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Review Article

Oxygen Aspects on Sensing and Utilization

Abstract

Oxygen is known to be one of the strongest electron acceptors and has one of its main functions in the electron transport chain producing ATP and heat, so important for energy expenditure and thermoregulation. However, some important mechanisms of oxygen functions are not completely delineated, yet. Sensing oxygen is purposeful and serves various specific functions. One mode of action is to initiate afferent neuronal activity which requires increased cytosolic Ca^{2+} concentrations. Another action is linked to the Hypoxia Inducible Factor, HIF-1, which in the normoxic state is produced in a prolyl-hydroxylase regulated reaction. The calcium generated neuronal response is usually described as a quick, acute, response that is set in action within seconds whereas the HIF related responses are slower, chronic, activated after several minutes to hours. Traditionally, it has been the opinion that oxygen can diffuse freely across plasma membranes. However, the lipid bilayer has higher viscosity than water by several times, and high oxygen permeability has not been proven. Hence, oxygen transportation across plasma or cell membranes cannot be explained by diffusion alone. It is therefore justified to ask the question if a specific oxygen channel or transport mechanism remains to be discovered.

Introduction

Oxygen is vital for life and plays a key role for the physiological homeostasis of the human body. It is known to be one of the strongest electron acceptors and has one of its main functions in the electron transport chain producing adenosine 5'-triphosphate (ATP) and heat, so important for energy expenditure and thermoregulation. Yet, some important mechanisms of oxygen functions are not completely delineated and oxygen research is an active scientific field in basic medical research, experimental investigations as well as in clinical research. In clinical medicine both hyperoxia and hypoxia are in focus. This presentation will mainly be dealing with reactions to low oxygen tensions.

There is a well-balanced sensory function to maintain oxygen tension in blood within narrow margines. The normal but small oxygen variations in blood are sufficient to trigger activities in the carotid body in order to create afferent impulses via the sinus nerve and the IXth cranial nerve to the central nervous system. Together with pH variations or carbo dioxide (CO_2), oxygen is an important factor for regulation of breathing.

In this communication some of the most highlighted mechanisms for the sensing of low oxygen tensions will be discussed and opinions on oxygen utilization will be presented with regard to plasma membrane passage of oxygen and intracellular electron transport. In addition, effects of different anesthetic agents on oxygen sensing and utilization will be commented upon.

Oxygen Sensing

Oxygen is sensed by most mammalian cells. Glomus cells in the carotid body, neuroepithelial body cells in the airways, smooth muscle cells in the systemic or pulmonary circulation, and chromaffin cells have been reported as typical cells having specific oxygen sensing capacities. In 1995, Wang, Semenza et al. discovered the hypoxia inducible factor 1 (HIF-1) as a key oxygen regulator in mammalian cells [1]. HIF-1 is a heterodimeric protein that is composed of HIF-1α and HIF-1β subunits with the HIF-1α subunit being responsible for the response to hypoxia [1].

Sensing oxygen is purposeful and serves various specific functions. One mode of action is to initiate afferent neuronal activity which requires increased cytosolic Ca^{2+}concentrations in order to release transmitters from synaptic vesicles for postsynaptic impulse generation [2]. Another kind of action is linked to HIF-1, which in the normoxic state is produced in a prolyl-hydroxylase regulated reaction in the presence of Fe^{2+} and α-ketoglutarate. HIF-1 reacts with von Hippel-Lindau protein, which labels HIF-1 for ubiquitination and protein degradation. During hypoxia, prolyl-hydroxylation is inhibited and HIF-1α accumulates. Via this mechanism all nucleotide cells in the body can sense and respond to hypoxia [3]. Hence, both calcium and HIF based mechanisms are most prominent for protective reactions against low oxygen tensions. The calcium generated neuronal response is usually described as a quick, acute, response that is set in action within seconds whereas HIF related responses are slower, chronic, activated after several minutes to hours [2,3] (Figure 1).

