Anesthesiology 2008; 109:7–13

Oxygen and Life on Earth

An Anesthesiologist's Views on Oxygen Evolution, Discovery, Sensing, and Utilization

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The advent of oxygenic photosynthesis and the accumulation of oxygen in our atmosphere opened up new possibilities for the development of life on Earth. The availability of oxygen, the most capable electron acceptor on our planet, allowed the development of highly efficient energy production from oxidative phosphorylation, which shaped the evolutionary development of aerobic life forms from the first multicellular organisms to the vertebrates.

THE mystery behind the roles of oxygen in life continues to challenge natural sciences and medical research. Despite its importance to life, humans did not discover oxygen in the atmosphere until approximately 230 yr ago.[1,2] The mechanism for oxygen sensing in humans is still not completely understood. We do know that our bodies have specialized tissues for oxygen sensing, such as the carotid body. But all cells in the human body live under different oxygenic conditions and are able to sense oxygen, even though the intracellular oxygen tension is much lower than in the air and blood. At intracellular oxygen tensions below 4–5 mmHg, oxidative metabolism is reduced and ceases when tensions decrease below 1.0–1.5 mmHg, the required level to load mitochondrial cytochrome *c*.[3]

Brown adipose tissue, which is present in mammalian neonates and hibernating animals, is an example of a specialized cell type that utilizes oxygen in ways that have potentially interesting implications for anesthesiology and medicine. The mitochondria in brown adipose cells can uncouple the electron transport chain and inhibit adenosine triphosphate production, leading to enhanced oxygen consumption and heat generation. This mechanism might have implications in the prevention of cardiac arrhythmias and for organ protection during ischemia.

In this article, evolution of oxygen in our atmosphere will be reviewed, and key steps in the discovery of oxygen will be highlighted. Then there will be focus on aspects of oxygen sensing, uptake, and utilization that are particularly relevant to anesthesiology and intensive care medicine. Finally, now-forgotten physiologic mechanisms from anoxic times and how they might be useful in modern medicine will be illustrated.

This article is accompanied by an Editorial View. Please see: Eisenach JC, Kersten J: Science and the mission of anesthesiology. ANESTHESIOLOGY 2008; 109:1–2.

Evolution of Oxygen in the Atmosphere

After the formation of oceans, land, and continents, Earth's atmosphere was transformed from an anoxic state to the present fairly robust oxygen concentration of 20–21%. The process by which Earth's atmosphere evolved from anoxic to oligoxic and oxic conditions continues to be a matter of debate and discussion, challenging many in this fascinating field of research.[4]

The increasing levels of atmospheric oxygen must have prompted anoxic life to an evolutionary race for survival. This race was won by oxic life, and in stages over at least 2 billion yr, the evolution of plants and animals, including humans, created the world we live in today (fig. 1). Oxygenic photosynthesis, the only significant known source of oxygen on our planet, is based on a precise sequence of events. Sunlight falls on plants, algae, and cyanobacteria, which in turn use chlorophyll and the process of photosynthesis to trap the sun's energy into carbohydrates. This process produces oxygen as a waste product of the splitting of water. The presence of gaseous oxygen in our atmosphere is the result of electrons being knocked off from chlorophyll molecules by photons of light and being subsequently replaced with electrons from water through the reaction $H_2O \rightarrow 2H^+ + 2e^- + 0.5\ O_2$.

Most experts agree that life on Earth began in the past 500 million yr of a timeline that started 5 billion yr ago with the geological formation of the planet (fig. 1). Until 4.5 billion yr ago, there were no living cells, not even bacteria. Gradually in the ensuing 1.5 billion yr, bacteria and other cells developed systems for energy metabolism under anoxic conditions. These systems were based on *anoxygenic photosynthesis*, which used hydrogen or

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Received from the Department of Physiology and Pharmacology/Section of Anesthesiology and Intensive Care Medicine, Karolinska Institutet/Karolinska University Hospital, Stockholm, Sweden. Submitted for publication November 5, 2007. Accepted for publication March 19, 2008. Support was provided solely from institutional and/or departmental sources.

