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High Altitude Sickness – Solutions from Genomics, Proteomics and Antioxidant Interventions

Springer

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ISBN 978-981-19-1007-4 ISBN 978-981-19-1008-1 (eBook)
https://doi.org/10.1007/978-981-19-1008-1

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

The mighty Himalayas and several other high mountains across the globe represent marvellous creations of nature which have always attracted the attention of humans by their mighty heights and breathtaking views. They have always been an abode of some of the most scenic and adventurous trekking and tourist destinations, some are, however, places of religious importance, and others form strategic borders across nations. Some of the international borders lying within these mighty mountains, such as India-Pakistan and Indo-China borders, are highly strategic and have routine deputation of soldiers and army personnel. On the one hand, while the beauty of these mighty elevations attracts people, tough terrain and reduced density of air due to their altitudes pose challenges for high-altitude travellers. Some of the human establishments at the astonishing heights of above 5500 m are known to cause drastic physiological changes which sometimes culminate in lethality. High-altitude pulmonary oedema (HAPE), high-altitude cerebral oedema, loss of cognitive functions, hypertension and other hemodynamic abnormalities are key problems that need a clinical resolution. Moreover, identification of susceptibility and adaptability contributing factors are warranted to be resolved. Researchers across the globe over several decades have therefore explored the molecular, and physiological bases of these pathologies and undermined various mechanisms, effects, and outcomes. Proteomics and genomics remain a highly promising domain to explore the aforementioned problems, and considerable success has been achieved in terms of biomarker discovery and deciphering the precise sequence of molecular events occurring during the hypobaric hypoxia exposure. This book is aimed at providing a current perspective of genomic and proteomic approaches implied to hypoxia research and also an exploration of various possible interventions for minimizing the physiological alterations. This book includes views of experts across the globe working on simulated hypoxia models or human subjects travelling to high altitudes and brings along their decades of experience. We believe that the text would be useful for novice to experienced researchers and aid them in bringing refined hypotheses for hypoxia-induced pathophysiological changes and shall be the lead reference for the development of clinical solutions in the coming time. We acknowledge the defence research and development organisation, New Delhi, for valuable

inputs and authors' contributions which enabled us to bring the book to its present shape. Any suggestions, comments, or critiques are welcome for the improvement of the book.

Tonk, Rajasthan, India — Narendra Kumar Sharma
New Delhi, India — Aditya Arya
December 2021

About the Book

This book illustrates the importance and significance of the proteomics studies in the domain of high-altitude physiology and associated sickness. More than 140 million people reside in high-altitude regions around the globe. A significant number of low landers visit high altitudes for professional activities, adventure sports, and leisure compounding occurrence of high-altitude illnesses. Hence, this book is intended for a global audience, health authorities, researchers, as well as professional sportsperson and coaches, to cover disorders and sickness associated with short-term and long-term high-altitude stay. The book starts with a brief introduction of high-altitude pathophysiology its cause and symptoms and later followed by a deeper understanding of ongoing research to develop proteomic based biomarkers for non-invasive diagnosis of altitude sickness susceptibility and also proven prophylactic and anaphylactic interventions. Therefore, this book will provide the reader a quick insight into contemporary methods in high-altitude proteomics and redox biology and new potential diagnostic and therapeutic strategies for clinicians for carrying forward to clinical trials. The book contains ten chapters, which include a sequential ascent of the text. The first few chapters have a primary focus on understanding the problem, while the latter half of the books includes discussion on various proteomic and molecular solutions emerging from current research. Self-explanatory illustrations and graphics, as well as research data from respective authors, have been used to enhance comprehension.

Contents

About the Editors

Narendra Kumar Sharma is working as Assistant Professor at the Department of Biosciences and Biotechnology of the Banasthali Vidyapith, India. He has earlier served as Assistant Professor in the Science Department at AKM, Kota University, India, Postdoctoral Fellow at Guangzhou Institutes of Biomedicine and Health (GIBH), Chinese Academy of Sciences (CAS), China, and Postdoctoral Fellow at Federal University of Sao Paulo (UNIFESP), Brazil. His research interest is in Genomics and Proteomics with specialization in hypoxia physiology, oxidative stress, posttranslational modification, protein biochemistry, signalling pathway, protein–protein interaction, infectious disease, regenerative medicine, and genome editing. He has been conferred with the prestigious award Dr. T. S. Vasundhara memorial best paper award, DRDO, India. He has served as a referee for a number of international journals. He has also published more than 20 research articles in peer-reviewed international journals and authored or co-authored books and book chapters. He has presented his research work at various international conferences held in India, Brazil, China, USA, and Germany. He is a member of many international scientific societies and organizations importantly, Indian Academy of Neuroscience (IAN), India, and International Organization of Scientific Research (IOSR), India.