Ca^{2+} related Oxygen sensing

Until the discovery of HIF-1, in 1995, research on oxygen sensing mechanisms has mainly been conducted with focus on physiological responses to acute hypoxia, as hypoxia induces critical damages in tissues and organs and jeopardizes physiological homeostasis. There are different mechanisms to accomplish the acute, calcium mediated, oxygen sensing. One of them, as described by Lopez-Barneo and colleagues [4], expresses an oxygen-sensitive potassium channel and it is now known that large-conductance Ca^{2+}-sensitive potassium

channels (BK_{Ca} channels), voltage-gated potassium channels, and TASK-like glomus-cell potassium channels are involved in arterial oxygen sensing [2]. The presented sequence of events is that hypoxia inhibits the potassium current in these channels which alters the cellular membrane potential promoting cellular depolarization. As a consequence, voltage-sensitive calcium channels are opened which enhances cytosolic calcium concentrations. Another route to get higher calcium concentrations is via inositol 1, 4, 5-triphosphate (IP3). IP3 is generated by phospholipase C which is a component of the plasma membrane. IP3 acts on its own receptor at the endoplasmic reticulum (ER) to open up channels for calcium to pass from the ER to the cytoplasm [5,6]. Again, as stated above, increased Ca^{2+} influx stimulates pre-synaptic vesicles to release transmitter substances.

There are many transmitters in the glomus cells of the carotid body and other chemoreceptor specific cells. They include ATP, gamma-aminobutyric acid (GABA), norepinephrine, dopamine, and acetylcholine (ACh). Among these transmitters, ACh and ATP seem to be important excitatory transmitters, whereas dopamine and GABA have modulatory and inhibitory functions, respectively [7,8].

Some inhaled anesthetics affect mostly inhibitory ion channels such as $GABA_A$ receptors, nicotinic ACh receptors, and potassium channels [9]. Both halothane and sevoflurane depress the increase of intracellular calcium caused by hypoxia-induced potassium channel closure in the carotid body type 1 cells [10]. In addition, it is also known that propofol and neuromuscular blocking agents prevent chemoreceptor activity in the carotid body [11-13]. Thus, common drugs, used during anesthesia, influence oxygen sensing which have implications on the function of the central neuronal control of breathing.

Furthermore, in a recent article, Takahashi et al. reported yet another interesting mechanism related to oxygen sensing. Transient receptor potential cation channel, member A1 (TRPA1), which is a membrane bound channel capable of detecting intra- and extra-cellular environments, is activated both by hyperoxia and hypoxia through mechanisms involving cystein oxidation and proline hydroxylation, respectively [14]. During hypoxia the prolyl hydroxylation is decreased which activates the TRPA1 channel. Hence, Takahashi el al's study indicates that there are possibilities also for TRPA1 to exist as a cell membrane bound oxygen sensor. It will be of great interest to, in the near future, follow the development of further functional mechanisms related dTRPA1.

HIF-1 related Oxygen Sensing

It is obvious from the above regarding TRPA1 and hypoxia that prolyl hydroxylation has a key role involved in oxygen sensing. It was Semenza et al. [1] who discovered HIF-1 and Ratcliff et al. who described the importance of prolyl hydroxylation [15]. In the normoxic state, HIF-1 is produced in a prolyl-hydroxylase regulated

