respiratory quotient is close to 1.0. On a molar basis, the brain uses a remarkable six times as much oxygen as glucose. Glucose is normally the sole substrate and is completely utilized.

The rate of electron transport, and thereby of oxygen use, is determined by the rate of consumption of ATP and the rate of accumulation of ADP and Pi. Most studies in humans have shown that oxygen consumed accounts for only 90–95 % of the glucose extracted, leading to the view that 5–10 % of the glucose extracted by the brain is metabolized to lactic acid. The cause of this is not known, but it may be an "emergency metabolic exercise" by the brain.

Pathways of cerebral metabolism (glycolysis, the citrus cycle, and the GABA pathway) are shown in Fig. 5.2. Glycolysis includes a series of enzymatic reactions by which the cytoplasmic glucose is built into two molecules of lactate. Thus no oxygen is necessary, but nicotinamide adenine dinucleotide (NAD+) is required. In all, glycolysis produces two molecules of NADH and ATP from each molecule of glucose. Under aerobic conditions, pyruvate is decarboxylated oxidatively:

$$\text{pyruvate} + \text{CoA} + \text{NAD+} \rightarrow \text{acetyl CoA} + \text{NADH} + CO_2$$
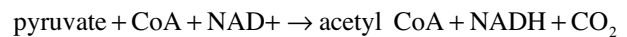
Acetyl CoA is transported in the mitochondria and goes into the citrus cycle; NADH is oxidized through mitochondrial electron transfer. Pyruvate and several other products of intermediate metabolism are oxidized through the citrate cycle, whereby the hydrogen of NAD+ and flavine adenine dinucleotide (FAD) is carried over by substrate-specific dehydrogenases. In summary, the balance of the cycle is

$$\text{acetyl CoA} + \text{NAD} + + \text{FAD} + \text{GDP} + \text{Pi} + 2H_2O \rightarrow 3\text{NADH}$$
$$+ \text{FADH2} + \text{GTP} + 2CO_2 + 2H + \text{CoA}$$

where lactate is the end product of the glycolytic reaction, and we obtain

$$\text{glucose} + 2\text{ADP} + 2P_i \rightarrow 2\text{ATP} + 2\text{lactate}$$
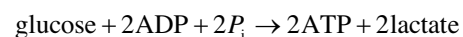
If we add up all ATP formed from the oxidation of one molecule of glucose, we find the following balance:

$$\text{glucose} + 6CO_2 + 38\text{ADP} + 38P_i > 6CO_2 + 44H_2O + 38\text{ATP}$$
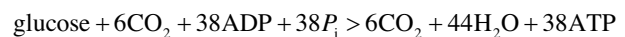
Thus the complete oxidation of a glucose molecule provides 19 times as much ATP as anaerobic glycolysis.

The key enzyme for the regulation of the rate of glycolysis is phosphofructokinase, which is activated by P_i, adenosine monophosphate (AMP), cyclicAMP (cAMP), ADP, and ammonia. It is inhibited by ATP and citrate. Glucose degradation is partly regulated by glucose availability.

