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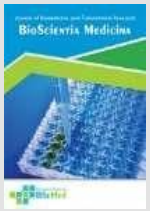

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Freediving, Hypoxia, and Inflammation: Physiological Adaptations and Interactions between HIF and NF-κB

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A B S T R A C T

Freediving presents a unique set of physiological challenges and adaptations, making it a subject of interest for researchers studying the effects of extreme environmental conditions on the human body. There is a complex interplay between freediving, hypoxia, immune responses, and inflammation, shedding light on the physiological effects of freediving on the human body. This article describes how HIF and NF-κB interact during hypoxia and inflammation, including their synergistic effects and signaling pathways. The regulatory loop involving these transcription factors is highlighted, providing insight into their linked roles in modulating the cellular response to hypoxia and inflammation.

1. Introduction

Freediving is an activity intended for entertainment or recreation, as a competition or part of the work commonly carried out by traditional fishermen in many different places of the world.[1-3] The ability to hold one's breath during freediving is controlled by a variety of physiological factors, including the "diving response," which directs increased blood flow to the brain, heart, and actively working muscles, while others may rely on anaerobic metabolism. This is a response to extreme environments in the form of asphyxia conditions and a progressive increase in hydrostatic pressure during freediving.[4,5] Humans' ability to hold their breath beyond physiological limits when freediving can certainly have negative consequences for body condition.[5-7] In freediving settings, there is a close link between hypoxia, inflammation, and the innate immune system, as evidenced by gene expression. NF-κB regulates gene transcription in inflammatory signaling, while HIF-1 regulates transcription during hypoxia. Both work together to regulate the genetic activity of immune cells. This literature review will discuss the relationship between transcription factors HIF-1 and NF-κB related to hypoxic and inflammatory conditions during freediving.

History of freediving

Human adaptations to freediving were first studied in the 1920s by observing and measuring diving habits, seasons, and equipment among the Ama people.[8] Ama, which means "women of the ocean" in Japanese, are female freedivers who dive to depths of up to 25 meters without the use of modern scuba equipment or fishing vessels to collect seafood such as shrimp, abalone, seaweed, and pearls for a living. Researchers began to discover what physiological alterations and adaptations these divers had that allowed them to go beyond what scientists thought was possible. Humans are naturally good divers. Freediving has been practiced for centuries all throughout the world, especially among traditional Indonesian fishermen.[3,6] Several fishing communities in Indonesia continue to use traditional methods to manage the abundant marine resources surrounding them, one of them is free diving. This freediving ability has been passed down from generation to generation. Traditional fisherman often uses basic equipment for freediving activities. This raises the danger of health and safety issues resulting from freediving activities without standardized diving equipment.[3,7]

Definition of freediving

Freediving is defined as a diving technique that is carried out by taking one breath above the sea surface, where the atmospheric pressure is 1 atm, and then holding the breath underwater without using a breathing apparatus or external gas supply.[9,10] When diving, hydrostatic pressure increases progressively in proportion to depth. The pressure rises by 1 atm for every additional 10 meters from the surface. Humans inhabit a pressured air environment. Pressure increases proportionally with depth during diving due to the increasing weight of the water column. According to Boyle's law, the pressure and volume of a gas are inversely proportional. Therefore, the deeper the dive and the pressure doubles, the volume of gas in the lungs decreases by half.[5,6]

Physiological response during freediving

Human activity is based on constant breathing, which provides the body with a sufficient supply of oxygen. Peripheral and central chemoreceptors primarily regulate the breathing rhythm.[11] The diving response also known as the mammalian dive reflex or diving reflex, is a protective, multidimensional physiological reaction that occurs in mammals, including humans, in response to water immersion. The diving reflex is thought to help humans conserve oxygen resources by triggering a number of particular physiological changes during aquatic immersion. When a person holds their breath and submerges in water, their face and nose become wet, resulting in bradycardia, apnea, and increased peripheral vascular resistance; these three major physiologic changes are collectively known as the diving reflex. Increased peripheral resistance is hypothesized to occur when blood is redistributed to vital organs while non-essential muscle groups consume less oxygen.[12] Blood circulation ensures that oxygen is given to the tissues while CO_2 is eliminated while divers hold their breath.[11] The oxygen stores in the lungs and blood are depleted when divers hold their breath, leading to a very low partial pressure of O_2 in the brain. This poses a risk of loss of consciousness. Anaerobic metabolism in apnea divers results a lactate accumulation. In freediving, an increase in blood lactate levels is seen as a mechanism to conserve oxygen by restricting oxygen supply to non-essential organs. This shift to anaerobic metabolism, indicated by lactate accumulation, is more pronounced in dynamic apnea than in stationary apnea.[13]