Aditya Arya is working as a scientist at the National Institute of Malaria Research, New Delhi, a flagship lab of the Indian Council of Malaria Research (ICMR). Previously, he worked as a staff scientist at Pathfinder Research and Training Foundation, Gautam Budh Nagar, India. His research interest is in nanomedicine and redox biology. He has been trained at some of the most prestigious institutions such as Wellcome Trust Sanger Institute, IBRO, EMBL and holds active membership in several research societies. He has published more than 20 research papers in peer-reviewed journals about redox biology, proteomics, and high-altitude physiology. Besides this, he is also an academician and authored several book and book chapters like Concise Biochemistry, Understanding Enzymes, to name a few.

Introduction to High Altitude and Hypoxia

1

Preeti Sharma, Poornima Pandey, Pooja Kumari, and Narendra Kumar Sharma

Abstract

Climbing to a high altitude causes breathing to shorten, which reduces the amount of oxygen in the tissues and causes hypoxia. High altitude sickness is a medical illness with lethal implications such as hypoxia, high altitude pulmonary oedema (HAPE), high altitude cerebral oedema (HACE), and several other neurological disorders. Acclimatization is a primary response that encounters hypoxia and during this time individuals adapt to the decreased level of oxygen at a specific height. To investigate this physiological process, several studies have been conducted in the last few years. These studies have indicated the changes in the transcriptional and translational levels of various stress-associated genes/proteins under hypoxia and hypoxia acclimatization. Reducing air pressure at high altitudes causes hypoxia, which is a potential threat to the normal functioning of the brain. The generation of excessive free radicals and their intracellular diffusion leads to oxidative stress. Recent studies on molecular signalling along with shreds of evidence from cognitive impairment in the animal model during hypoxia have demonstrated that the cortex and hippocampus as anatomically and biochemically most vulnerable to oxidative stress in contrast to other regions of the brain. The emerging tools such as omics can be a milestone to study the physiological response of high altitudes and can decrease the adaptation time at high altitudes.

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N. K. Sharma, A. Arya (eds.), *High Altitude Sickness – Solutions from Genomics, Proteomics and Antioxidant Interventions*,
https://doi.org/10.1007/978-981-19-1008-1_1

Keywords

Hypoxia · High altitude pulmonary oedema · High altitude cerebral oedema · AMS

1.1 Introduction

Altitude is defined as vertical height above sea level and is directly associated with the relative air pressure present in the atmosphere. As the height increases, the air pressure decreases simultaneously and as the name indicates high means 'excessive' and altitude means 'elevation'. Thus high altitude (HA) is the term used for the specific vertical distance at which it becomes more difficult to survive and even may lead to life-threatening events because of the lack of availability of oxygen and some basic human body needs. Altitude is classified based on height above the sea level and categorized as high, very high, and extreme altitude. The specified distance of high altitude is about (8000–12,000 ft), very high (12,000–18,000 ft), and extreme (>18,000 ft, Fig. 1.1, Wilson et al. 2009).

People like to go to the mountains for various activities such as trekking and scenic views without knowing the fact that reduced oxygen at high altitude may