In the presence of glucose, norepinephrine-induced glycogenolysis is blocked despite elevations in cAMP. On the whole, the brain energy turnover is 7 molecules/min. One molecule of ATP contains 29.7 kJ of energy. It is postulated
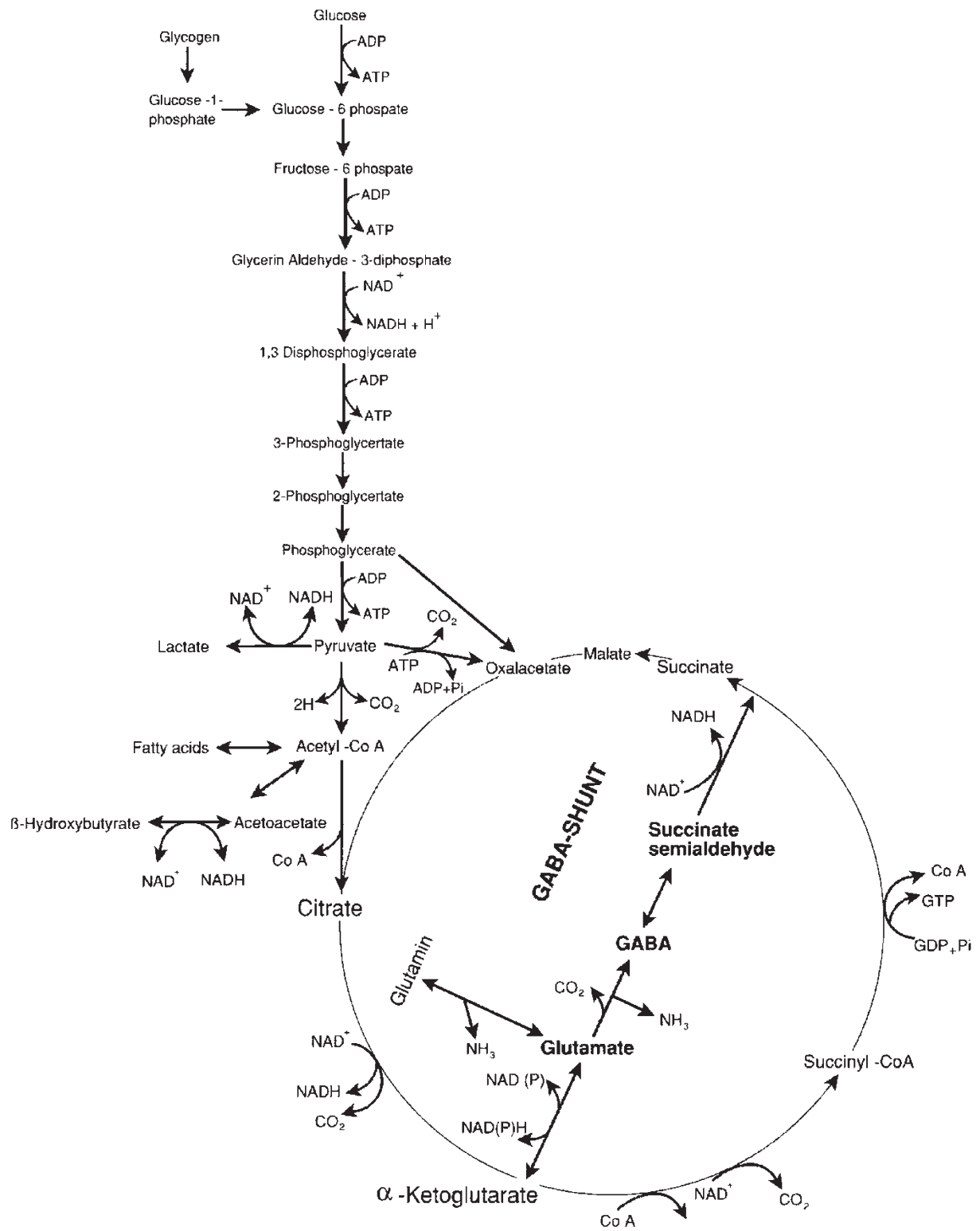
**Fig. 5.2** Glycolytic pathway, critic acid cycle, and GABA shunt

that the relative concentration of adenine nucleotide, also expressed as energy charge (EC), has the most important metabolic regulatory effect:

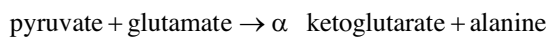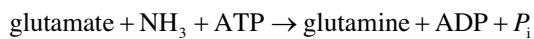$$\frac{EC + ATP + \frac{1}{2}ADP}{AMP + ADP + ATP}$$

Under physiological conditions this quotient generally has a value between 0.85 and 0.95, and this value falls significantly in cerebral ischemia.

The GABA Shunt

It has been shown that 10 % of the carbon atoms from pyruvate molecules are metabolized via the GABA shunt. When coupled with the aspartate aminotransferase (AST) reaction, aspartate formation results:

glutamate + oxaloacetate > aspartate + α ketoglutarate
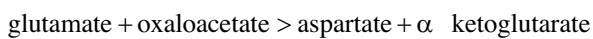
Two associated reactions give rise to the formation of glutamine and alanine:

glutamate + NH_3 + ATP $\rightarrow$ glutamine + ADP + P_i

pyruvate + glutamate $\rightarrow$ α ketoglutarate + alanine

The GABA shunt pathway and its associated reactions allow the synthesis of glutamate, GABA, aspartate, alanine, and glutamine from ammonia and carbohydrate precursors. They have two main functions: detoxification of ammonia and resynthesis of amino acid transmitters that are lost from neurons during functional activity.