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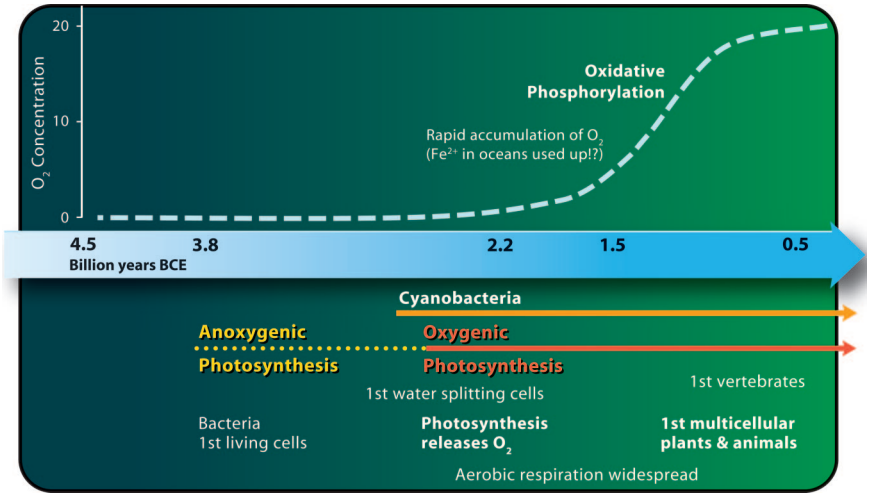

Fig. 1. Geological time scale and development of oxygen in Earth's atmosphere. BCE = before current era.

sulfur as electron donors instead of water. Much information regarding anoxygenic photosynthesis has been worked out based on our knowledge of photosystems I and II, the multiprotein complexes that perform *oxygenic photosynthesis*. During oxygenic photosynthesis, photons of light act on chlorophyll and enhance its energy level to a degree that makes it possible to drive the splitting of water enzymatically in photosystem II, to create oxygen and hydrogen *via* the extraction of electrons from water. These electrons are then used in the electron transport chain to produce adenosine triphosphate (fig. 2A).[5] This reaction is catalyzed in the oxygen-evolving complex by an enzyme that contains four manganese and one calcium (Mn_4Ca). The photon-induced enhancement of the chlorophyll energy level is used to extract four electrons from Mn_4Ca, which are then replaced by four electrons from two molecules of water.[5–7]

Protocyanobacteria and other cells from the anoxic era used photosystems I or II, never both (fig. 2B).[5] Although no protocyanobacteria have been found living today, there are some present-day cells that retain some of their ancestral characteristics. For example, *Oscillatoria limnetica*, a true cyanobacterium, turns off its genes for photosystem II when exposed to dihydrogen sulfide and reverts from oxygenic to anoxygenic photosynthesis.[8] Although it may be arguable to state that oxygenic photosynthesis started approximately 2.3 billion yr ago, there is geochemical evidence indicating that oxygen was present in the atmosphere at 10^{-5} of the present concentration.[9] These types of data indicate the minimum age for the origin of oxygenic photosynthesis.

Iron seems to have played an important role in establishing oxygen in our atmosphere. In oceans, iron is better transported in its ferrous state. Ferrous iron (Fe^{2+}; already lost two electrons) is oxidized to ferric (Fe^{3+}; a third electron removed) and forms insoluble ferric compounds that precipitate.[10] When aerobic respiration became more widespread, ferrous iron was oxidized to its ferric state, which in turn resulted in diffusion of oxygen from the ocean. This led to a rapid accumulation of oxygen in the atmosphere. Later, when the creation of high-energy phosphates, especially adenosine triphosphate from oxidative phosphorylation, became well established, multicellular plants, animals, and vertebrates appeared. Oxidative phosphorylation relies on a not-so-well-understood phenomenon: the maintenance of a proton gradient across mitochondrial membranes. This