Lactate, which is no longer considered the end product of the glycolytic pathway or anaerobic metabolism, is being more widely studied as a signaling molecule. Lactate has been demonstrated to signal through its particular receptor, G protein-coupled receptor 81 (GPR81), or to be transported into cells via monocarboxylate transporters (MCTs).[14] Lactate may influence the inflammatory response in various cells. Immune cells produce and secrete a substantial amount of lactate throughout the

inflammatory process. Immune cells' adaptability to lactate concentrations in the microenvironment may have an effect on tissue-specific immune cell activity. Lactate has been proposed as a signaling mechanism in endothelial cells that modulates the inflammatory response. Endothelial cells (ECs) regulate the extravasation of circulating immune cells into tissues by producing cytokines, chemokines, and adhesion molecules. Lactate influx via MCT1 activates NF-κB in endothelial cells. NF-κB is made up of p65 (RelA) and p50 (NF-κB1) subunits that are inactive in the cytosol and form a complex with IκB proteins. IκB phosphorylation is necessary for polyubiquitination, proteasomal degradation, and NF-κB activation. Lactate phosphorylates and degrades IκBα, activating NF-κB and regulating many inflammatory genes, including IL-8. Lactate activates NF-κB by inhibiting prolyl hydroxylase (PHD), a dioxygenase that requires Fe (II) and 2-oxoglutarate. Lactate oxidation by lactate dehydrogenase-B (LDH-B) raises the intracellular pyruvate pool, which competes with 2-oxoglutarate and limits PHD's hydroxylase activity. PDH-catalyzed hydroxylation of proline leads to polyubiquitylation and degradation of HIF-1α in the proteasome. Pyruvate inhibits pyruvate dehydrogenase (PDH), which stabilizes HIF-1α, allowing it to migrate into the nucleus and influence target gene transcription in ECs like proangiogenic effectors (i.e., VEGF). Lactate stimulates NF-κB and HIF-1α transcription factors in ECs, requiring a decrease in PHD catalytic activity. Antioxidants suppressed lactate-induced NF-κB activity, indicating the role of reactive oxygen species (ROS) in regulating the lactate-induced inflammatory response in endothelial cells. GPR4, a proton-sensing receptor, is expressed by endothelial cells. Lactic acid can stimulate the pro-inflammatory response in ECs, and the cellular mechanisms connected with G protein-coupled receptor.[15] The accumulation exacerbates the inflammatory reaction. Lactate accumulation in the microenvironment, rather than being inert, has a significant impact on immune cells that live in and infiltrate the tissue. Lactate is primarily produced in the cytoplasm during hypoxia or as a result of aerobic glycolysis in proliferating cells, and then secreted across the plasma membrane. This transportation depends on the transporter of a solute carrier importing proton-lactate (i.e., MCT1-4) or sodium transport (i.e., SLC5A8 and SLC5A12).[16]