Pyruvate and the Citric Acid Cycle

Under some conditions pyruvate can be introduced into the citric acid cycle via pyruvate decarboxylase or malate dehydrogenase. Pyruvate dehydrogenase is an intramitochondrial enzyme complex that catalyzes the conversion of pyruvate into acetyl CoA and CO_2. The proportion of pyruvate dehydrogenase in active form in the brain intramitochondrial enzyme complex that catalyzes the conversion of pyruvate into acetyl CoA and CO_2 changes inversely with changes in mitochondrial energy charge. Normally there is a slight excess of pyruvate dehydrogenase in comparison with pyruvate flux, as the brain usually depends on carbohydrate utilization.

Cerebral Metabolism During Hypoxia

During tissue hypoxia, molecular oxygen or the final receptor of hydrogen is reduced. This results in diminution in the amount of hydrogen which can reach the molecular oxygen via the respiratory chain. As a sequel, not only is the oxidative energy production reduced, but the redox systems are shifted to the reduced side with ensuing tissue acidosis.

The reduction of oxidative ATP formation leads to an increase of nonoxidative energy production, i.e., by glycolysis due to decrease of the ATP/AMP quotient. The increased glycolysis results in an accumulation of pyruvate and NADH within the cytoplasm of the cell.

Since triose phosphate dehydrogenase is an enzyme of glycolysis dependent on NAD, the activity of this enzyme, and thus of the glycolytic pathways, requires NAD within the cytoplasm for maintenance of the cell function. Under hypoxic conditions NAD is provided within the cytoplasm by means of the following reaction catalyzed by lactate dehydrogenase:

pyruvate + NADH $\rightarrow$ lactate + NAD
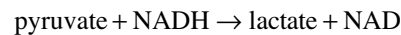
This causes a reduction of intracellular pyruvate and NADH concentration, and a supply of NAD and lactate. Whereas lactate, the final product of glycolysis, is bound, NAD is made available as hydrogen receptor to the triose phosphate dehydrogenase. This is how glycolysis, with its relatively low energy production, may be maintained even under hypoxic conditions. This biochemical process is extremely valuable for the structural conservation of the neurons under hypoxic conditions.

Hypoxia also disturbs the acid–base balance of the tissues by an increase of H+ ion concentration and an excess of lactate as a result of intensified glycolysis. It affects the cytoplasmic NADH/NAD as well as lactate/pyruvate ratios, as expressed in the following equation:

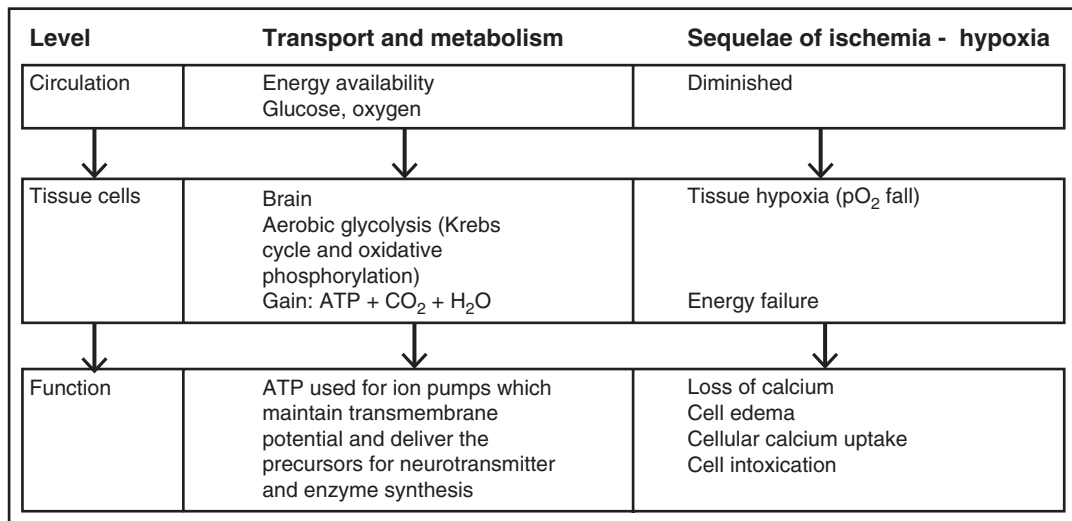$$\frac{lactate}{pyruvate} \times \frac{K}{H} = \frac{NADH}{NAD}$$