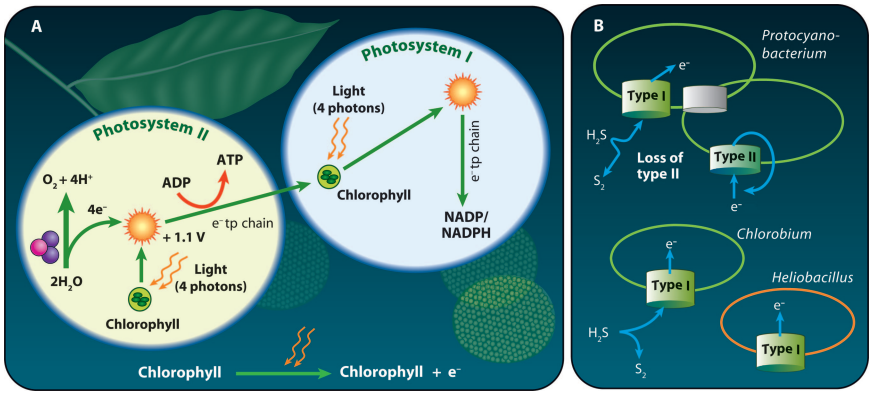

Fig. 2. (*A*) Oxygenic photosynthesis consists of photosystems I and II. Photosystem II performs only when photosystem I is present to donate electrons. Four photons acting on chlorophyll enhance its energy level and capture four electrons from water. This reaction is enzymatically controlled. The enzyme is in a complex structure with Mn_4Ca. After four electrons are removed from each manganese atom, two water molecules are oxidized to produce one diatomic oxygen molecule. (*B*) Anoxygenic photosynthesis consists of either photosystem I or II, never both. In the example, photosystem I is active. Most likely, as in the presence of chlorophyll during oxygenic photosynthesis, an excitation of a molecule occurs, also during anoxia, photoelectrically to capture electrons, *e.g.*, using dihydrogen sulfide as a donor molecule. ADP = adenosine diphosphate; ATP = adenosine triphosphate; NADP = nicotinamide adenine dinucleotide phosphate; NADPH = nicotinamide adenine dinucleotide phosphate (reduced form).

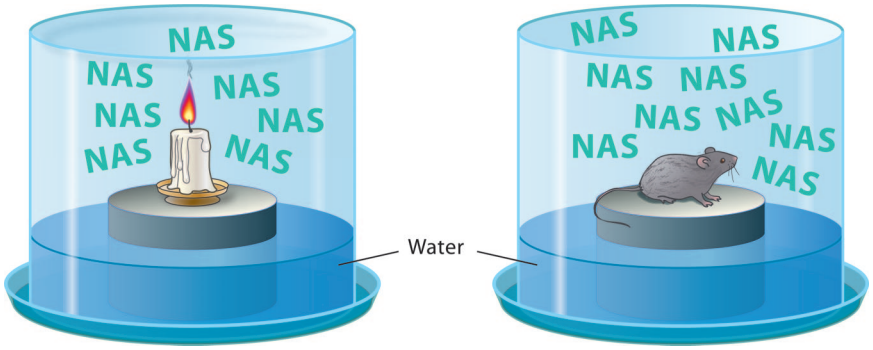

Fig. 3. The first experiment (by John Mayow in 1674) to indicate that air contained, in addition to nitrogen, an important part necessary for life ("spirit"). The design of Mayow's experiment is shown in the figure. NAS = "nitro ariel spirits."

phenomenon remains one of the top challenges in modern biochemistry (Per Siegbahn, Ph.D., Professor, Department of Physics, Stockholm University, Stockholm, Sweden, verbal communication, December 2007).