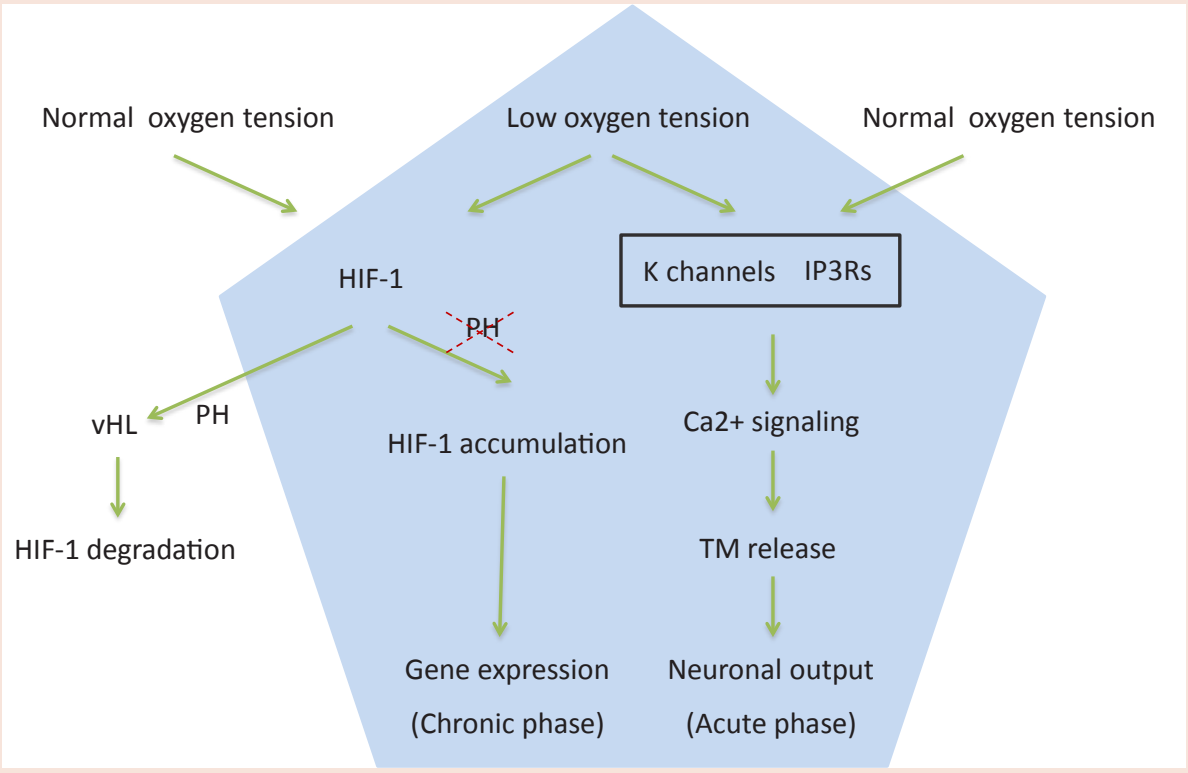

Figure 1: There are two main oxygen sensing mechanisms, one via Ca^{2+} signaling (acute) and another (chronic) based on the Hypoxia Inducible Factor 1 (HIF-1). During normoxia prolyl hydroxylase (PH) functions normally and HIF-1 reacts with von Hippel Lindau protein to tag for degradation of HIF-1. PH is inhibited during hypoxia (see also text).
HIF; hypoxic inducible factor 1, PH; prolyl-hydroxylase, vHL; von Hippel-Lindau protein, IP3Rs; inositol 1, 4, 5-triphosphate receptors, TM; transmitter

reaction in the presence of Fe^{2+} and alpha-ketoglutarate. HIF-1 reacts with von Hippel-Lindau protein, which labels HIF-1 for ubiquitination and protein degradation [16]. During hypoxia, the prolyl-hydroxylation is inhibited and HIF-1α accumulates. It is most likely so that all nucleotide cells in the body can sense and respond to hypoxia via this mechanism.

As pointed out above this is a fairly slow responding system that takes minutes to hours. HIF-1 regulates the expression of more than hundred genes that mediate important adaptive physiological responses such as angiogenesis, erythropoiesis, and glycolysis [2] (Figure 1).

Several studies have reported about the effect of anesthetic drugs on HIF-1 expression and activity. In hypoxic cells with accumulation of HIF-1 both halothane and propofol inhibit the HIF-1 accumulation [17,18]. It is reported that isoflurane and xenon enhance HIF-1 accumulation during hypoxia [19-21].

Oxygen utilization

Oxygen and passage of the plasma membrane.