where K is an equilibrium constant. The redox system is shifted to the reduced side. There is increased pyruvate concentration, which, however, falls short of the increase in lactate.

In total anoxia the glycolysis increases four to seven times. There is a decrease of glucose, glucose-6-phosphate, and fructose–hexose phosphate and an increase of all substrates from fructose diphosphate to lactate. These changes can be interpreted as resulting from facilitation of phosphorylation of glucose to fructose–hexose phosphate.

Studies with labeled glucose uptake in the brain under hypoxic conditions show that the hippocampus, the white matter, the superior colliculi, and the geniculate bodies are the areas most sensitive to the effects of hypoxia. The relatively greater sensitivity of the white matter to hypoxia may lead to an understanding of the white matter damage in postanoxic leukoencephalopathy and its possible prevention with HBO. The relative paucity of capillaries in white matter may predispose them to compression by edema.

Anoxia and hypoxia have different effects on the brain. In hypoxia, the oxidative metabolism of the brain is impaired but not abolished. A three-stage model of ischemic–hypoxic disturbances of the brain is shown in Fig. 5.3.

Level	Transport and metabolism	Sequelae of ischemia - hypoxia
Circulation	Energy availability Glucose, oxygen	Diminished
Tissue cells	Brain Aerobic glycolysis (Krebs cycle and oxidative phosphorylation) Gain: ATP + CO_2 + H_2O	Tissue hypoxia (pO_2 fall) Energy failure
Function	ATP used for ion pumps which maintain transmembrane potential and deliver the precursors for neurotransmitter and enzyme synthesis	Loss of calcium Cell edema Cellular calcium uptake Cell intoxication

Fig. 5.3 A three-stage model of ischemic–hypoxic disturbances of the brain

Changes in Neurotransmitter Metabolism

The following changes in neurotransmitter metabolism during hypoxia are particularly significant:

Synthesis of Acetylcholine Is Impaired by Hypoxia. Decrease of acetylcholine following cerebral hypoxia correlates with impairment of memory and learning processes. Indirect evidence for this includes the ameliorating effect of cholinergic drugs in cerebral insufficiency due to hypoxia.

Reduction of Brain Catecholamines. Norepinephrine, epinephrine, and dopamine are synthesized by a combination of tyrosine and oxygen. Hypoxia limits this biosynthesis; the turnover of 5-HT is reduced. A reduction has also been observed in the synthesis of glucose-derived amino acids.

Disturbances of CBF Regulation

In the normal person, CBF remains constant in spite of variations in blood pressure up to a certain extent by virtue of autoregulation. This reflects an inherent capacity of the brain to regulate the circulation according to its requirements. The arteries and arterioles contract when the blood pressure rises and dilate when the blood pressure falls. Hypoxia impairs and blocks this critical mechanism; indeed, there may be marked vasodilatation in the hypoxic brain. Thus, the blood supply of the affected brain region is dependent upon the prevailing blood pressure. The disruption of autoregulation accompanied by focal ischemia and peripheral hyperemia is called the "luxury perfusion syndrome." Following hypoxia, CBF increases as much as twofold initially, but the blood flow increase is blunted somewhat by a decreasing arterial pCO_2 as a result of the hypoxia-induced hyperventilatory response. After a few days, however, CBF begins to fall back toward baseline levels as the blood oxygen-carrying capacity is increasing due to increasing hemoglobin concentration and packed red cell volume as a result of erythropoietin upregulation. By the end of 2 weeks of hypoxic exposure, brain capillary density is increased with resultant decreased intercapillary distances. The relative time courses of these changes suggest that they are adjusted by different control signals and mechanisms.