Discovery of Oxygen

Scientists began to understand that there was a part of air that was necessary for life in the 1600s, when John Mayow[11] performed experiments demonstrating that some aspect of air necessary for life could be removed both by mouse respiration and by fire (fig. 3). He called the part of air that was necessary for respiration and for fire "nitro ariel spirits," a description that illustrates the understanding that there is a component of air in addition to nitrogen, and it is this component that gives us "spirit," meaning life. Mayow's experiments were not widely accepted by the scientific community that still believed in the "phlogiston theory," which postulated that all combustible materials contain a "phlogiston" that escapes during burning. It was not until Joseph Priestley's experiments in the fall of 1774, showing that mice survived longer in air from heated mercury oxide, that the phlogiston theory started to crack. Priestley called this air "dephlogisticated air" or "fire air." Interestingly, the Swedish scientist Carl Wilhelm Scheele had performed identical experiments in 1773. In 1774, both Priestley (in person) and Scheele (by letter) had communicated these results with Antoine Lavoisier in Paris. After Priestley's October 1774 visit at Lavoisier's laboratory in Paris, Lavoisier repeated the experiments and confirmed the results, which he promptly published without referring to either Priestley or Scheele. In this initial publication, Lavoisier called the air "eminently breathable air." Several years later, he coined the term "oxygen." Scheele's letter was found much later and proved that his role in the discovery of oxygen occurred in parallel to Priestley's.[2]

Oxygen Sensing

In 1938, Corneille Heymans received the Nobel Prize in Physiology or Medicine for "the discovery of the role played by the sinus and aortic mechanisms in the regulation of respiration." Heymans put the carotid body in focus and initiated the line of work from which we today can conclude that specialized cells in the carotid body are highly sensitive to even minor variations in blood oxygen tension. Although the exact mechanism of the "oxygen sensor" has not yet been discovered, accumulating evidence indicates that hypoxia inhibits the potassium current in potassium channels. This alters the cellular membrane potential, which in turn opens up voltage-sensitive calcium channels. The ensuing increased intracellular calcium stimulates the release of transmitter substances that result in afferent impulses in the carotid sinus nerve. These impulses travel through the ninth cranial nerve *via* the petrosal ganglion and continue to dorsal respiratory neurons in the medulla oblongata. Many transmitters in the glomus cells of the carotid body have been described, including norepinephrine, dopamine, acetylcholine, and various opioids.

When spontaneously breathing individuals are exposed to hypoxia, ventilation increases, primarily because of increased motor activity and enhanced tidal volumes. During inhalational anesthesia with isoflurane and sevoflurane, this motor response is altered into a timing response associated with increased respiratory rates.[12] In addition, even at low concentrations in humans, nondepolarizing muscle relaxants are well known to inhibit hypoxic ventilatory responses.[13]

Although the chemoreceptor cell is most frequently described based on hypoxic responses, these cells are believed to also react to hypercapnia, hypoglycemia, osmolality, and temperature. Therefore, the carotid body can no longer be regarded as a single-mode oxygen sensor; rather, it fulfills the criteria for a polymodal sensor that is very much involved in metabolic homeostasis (fig. 4).[14]

Even if glomus cells in the carotid body are specialized for sensing oxygen tensions, all oxygen-consuming cells in the body must be able to respond to variations in oxygen. In 1995, Wang *et al.*[15] discovered and characterized the transcription factor, hypoxia inducible factor (HIF), a key oxygen regulator in mammalian cells. This discovery opened up for delineation the molecular

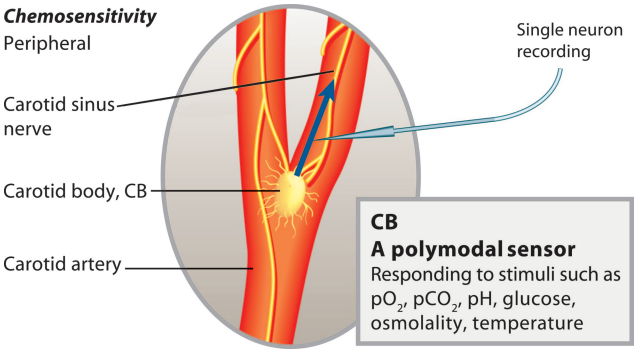

Fig. 4. The specialized glomus cells in the carotid body (CB) sense even minor changes in blood oxygen tensions eliciting afferent signals in the carotid sinus nerve. Today, it is known that other stimuli, such as plasma glucose concentrations and changes in blood osmolality, also trigger the CB. Therefore, CB serves as a polymodal sensor involved in metabolic homeostasis. P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen.