Traditionally, it has been the opinion that oxygen can diffuse freely across plasma membranes [22]. However, the lipid bilayer has higher viscosity than water by several times, and high oxygen permeability has not been proven. In model experiments using biological monolayer membranes, it was shown that oxygen permeability is lower than previously reported [23]. Hence, oxygen transportation across plasma or cell membranes cannot be explained by diffusion alone. It is therefore justified to ask the question if a specific oxygen channel or transport mechanism remains to be discovered.

One way to address this is whether oxygen uses established pores or channels. Currently, one of the best candidates for a collaborative function is aquaporin (AQP). AQP is a water channel protein and facilitates the transport of water across plasma membranes. In 1992, Peter Agre et al. first purified AQP1 from red blood cell membranes [24], and 13 isoforms (AQP0-12) have since been identified in humans. Among them, AQP 1, 2, 4, and 5 are primarily aquaporins, and some of them have function also as gas channels. It is especially AQP1 that have been reported as a gas channel, transporting CO_2 and nitric oxide (NO) across the plasma membrane [25,26]. The first suggestion that AQP1 might be a gas channel was reported in 1998, by Nakhoul NL, et al. [25]. The investigators measured the rate of cellular acidification caused by CO_2 influx across the cell membrane using intracellular electrodes.

Concerning oxygen, Jose Lopez-Barneo et al. showed, in 2007 [26], that AQP1 functioned as an oxygen channel. They found that HIF1-α and other oxygen dependent genes (tyrosine hydroxylase, phosphoglycerate kinase 1, and vascular endothelial growth factor mRNA) had a higher expression during hypoxia. Moreover, AQP1 mRNA expression was also upregulated in rat lung during hypoxia. In this study, cellular oxygen fluxes were not directly measured because of the technical difficulties as authors described. However, the Lopez-Barneo study strongly indicated that AQP1 is permeable for oxygen and thus could facilitate oxygen uptake into cells [27]. In support of such a suggestion, Ivanov II et al. reported that the two AQP channel blockers, mercury chloride ($HgCl_2$) and *p*-chloromercuribenzoate (PCMB), dose-dependently inhibited oxygen absorption by erythrocytes [28]. Although, $HgCl_2$ and PCMB are not AQP1 specific but inhibit almost all aquaporins, except AQP6 [29], the Ivanov et al findings indirectly support the suggestion by Lopez-Barneo et al. Future investigations regarding possible oxygen channels on plasma membranes are of great importance.

Thermogenesis and oxygen consumption

As stated above the most important role of oxygen is to accept electrons. Via the proton gradient over the mitochondrial membrane ATP is generated. There are numerous investigations about oxygen utilization in mitochondria for ATP synthase and ATP production. In this presentation it was therefore chosen to highlight aspects on the un-coupling mechanism in brown adipose tissue and how anesthesia can improve the utilization of amino acids for heat production and also to concentrate on the recent findings that H_2S induced decreasing oxygen consumption.

Thermogenesis in brown adipose tissue

Brown adipose tissue, unlike white adipose tissue, has the ability to dissipate energy by producing heat rather than storing it as triglycerides. The uncoupling protein 1 (UCP1) is expressed in brown adipose tissue and plays an important role for thermogenesis (oxygen consumption). The classic opinion is that brown adipose tissue mainly exists in neonates and young infants and in hibernating animals. In neonates and young infants the brown adipose tissue is important for temperature balance [30]. Brown-fat cells are stimulated by norepinephrine released from the sympathetic nervous system. This leads to cellular respiration in the mitochondria that is un-coupled from ATP synthesis [31].

During the latest few years it has been proven that brown adipose tissue is also present and have an active function in adult humans. Positron emission tomography- computed tomography (PET-CT) investigations showed, in adult humans, a high uptake of ^{18}F-FDP in the neck, in the supraclavicular region, and at classical locations for brown adipose tissue in para-aortic and paravertebral areas as well as suprarenally indicating the existence of brown adipose tissue also in adults [32]. In 2009, three different articles supported these findings and identified the presence of brown adipose tissue in adult humans [33-35]. In these studies, investigators reported that cold-induced glucose uptake was increased in paracervical and supraclavicular adipose tissue in healthy human adults and moreover, biopsy specimens obtained from the high uptake area of ^{18}F-FDP contained UCP1 [36].