Physiological effect of freediving

Changes in physiological circumstances occur before diving when floating on the water surface in a partially submerged position. Fluid transfers from cells to vascular compartments while floating, resulting in regional blood flow redistribution, changes in cardiopulmonary hemodynamics, and autonomic activity.[17] Free diving is subjected to extreme environmental conditions, beginning with larger pressure changes as the diver descends deeper into the sea. Arterial oxygen saturation will also decrease during apnea situations, resulting in hypoxia and hypercapnia. Most people's desire to breathe is controlled by peripheral chemoreceptors, which sense little changes in blood pH caused by elevated carbon dioxide levels in hypercapnia. Many divers rely on this urge to breathe to prevent loss of consciousness underwater and determine when to turn to the surface.[6,10] This change in underwater pressure alters the volume of air-filled cavities in the body, including the ears, sinuses, and lungs, increasing the risk of barotrauma. Barotrauma refers to injuries sustained owing to variations in pressure on soft tissue in the body. Therefore, divers can manually equalize the pressure conditions between the inside of the ear and the underwater environment using Valsalva techniques or the Frenzel maneuver when they undergo barotrauma in the ears.[6] Besides that, breath-hold divers, especially those diving repeatedly (i.e., spearfishing for traditional freediving fishermen, and freediving athletes) at extreme depths, are at risk of decompression sickness, and perhaps not surprising that lung injuries can occur due to freediving.[5] Pressure on gas exchange can also raise the risk of blackout, which significantly reduces arterial oxygen saturation (SpO_2). Freedivers experience oxygen desaturation, resulting in shallow

water blackout episodes caused by a rapid reduction in alveolar oxygen pressure during dives at depth where oxygen intake is decreased or even reversed[1]. Diving to a depth of more than 20 meters can pose risks to health and safety. The risk of hypoxic syncope due to diving for a long time, caused by a decrease in arterial oxygen saturation or incidents of shallow water blackout due to decreased hydrostatic pressure when rising to the surface, as well as impaired lung function through atelectasis, pulmonary edema, and hemoptysis, can occur in free divers.[1,3] This is clearly dangerous for freedivers. When a diver descends, his body will be exposed to extreme pressure. The further he is from the surface, the more limited his options for saving himself will be if something goes wrong during the dive. Death can occur when divers push themselves beyond the limits of their abilities.[6]

The diving response in humans is highly variable and involves a number of physiological changes characterized by synergistic sympathetic and parasympathetic activation, increased catecholamines, peripheral vascular vasoconstriction that selectively redistributes blood flow to the organs most sensitive to hypoxia, bradycardia, or a decreased heart rate that decreases consumption. At the same time, there is a decrease in metabolism and contraction of the spleen, which brings a supply of red blood cells rich in oxygen into the circulation of the circulatory system.[6,18,19] The diving responses, which is similar to the response in semi-aquatic mammals, can decrease heart rate by half in trained divers and have been proven to prolong apnea while conserving oxygen. The response of the spleen during diving is also known to release red blood cell reserves into the circulation and increase hematocrit, thereby increasing oxygen transport capacity, which also increases the duration of apnea. In humans, a decrease in spleen volume by 18–35% causes an increase in hematocrit by 2–6% during breath holding.[4,5]

The relationship between freediving, hypoxia, and inflammation

Freediving exercises expose the body to intermittent hypoxia and recurrent reoxygenation.[20] This hypoxic situation promotes a rapid and unexpected increase in the number of reactive oxygen species (ROS), resulting in a redox imbalance that contributes to oxidative stress.[21,22] In healthy individuals, there is a balance between ROS generation and the antioxidant defense system. Human cells' redox state is maintained by an antioxidant mechanism that constantly balances ROS produced during normal metabolism. The thioredoxin redox system and the reduced glutathione (GSH)/oxidized glutathione (GSSG) system function as "redox buffers" in cells, protecting proteins from oxidation and maintaining redox balance. Oxidative stress occurs when ROS production surpasses its antioxidant capacity, disrupting the pro-oxidant/antioxidant equilibrium and potentially damaging cells and tissues. However, little is known about the pro-oxidant effects and antioxidant responses associated with diving.[21,23] The kinetics of ROS in oxidative stress allow stimulation of the immune system, such as an increase in neopterin and IL-6, which can trigger inflammation and NOx production during diving.[20,24,25] Extensive research on the activities of free-diving athletes suggests immune and inflammatory responses that alter peripheral blood transcriptomic profiles. During this transcriptome deconvulsion, neutrophil granulocytes increased while CD8 T cells and NK cells decreased. The biological pathway suggests the possibility of a protective mechanism through the upregulation of genes encoding pro-resolving lipid mediators involved in the anti-inflammatory response and downregulation of genes encoding components of lymphocyte cytotoxicity.[10] In addition, during free diving under anaerobic conditions, cytotoxic immune cells temporarily change their functional profile to limit tissue damage by reducing the production of granzyme B and IL-2 and increasing the secretion of IFNγ and TNF.[26] During an inflammatory response, TNF-α is the

first cytokine released, followed by IL-1β and IL-6. These pro-inflammatory cytokines trigger an initial acute inflammatory response by activating granulocyte colony-stimulating factor (G-CSF) and chemokines. In inflammatory conditions, anti-inflammatory responses such as IL-10, IL-4, and IL-1 receptor antagonists are released into the blood circulation, therefore reducing the synthesis of pro-inflammatory cytokines to restore baseline conditions.[22]