mechanisms of oxygen-regulated gene expression. In the normoxic state, HIF-1 is produced in a prolyl-hydroxylase–regulated reaction in the presence of Fe^2 and α-keto glutarate. HIF-1 reacts with von Hippel-Lindau protein, which labels HIF-1 for ubiquitination and protein degradation (*i.e.*, HIF-1 is inactivated).[16] During hypoxia, prolyl-hydroxylases are inhibited and HIF-1 does not bind to von Hippel-Lindau protein to be marked for degradation. Therefore, in response to hypoxia, HIF-1 is stabilized and activates at least 70 genes, setting in motion physiologic responses such as angiogenesis, erythropoiesis, and glycolysis.[16]

Oxygen sensing can be classified into two types of response. Acute responses, such as that which occurs in the highly specialized glomus cells, take place in seconds or a few minutes and involve preexisting proteins. Chronic responses, similar to the ones operating *via* HIF mechanisms, occur in a few minutes or longer and involve gene expression and synthesis of new proteins.[16] Although much is known, in both acute and chronic oxygen sensing, many scientists in the field of oxygen biology are searching for a general oxygen sensor. When, or if, this missing link is discovered, it will most certainly cause a paradigm shift.

Another interesting aspect of oxygen sensing is illustrated by experimental work in the 1-mm worm, *Caenorhabditis elegans*. When allowed to freely choose the oxygen concentration while being fed, *C. elegans* prefer oxygen concentrations between 7% and 14%. However, the worms vary their choices depending on the presence of soluble guanylyl cyclases, which bind oxygen. Obviously, soluble guanylyl cyclases play important roles in oxygen sensing.[17]

Pulmonary Function and Blood Oxygenation

Humans are very much dependent on pulmonary function for uptake of oxygen from the atmosphere. In severe acute lung insufficiency and in adult respiratory distress syndrome, the lung is functionally disturbed because of the disease processes. This forces intensivists to use high inspired concentrations of oxygen that are known to be toxic when long-term use is practiced.[18,19] When using high inspired oxygen concentrations (up to 80%) in healthy individuals for shorter times approaching 8 h, Fleischmann *et al.* were not able to detect negative pulmonary effects.[20] This information is important for short exposures in healthy humans. However, in a pathologic lung which has abundant inflammatory reactions, reactive oxygen species are produced and toxicity is likely to be enhanced. Therefore, to survive, patients with severe lung disease require high concentrations of oxygen in inspired air for a long time, sometimes several weeks. This adds to the lung damage because high oxygen concentrations in combination with reactive oxygen species cause cellular injuries. Therefore, all efforts must be taken to keep inspired oxygen concentrations as low as possible—at least lower than 50%.

In 1977, Douglas *et al.*[21] reported that placing supine patients prone improved oxygen uptake. More recent research by different groups has supported these early observations. My colleagues and I were interested in finding out why the prone position improved oxygenation. In a series of studies, we discovered that in lung biopsies from humans subjected to pulmonary surgery, the expression of endothelium-derived nitric oxide synthase in dorsal parts of the lung were higher than in the ventral parts (fig. 5).[22] Nitric oxide relaxes pulmonary vasculature and decreases circulatory resistances in dorsal lung regions. Because turning patients with severe acute lung insufficiency from supine to prone improves oxygenation in more than 60% of all cases,[23–25] this simple positional treatment often allows the use of decreased inspired oxygen concentrations, diminishing lung damage.