So far, there are few studies that investigate the activities and thermogenetic effects of human adult brown adipose tissue during anesthesia. From previous studies it is known that volatile anesthetics attenuate oxygen consumption in response to norepinephrine of isolated brown fat cells, but non-volatile anesthetics such as pentobarbital, propofol, and ketamine, have not been proven to have such effects [37,38]. It is also known that volatile anesthetic agents inhibit heat production, oxygen consumption, in studies of animals and infants known to have brown adipose tissue [39-41]. It is likely that not only neonates and infants but also adults with brown

adipose tissue will have a disturbed temperature balance during long duration surgery most likely, at least partly, due to effects on oxygen consumption in brown adipose tissue. The area is indeed open for further important clinical studies during anesthesia.

Amino acid –induced thermogenesis

It has for a long time been a dogma that amino acids during anesthesia and surgery do not contribute to heat production and recovery. Sellden et al. reported, in 1994, that amino acids induced thermogenesis and diminished hypothermia under general anesthesia [42]. They found that the energy value of an amino acid solution was 4 Watts in awake humans whereas the energy value from an identical amino acid infusion was 21 Watts during general anesthesia. Thus, this means that amino acid-induced heat production during anesthesia is five times higher, compared to in the awake state [43]. In the same series of investigations it was also reported that this thermogenetic effect occurred in extra-splanchnic tissues and that it was not associated with stress response [44,45].

As referred to above, the heat production from amino acid infusions during anesthesia occurred in extra-splanchnic tissue, most likely skeletal muscle. However, the mechanism for this heat production is still not completely understood [41]. In one study it was reported that amino-acid infusions during general anesthesia increased plasma insulin concentrations and systemic oxygen consumption [42]. Since brown adipose tissue can be activated by insulin [43], this challenges the assumption that the amino acid-induced thermogenesis might be caused by an un-coupling mechanism in skeletal muscle.

H_2S and oxygen consumption

Hydrogen sulfide (H_2S) has been known for a long time because of its toxicity and environmental hazard [44]. The main mechanism of H_2S toxicity is inhibition of mitochondrial respiration resulting from blockade of cytochrome c oxidase [45].

Recently, H_2S has been the subject of a great interest as a gas with possible pharmacological potentials. In 2005, Blackstone E, et al. reported that H_2S decreased oxygen consumption and heat production which resulted in a suspended animation-like state in mice [46]. Mice exposed to 80 ppm of H_2S, which is a safe dose for these animals, decreased their oxygen consumption by ~50%, and carbon dioxide production by ~60% during the first 5 minutes, and 6 hours later, their metabolic rates were decreased by ~90%. In parallel, H_2S caused dose-dependently decreased core body temperature.

After this report, many experimental investigations have been conducted and in a study of hemorrhagic shock, H_2S stabilized hemodynamics [47,48]. Several studies also reported that H_2S attenuated ischemia reperfusion injury in heart and liver [49-51]. It was also reported that H_2S prevented sepsis-induced inflammation and protected vital organs [52,53]. Many studies have reported the efficacy of H_2S in animal experiments using rodent models, whereas other studies failed to show the effects, especially in larger animal models such as piglets and sheep. For future clinical applications, there are many questions that will have to be answered. It will be most interesting to follow the development of this scientific field with the goals to find correct indications for the use of H_2S, to work out therapeutic strategies and to rule out possible side effects.

In conclusion, supplying oxygen to tissues or organs is one of the most important treatments of patients in particular during surgery or critical conditions. However, in these situations, several factors like as inflammatory, oxidative stress, activation of sympathetic nerve system and renin angiotensin system disturb the balance between oxygen demand and supply. Clinicians need to recognize the mechanism of oxygen sensing, oxygen transport, and oxygen utility in the cells to maintain the homeostasis of patients in clinical conditions.

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