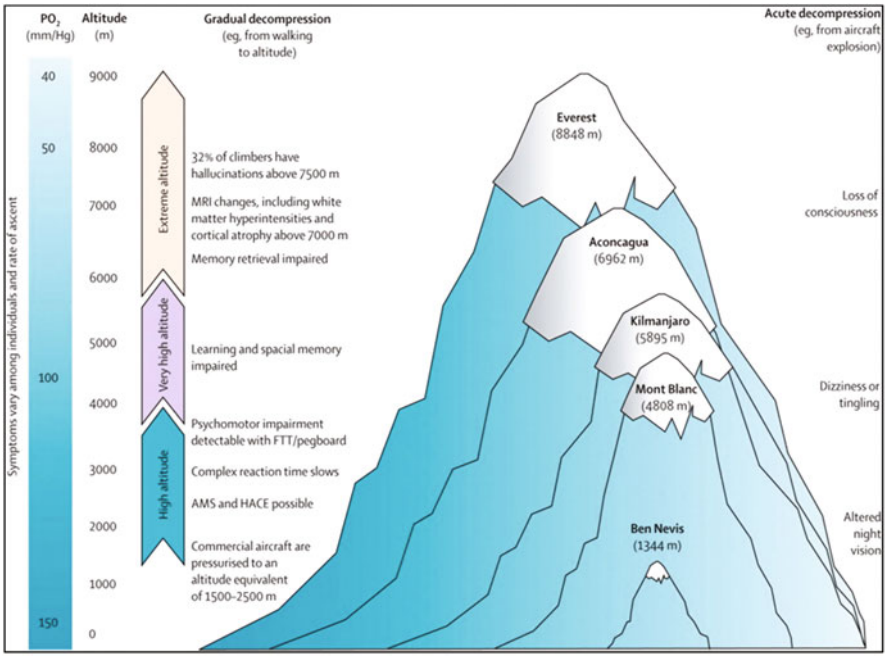

Fig. 1.1 The relationship between altitude and oxygen partial pressure, as well as the neurological effects of abrupt and progressive pressure shifts. (Adapted from Wilson et al. 2009)

affect them adversely. Hence, it is important to know the physiological consequences of HA to avoid HA associated disorders and life-threatening conditions. The aerial route nowadays becomes the prime choice of the middle-class family as it cuts the time of travel as well as easy availability of flights with affordable prices. These people reach the various touristic spots at high altitudes without acclimatization and start exploring HA. In the lack of knowledge, they develop HA sickness and other HA associated diseases. Even in this circumstance, aircraft would not operate over the Himalayan regions because of lower aerial pressure compared to required. The HA travellers have developed the acute mountain sickness (AMS) at the altitude of 2000 m and some of them have developed the HAPE and HACE when continued travel to HA (Dünnwald et al. 2021). Psychomotor retardation has occurred at very high altitudes that affected walking movement, talking, and other basic activities. Furthermore, impairment of learning and special memory has resulted in confusion or disorientation. At extreme altitudes, travellers fail to recall memory. The travellers have felt illusions at above 7500 m and other symptoms such as night vision alteration, dizziness or tingling and loss of consciousness.

The mortality rate is low, i.e. 4% at high altitudes but it is still important as soldiers reside most of the time at high altitudes. Each year, several pilgrims have died due to HA during the holy pilgrimage. There were more than 130 deaths reported yearly. The highest mortality was found at the death zone of Mount Everest and it increases with the increase in the number of climbers proportionally. When we talk about the HA, India has a long, sensitive border along with the world's highest mountain range (Khanna et al. 2018). The world's highest battlefield also lies in India, Pakistan, and China. The soldiers have to stay from 9000 to 20,000 ft for occupying their positions and it affects both mental as well as a physical condition due to the development of hypobaric hypoxia. The term hypobaric hypoxia (HH) is used when oxygen is limited due to reduced pressure at altitude. HH is a major physiological threat during the stay at a high altitude. It is associated with the increased number of RBSs and hemoglobulin to counter the low oxygen. There are no specific factors such as age, sex, and capacity that correlate with altitude sickness.

1.2 High Altitude and Oxygen Availability

The air is present up to 10,000 m at the end of the troposphere. The air is a mixture of gases in a definite concentration, for example, oxygen is present around 21% in the air. Most people are confused with the percentage of oxygen availability at HA. Atmospheric pressure is low at high altitudes when compared to sea level due to the gravity that pulls the air as close as to the ground. In case of high altitude (HA) the oxygen percentage remains constant, while the partial pressure changes according to elevation. So the partial pressure of oxygen lowers as the barometric pressure decreases, that cause the reduction of oxygen at tissue level. The gaseous exchange depends on the difference of the partial pressure. Oxygen exchange is