There are two important transcription factors that are involved in inflammation and hypoxia. Nuclear factor kappa B (NF-κB), which modulates gene transcription in inflammatory signaling, and hypoxia inducible factor (HIF), which is considered the main regulator of transcription in hypoxia. Hypoxia-induced gene expression affects immune cells in a variety of ways, including inducing innate immunity and suppressing some aspects of adaptive immunity, such as promoting regulatory T cell differentiation and negatively regulating CD4+ T cell, CD8+ cytotoxic T cell, and Th1 cell polarization. Negative regulation of adaptive immunity during hypoxic conditions can prevent excessive activation of the body's immune defense system which has the potential to cause additional tissue damage.[10,27]

HIF and immune cells

Hypoxia-inducible factor (HIF) is a heterodimeric transcription factor consisting of α and β subunits that play an important role in Cellular ability to adapt to changes in low oxygen levels. When energy requirements are accompanied by an adequate oxygen supply under normoxia conditions, HIF-1α will be degraded by the proteasome. The HIF-α protein contains an oxygen-dependent degradation (ODD) domain with 2 proline sites, namely Pro402 and Pro564, which are hydroxylated by PHD (oxygen-dependent prolyl hydroxylase), which controls degradation through the ubiquitin-proteasome pathway. Hydroxylated proline interacts with VHL to increase HIF-α ubiquitin-proteasome degradation. However, in hypoxic settings, PHD enzymatic activity is inhibited due to a lack of oxygen, preventing HIF-α hydroxylation. The HIF-α subunit binds with HIF-1β to produce a dimerization transcriptional complex. HIF-1α can accumulate and translocate to the nucleus, merging with hypoxia-responsive elements (HREs) to activate downstream genes including EPO and VEGF. Cells will remain in redox balance with low levels of ROS production and use oxidative phosphorylation as the main means of providing energy. Inflamed tissue also often experiences hypoxia, and HIF helps these immune cells adapt. HIF-1α regulates innate immune cells, including M1 macrophage polarization, dendritic cell maturation and migration, and neutrophil extracellular trap formation.[27-29] Hypoxia signaling and HIF activation have both anti-inflammatory and pro-inflammatory effects on immune system cells. In inflammatory circumstances, active neutrophils increase oxygen consumption, whereas macrophages and lymphocytes enhance glycolysis. As a result, local oxygen levels drop and the microenvironment becomes hypoxic, which activates HIF signaling and modulates immune cell activity. This regulatory loop demonstrates a link between inflammation, hypoxia, and immune cell metabolism. HIF-1α is expressed in all immune cells, where it directly regulates the production of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. In pathological conditions, HIF-1α translocation to the nucleus increases and results in the production of TNFα and IL-6, while IL-10 production decreases, causing an inflammatory response.[30-32]

NF-κB and inflammation

On the other hand, NF-κB regulates various aspects of Innate and adaptive immune function and plays a crucial role in inflammation. NF-κB induces the expression of proinflammatory genes, such as cytokines and chemokines, which regulate immune responses. NF-κB activation comprises two basic signaling pathways: canonical and noncanonical pathways. In addition, NF-κB regulates the activation, differentiation, and effector function of inflammatory T cells and plays a role in regulating the activation of inflammasomes. When the canonical NF-κB pathway is activated, M1 macrophages release pro-

inflammatory cytokines such IL-1, IL-6, IL-12, TNF-α, and chemokines, which contribute to numerous inflammatory processes. M1 macrophages also encourage the differentiation of inflammatory T cells, such as Th1 and Th17 cells. M2 macrophages, on the other hand, create anti-inflammatory cytokines such as IL-10 and IL-13, which are essential for inhibiting inflammation and mediating wound healing. NF-κB directly regulates HIF expression during inflammatory and hypoxic responses.[30,33]