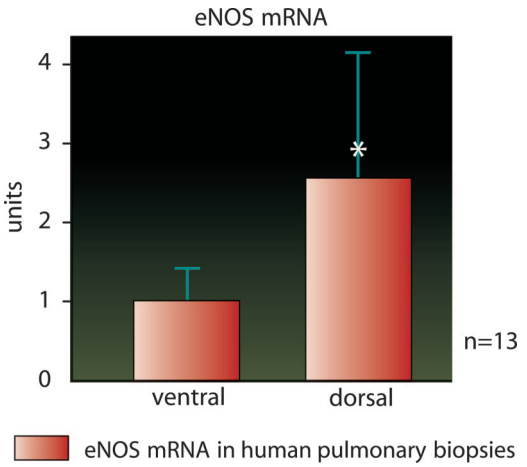

Fig. 5. The two columns represent means of messenger RNA (mRNA) expressions of endothelium-derived nitric oxide synthase (eNOS), from ventral and dorsal pulmonary biopsies in patients subjected to lung surgery.[22] * $P < 0.05$.

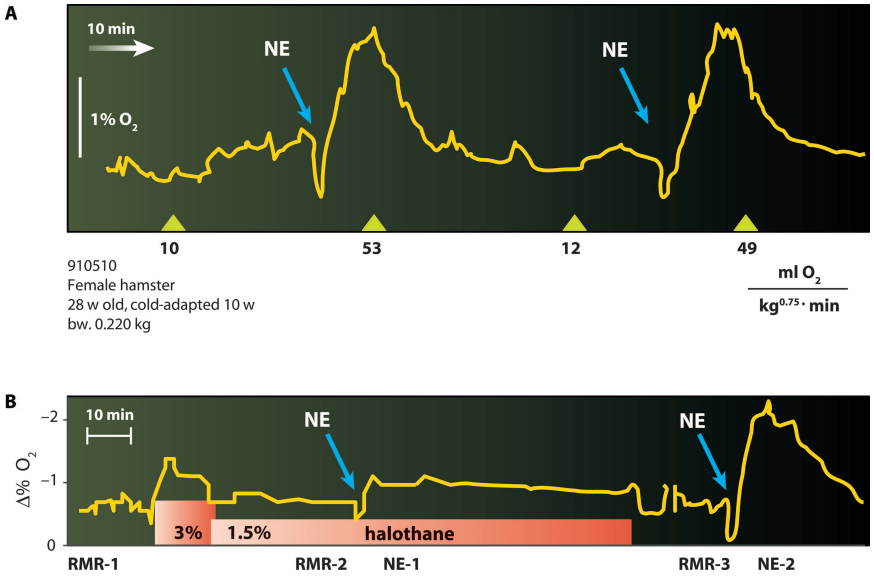

Fig. 6. Response in oxygen consumption to intraabdominal injections of norepinephrine (NE) in cold-acclimatized hamsters: in awake hamster showing good responses (*A*) and in anesthetized hamster with nearly eliminated responses (*B*). bw = body weight; RMR = resting metabolic rate.

An unanswered question is why the expression of endothelium-derived nitric oxide synthase and production of nitric oxide differs between dorsal and ventral lung regions. One possibility is that this is due to evolutionary factors, derived from the quadruped stage when lower vascular resistance in the uppermost dorsal parts of the lungs was an advantage to counteract gravity and guarantee efficient matching between ventilation and perfusion. Clearly, vasoregulation in the lung is important for gas exchange. In addition, experiments we conducted using a human centrifuge showed that when the gravitational force increased from 1 to 3*g*, lung perfusion did not follow the gravitational force.[26] These results suggest that structural anatomical factors also influence ventilation/perfusion matching in the lung. Therefore, to optimize lung treatment in severe acute lung insufficiency, treatment strategies must be worked out to support both vasoregulation and lung structure, ideally at the same time.

Oxygen Utilization

Two aspects of oxygen utilization provide interesting insights regarding nonshivering thermogenesis: (1) the unique capacity of brown adipose tissue to consume oxygen and produce heat and (2) the use of amino acids as fuel for heat production during anesthesia.