Disturbances of Microcirculation

In the hypoxic brain, there is aggregation of thrombocytes regardless of the etiology of hypoxia. This is followed by aggregation of red cells, and the phenomenon of "sludging" in the blood. This is aggravated by a reduction of velocity in the blood flow and can result in stasis with its sequelae, such as extension of the area of infarction.

Disturbances of the Blood–Brain Barrier

The hypoxic brain tissue is readily affected by disturbances of the permeability of the blood–brain barrier (BBB) and the cell membranes, because the energy-using mechanisms are dependent upon the integrity of these membranes. Disturbances of the BBB impair the active transport of substances in and out of the brain tissues. This may particularly affect glucose transport to the neurons during its metabolism. The oxygen deficiency can also result in a secondary disturbance of the utilization of the substrate.

Cerebral Edema

A further sequel of BBB damage is cerebral edema. Although injury to the brain contributes to the edema, the loss of autoregulation is also an important factor. The rise of intracapillary pressure leads to seepage of fluid into the extracellular
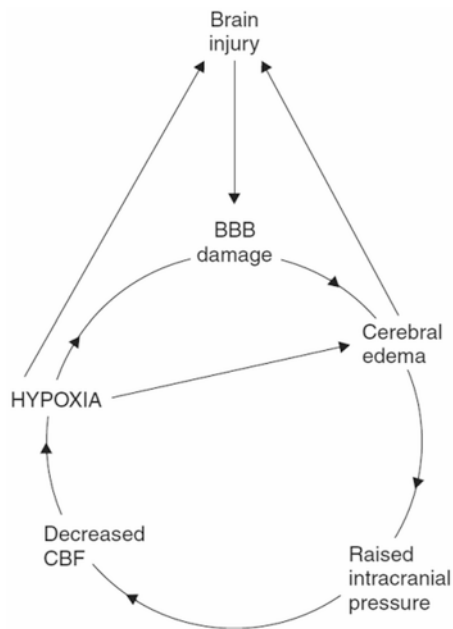
Fig. 5.4 Hypoxia as a central factor in edema due to brain injury

space. The edema impairs the oxygen supply to the brain and leads to an increase of intracranial pressure and a decrease of CBF. Hypoxia which complicates a brain injury is a dreaded phenomenon and represents a decisive factor in the outcome of the illness. Hypoxia is the central factor in the vicious circle shown in Fig. 5.4.

Effect of Hypoxia on the Electrical Activity of the Brain

The electrical activity of the neurons in the human CNS is remarkably sensitive to hypoxia. EEG activity is attenuated after 10–30 s, and evoked potentials are depressed within 1–3 min of hypoxia. Little is known of the important mechanisms underlying these effects.

Disappearance of EEG activity with hypoxia and reappearance on oxygenation are related to the creatine phosphate (CrP)/creatine (Cr) quotient, pointing to a close functional relationship between brain energy potentials and EEG activity. Computer analysis of EEG in induced hypoxia in human subjects shows that both the mean frequency and the mean amplitude closely reflect the degree of hypoxia.

Electrocerebral silence occurs when cerebral venous pO_2 reaches 20 mmHg or after only 6 s of total anoxia.

Disturbances of Mental Function in Cerebral Hypoxia

McFarland et al. (1944) demonstrated that oxygen deprivation, whether induced by high altitude or CO poisoning, leads to loss of capacity of sensory perception and judgment. The subjects recovered when oxygen supply was resumed.

Some important causes of hypoxia that lead to impairment of mental function are:

- Chronic carbon monoxide poisoning
- High altitudes, climbing peaks over 8000 m without supplemental oxygen
- Sleep-disordered breathing
- Chronic obstructive pulmonary disease

Hypoxia has been considered a causal factor in the decline of intellectual function in the elderly. Cerebral symptoms appear at even a moderate degree of hypoxic hypoxia, demonstrating that certain higher functions are very sensitive to restriction of the oxygen supply, as suggested in Fig. 5.5. Delayed dark adaptation has been reported at alveolar oxygen tensions of 80 mmHg, but abnormalities in psychological tests do not occur until alveolar pO_2 is reduced below 50 mmHg, and gross deterioration of mental functions appears only below alveolar pO_2 values of 40 mmHg.