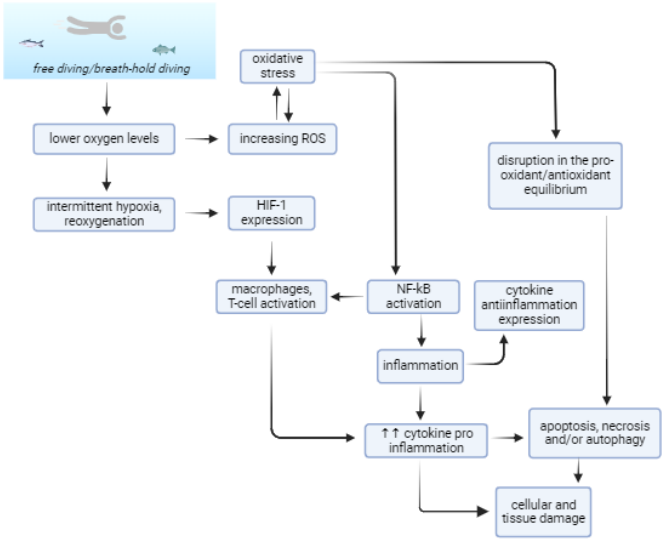

Figure 1. Illustration of the relationship between freediving, hypoxia, and inflammation.

Regulation of NF-κB and HIF during hypoxia

Hypoxia triggers a regulatory loop involving NF-κB and HIF transcription factors, resulting in a synergistic response to stress. However, the exact mechanism of NF-κB activation under hypoxia remains unknown. Furthermore, hypoxia has been linked to increased NF-κB activation by inhibiting IKKβ catalytic activity through prolyl hydroxylase inhibition[33]. Hypoxia can increase gene expression in human and murine macrophages in an HIF-independent manner by upregulating NF-κB, ATF4, and Egr1. Additionally, NF-κB may increase HIF-1α transcription in macrophage cells during hypoxia. Increased NF-κB and HIF levels trigger an inflammatory response by upregulating the production of pro-inflammatory cytokines. In T cells, HIF suppresses NF-κB activation. Hypoxia, TCR activation, IL-6, and bacterial infection trigger an increase in HIF and NF-κB, leading to enhanced T cell proliferation, survival, and activation. HIF activity through NF-κB activation is increased by hypoxia and infectious stimuli. As a result, it raised B cell development and triggered a humoral response. HIF enhances NF-κB activation in neutrophils. An increase in this transcription factor stimulates neutrophil activation, which increases NO and pro-inflammatory cytokine production while decreasing cellular apoptosis.[34] Hypoxia activates NF-κB through IKK and the canonical route signaling cascade. Research suggests that PHD and FIH (factor-inhibiting hypoxia-inducible factor) play a crucial role in controlling the NF-κB pathway in many cellular circumstances following sustained hypoxia exposure. Other proposed mechanisms include activation of the NF-κB pathway due to hypoxic stimuli via TAK1-IKK and activation mechanisms that are independent of IKK. IκBα plays a significant role in the hypoxia-induced cytoplasmic signaling cascade that activates NF-κB. IκBα has been known to inhibit NF-κB. IκBα degradation did not correlate to hypoxia-induced NF-κB activation. Thus,

an independent mechanism of IKK activation was postulated.[33]

2. Conclusion

Scientific investigation of the human breath-holding ability through freediving and its impact at the molecular level provides an understanding of human physiology and adaptation to the hypoxic circumstances observed during freediving. Breath-hold diving requires highly integrated physiology as well as extreme responses to both physical activity and hypoxia as hydrostatic pressure increases gradually. Additional studies are needed to address the various possible mechanisms of NF-κB activation in hypoxia and clarify the crosstalk of HIF with NF-κB and its impact on immune cells. The potential medical consequences and risks of freediving (i.e., barotrauma, decompression sickness, loss of consciousness, or shallow water blackout incidents) are outlined. Future investigations are required to properly understand the clinical implications of apnea and freediving in order to minimize occupational ailments and accidents in both traditional freediving fishermen or freediving athletes.

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