Anesthesia and Brown Adipose Tissue

Isolated brown fat cells respond to norepinephrine with increased oxygen consumption. Brown fat cells exposed to volatile anesthetic agents inhibit oxygen consumption (*i.e.*, heat production). Furthermore, animals that are cold-acclimatized to induce development of brown adipose tissue do not respond to norepinephrine during anesthesia. Therefore, volatile anesthetic agents are likely to cause thermoregulatory problems in neonates during anesthesia and surgery (fig. 6).[27] Other lessons that can be applied from hibernation mechanisms to medicine pertain to cardiac arrhythmias in neonates and organ protection.

Cardiac Arrhythmias and Brown Adipose Tissue

Like hedgehogs, ground squirrels, and other hibernators, neonates almost never develop ventricular fibrillation. The value of this adaptation in hibernating animals is that during spring warm-up, when they approach core body temperatures of 25°–28°C, they pass a point at which ventricular fibrillation frequently occurs. A protective mechanism for cardiac arrhythmias must exist to preserve the species in the face of wide cooling and warming fluctuations in body temperature associated with hibernation and torpor. Interestingly, neonates rarely develop ventricular fibrillation during their first 6 months of life, when they have active brown adipose tissue, which later in life becomes dormant. The mechanism behind this "rhythm protection" is not well understood. Potentially relevant mechanisms include the pattern of adrenergic innervations that is different in neonates from that seen in older infants and adults, and an increase in size and number of connexin 43 gap junctions.[28,29] Identifying this protective mechanism might be useful in the development of new antiarrhythmic drugs. Such a discovery would most likely be a major leap forward in cardiology.

Organ Protection and Hibernation

Oxygen-dependent oxidative phosphorylation produces adenosine triphosphate that is consumed within

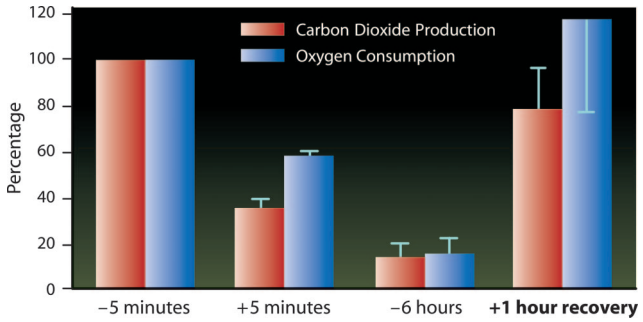

Fig. 7. The columns indicate decreasing (in percent of control) carbon dioxide production (*red*) and oxygen consumption (*blue*) in mice exposed to 80 ppm H_2S for 6 h and 1 h after recovery. From Blackstone E, Morrison M, Roth MB: H_2S induces a suspended animation–like state in mice. Science 2005; 308: 518. www.sciencemag.org. Modified with permission from AAAS.

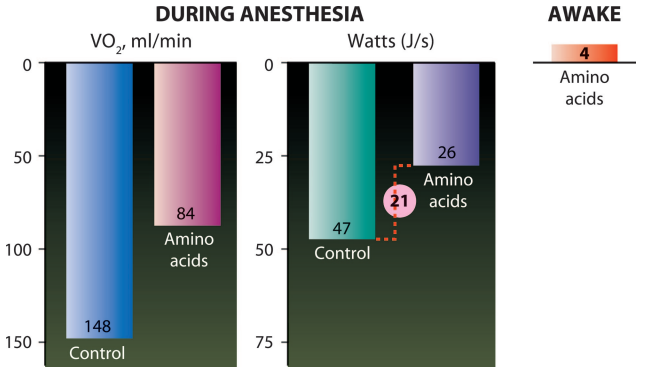

Fig. 8. Means of decreasing oxygen consumption (expressed in oxygen uptake [Vo_2, ml/min] and in watts [J/s]) in anesthetized humans without (control) and with infusions of amino acids during the procedure. For comparison, the graph also shows the increased energy expenditure (watts [J/s]) in awake humans after infusion of the same amount of amino acids. These investigations were performed using thermistor-equipped catheters in the pulmonary artery and in a hepatic vein. Arterial catheters were also used, and arteriovenous differences were calculated also with the aid of indocyanine dye. Note the fivefold increase in energy from the amino acids during anesthesia.[35]