A mild and rapid hypoxic challenge, by breathing 14.5 % oxygen or rapid ascent by helicopter to a mountain peak 3450 m high, may improve a simple measure of cognitive performance (Schlaepfer et al. 1992). Effects of hypoxia vary according to the mode of induction, severity, and duration.

Structural Changes in the Brain After Hypoxia

Patients who recover following resuscitation for cardiopulmonary arrest may not show any structural changes demonstrable by imaging studies. Patients with a residual vegetative state usually develop cerebral atrophy with decrease of rCBF and oxygen consumption. In the subacute phase, these patients may show white matter lucencies on CT scan. PET findings (decrease of rCBF and rCMRO), weeks after the ischemic–hypoxic insult, correlate with the neuropsychiatric deficits due to cardiopulmonary arrest.

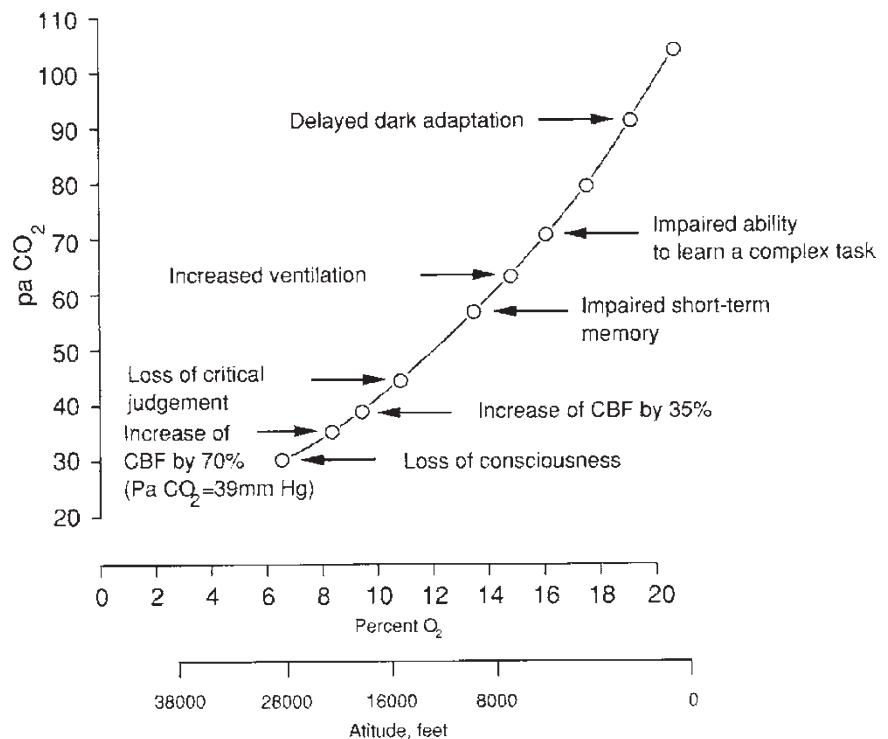### Conditions Associated with Cerebral Hypoxia

Various conditions associated with cerebral hypoxia are shown in Table 5.2. Pathophysiology and management of these are discussed in various chapters of this book.

Assessment of Hypoxic Brain Damage

Various abnormalities demonstrated on brain imaging are described in Chaps. 18 and 19. Delayed hypoxic changes are likely to manifest by changes in basal ganglia. The classical example of hypoxic brain damage is that after cardiac arrest. Hypoxic brain damage after cardiac arrest can be estimated by measurements of concentrations of serum S protein which is an established biomarker of central nervous system injury. It is a reliable marker of prediction of survival as well as of outcome.