seconds. When oxygen decreases, oxidative phosphorylation becomes less efficient and free radicals are produced. Because these free radicals are toxic, protection from them is a clinical target with implications for surgical procedures, trauma, organ preservation, and transplantation. In a 2005 publication, Blackstone *et al.*[30] demonstrated that dihydrogen sulfide at 80 ppm reduced carbon dioxide production and oxygen consumption in mice. After a 6-h exposure, the animals' metabolic rates decreased and the core body temperatures decreased significantly. When the mice were returned to room air after this 6-h exposure, their metabolic rate and core body temperatures normalized (fig. 7). The authors noted no behavioral or functional differences in the mice after this treatment. The most likely mechanism behind this effect of dihydrogen sulfide is that oxidative phosphorylation is reduced due to a specific and reversible binding to cytochrome *c* in complex 4 of the mitochondrial electron transport chain, preventing oxygen from binding.[31] Hence, it is possible that as an ancient mechanism, sulfur binding occurred to cytochrome *c*, which in modern oxygenic times has been replaced by oxygen binding. Like *O. limnetica*, mammals might also in the presence of dihydrogen sulfide revert to anoxygenic sulfur-based respiration, hindering oxygen from binding to cytochrome *c* and thereby decreasing metabolism.[31] If so, these observations could very well, in the near future, be proven of clinical value to protect from damages caused by ischemia–reperfusion.

Amino Acid–induced Thermogenesis during Anesthesia

The administration of oral proteins or intravenous amino acids in the awake state is accompanied by an approximately 20% increase in energy expenditure and heat production.[32] In a patient with tetraplegia caused by a traumatic high spinal cord injury, the thermic effect of the same amount of intravenous amino acids caused increases in energy expenditure and heat production.[33] In a series of clinical investigations of anesthetic effects using different general anesthesia techniques, the reduction of energy expenditure (*i.e.*, the decrease in the body temperature) was diminished by infusions of amino acids.[34,35] When no infusion of amino acid was given, it was found that the extra energy from infused amino acids represented an energy value of 21 W. The energy value from the same amount of infused amino acids in a normal awake human is 4 W (fig. 8). This means that during anesthesia, the heat production from this amount of amino acids was five times higher.[34] This extra heat production during anesthesia has also been shown to be produced in extrasplanchnic (*i.e.*, nonvisceral) tissues, presumably skeletal muscles.[35]

Could this increased heat production be due to uncoupling of the respiratory chain similar to what occurs in hibernating animals and caused by a similar mechanism as in brown adipose tissue? Two reports indicate that uncoupling proteins are present in adult skeletal muscle and that uncoupling proteins may be increased in patients with tetraplegia.[36,37] These data lead to the following interesting questions: Is there a release of central metabolic inhibition caused by anesthesia? Or is an uncoupling mechanism triggered during anesthesia? If so, could this be due to uncoupling caused by a similar mechanism as in brown adipose tissue?

Conclusion

Chlorophyll and light are essential elements for life. Oxygen is the most capable electron acceptor. It is easily imaginable that biology was at an important turning point when the dominant physiology shifted from an

anoxygenic to an oxygenic mode. The important prerequisite conditions for human life on Earth began when water became widely used as an electron donor. After that, it took almost 2 billion yr until humans appeared. Today, oxidative phosphorylation, to get energy-rich chemical bindings, is a well-established mechanism that is highly dependent on electron transport in the mitochondrial respiratory chain. This puts oxygen in a special position with its high capacity to act as an electron acceptor. Without that function, the cellular machinery would collapse. The irony is that recent research points toward a renaissance of ancient anoxygenic physiologic mechanisms that might be proven to act protectively against hypoxia.

Human life on Earth depends on three things: (1) oxygen, a waste product; (2) one enzyme, one alone, that catalyzes water splitting; and (3) an intact ozone layer. Damage to Earth's ozone layer will impair this one and only enzyme, with most serious consequences for life on Earth.

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