Fig. 5.5 Influence of inspired oxygen concentration on alveolar pO_2 in man, with symptoms of and physiological responses to hypoxia. Reproduced from Siesjö et al. (1974)

Table 5.2 Conditions associated with cerebral hypoxia

- Air embolism
- Carbon monoxide poisoning
- Cardiac arrest
- Cardiac arrhythmia
- Complications of general anesthesia
- Cyanide poisoning
- Decompression sickness involving the brain
- Drowning
- Drug overdose
- Fat embolism
- Malignant brain tumors, e.g., glioblastoma multiforme
- Severe head injury
- Strangulation
- Stroke
- Very low blood pressure

in other chapters: myocardial ischemia in Chap. 25, CO poisoning in Chap. 13, stroke in Chap. 19, and global ischemia/anoxia and coma in Chap. 20.

Neurons can tolerate between 20 and 60 min of complete anoxia without irreversible changes. Following these severe insults, neurons regain the ability to synthesize protein, produce ATP, and generate action potentials. HBO can facilitate this recovery process. The most significant effects of hypoxia are on the brain, and a review of the metabolic effects leads to the rationale of HBO therapy in hypoxic conditions of the brain, particularly those due to cerebrovascular ischemia.

Hypoxia is also a common feature of the tumor microenvironment and a major cause of clinical radioresistance. Role of HBO in enhancing cancer radiosensitivity is discussed in Chap. 38.

Role of HBO in the Treatment of Hypoxic States

Hypoxia due to inadequate oxygenation in the lungs, either from extrinsic factors or owing to pulmonary disease, can usually be corrected by oxygen. The role of HBO in pulmonary disorders is discussed in Chap. 29. The major applications of HBO are in conditions with inadequate transport and delivery of oxygen to the tissues or inadequate capacity of the tissues to use oxygen. The uses of HBO in the treatment of circulatory disturbances and tissue edema are discussed

The Role of Nitric Oxide Synthase in the Effect of HBO in Hypoxia

The adhesion of polymorphonuclear leukocytes to endothelial cells is increased following hypoxic exposure and is reduced to control levels following exposure to HBO. In experimental studies, HBO exposure induced the synthesis of endothelial cell nitric oxide synthase (eNOS). The NOS inhibitor nitro-L-arginine methyl ester attenuated HBO-mediated inhibition of intercellular adhesion molecule-1 (ICAM-1) expression. These findings suggest that the beneficial effects of HBO in treating

hypoxic injury may be mediated in part by inhibition of ICAM-1 expression through the induction of eNOS.

Possible Dangers of HBO in Hypoxic States

Although it appears logical that HBO would be useful in hypoxic states, some concern has been expressed about the free radical damage and damage to the carotid bodies which impairs hypoxic ventilatory drive.

Free Radicals

Hypoxia can potentiate tissue injury due to oxidative stress and free radicals and there is theoretical concern that oxygen given in hypoxia may cause further cell damage. The counterargument is that correction of hypoxia by HBO would reduce the free radical formation resulting from hypoxia. Although the concept of oxygen toxicity at reduced oxygen tensions is a paradox, it cannot be dismissed. It is conceivable that partial lack of oxygen, by impeding electron acceptance at the cytochrome oxidase step, increases the "leak current," i.e., free radical formation. This subject is discussed further in Chap. 6 (oxygen toxicity).

Damage to Carotid Bodies

The carotid body chemosensory response to hypoxia is attenuated following prolonged exposure to normobaric hypoxia in the cat and is attributed to generation of free radicals in the carotid bodies. Further studies on the cat using exposure to 5 ATA showed diminution of chemosensory responsiveness to hypoxia within 2 h which was not considered to be due to lack of neurotransmitters (Torbati et al. 1993). Ultrastructural changes in the carotid bodies (increased number of mitochondria in the glomus cells) after HBO exposure could be explained by the oxidative stress.

Besides their role in ventilation, carotid bodies also regulate peripheral insulin sensitivity. Based on the knowledge that carotid bodies are functionally blocked by hyperoxia and that HBO therapy improves fasting blood glucose in diabetes patients, a study has investigated the effect of HBOT on glucose tolerance in type 2 diabetes patients (Vera-Cruz et al. 2015). The results show that HBO ameliorates glucose tolerance and can be used as a therapeutic intervention in type 2 diabetes.

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