occurred in lung cells and is carried by haemoglobin. One gram of haemoglobin carries 1.39 mL of oxygen. The level of haemoglobin increases to enhance the oxygen availability for the adaptation at HA. Once the oxygen availability is limited at HA, the heart rate is affected by blood viscosity, resulting in CMS (chronic mountain sickness) in which the blood pressure rises as the altitude rises (Crocker et al. 2020). Most of the travellers face AMS that is very common at HA with mild symptoms around 10,000 ft. The extreme altitude around 18,000 ft or higher cannot be tolerable without oxygen supplementation. With the elevation of height, physiological changes occur in our bodies. The first system that responds to HA is the respiratory system. The atmospheric pressure at sea level is 760 mmHg that corresponds to approximately 159 mm of partial pressure of oxygen (PO_2). During respiration, inhaled air is warmed and humidified that resulted in the addition of water vapour in the inhaled air and affects the partial pressure of the gases. At sea level, the oxygen levels in the blood within the capillaries exceeds that found inside the alveoli about 0.25 s of inhaling air (Zubieta-Calleja and Zubieta-DeUrioste 2021). Furthermore, while PAO_2 levels are lower at higher elevations, the pace of building oxygen tension in capillary blood is slower than at sea level. At rest, the capillary transit time is still sufficient to allow the oxygen tension to approach that within the alveoli, but when the transit time is reduced by exercise there will be a marked worsening of any hypobaric hypoxia. When PO_2 is decreased, chemoreceptors from the central nervous system (CNS) are stimulated in the dorsal respiratory groove that resulted in hyperventilation. It suggests that during hyperventilation, more oxygen is delivered to the HA for the acclimation process. Blood remains in the lungs for about 0.75 s. The atmospheric carbon dioxide level is also very less at high altitudes (Storz and Cheviron 2021).

1.3 Acclimatization at High Altitude

Acclimatization refers to the process where our body compensates for the low partial pressure of oxygen by either amplifying certain receptors or increasing the number of RBCs. A finger pulse oximeter is used to measure physiological consequences at HA as an acclimatization process. There are several physiological changes occurred in respiration and circulation when going to HA. By acclimatization process, we can reduce the deleterious effect of low oxygen on the body increases ventilation and circulation (Fig. 1.2).

When people travel to HA above 3000 m for various activities with a lack of knowledge of HA physiology, they have noticed several HA associated sicknesses including headache, dizziness, nausea, hyperventilation, etc. When they did not acclimate at HA and have begun their activities there, their symptoms may intensify, and in rare circumstances, life-threatening scenarios will occur. Some of the travellers and soldiers have developed pulmonary oedema/cerebral oedema. In this case, they have to come back at sea level immediately, however, now we have some medications so the treatment can be done at HA itself. Rapid ascent to HA is associated with decreased health and fitness, while they feel normal after returning to sea level. The acclimatization process helps the travellers to adopt the adverse

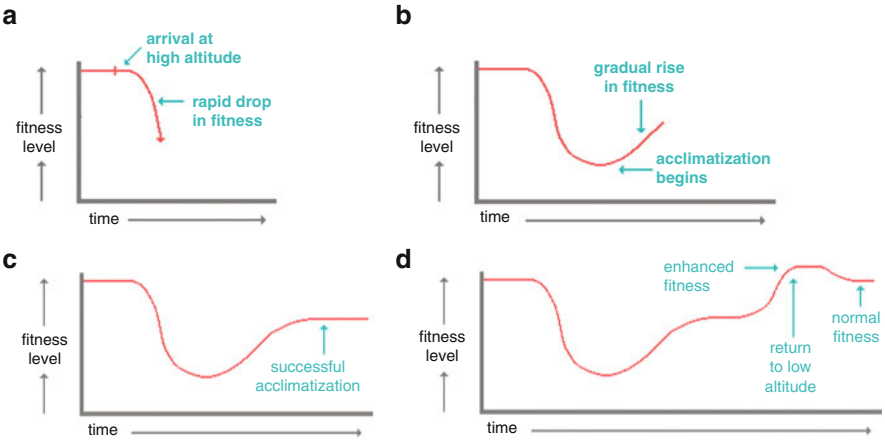

Fig. 1.2 Process of acclimatization. (**a**) Initial inefficient response to low oxygen pressure (**b**) Beginning of successful acclimatization to low oxygen pressure (**c**) Increased fitness level after successful acclimatization to low oxygen pressure and (**d**) Enhanced fitness level for a short period after returning to low altitude. (Source: http://anthro.palomar.edu/adapt/adapt_3.htm)

conditions quickly at HA and reduces the risk of development of AMS, HACE, and HAPE (Bärtsch and Swenson 2013). The successful acclimatization process has been reported at 5500 m, further ascent after this height depends on the individual's physiology and immunity (Fig. 1.3).

Slow stepping and staging is the most common strategic event for high altitude sickness and speedy acclimatization, as the cliché goes, slow and steady wins the race. After ascending to 1000 m, it is typically recommended that HA travelers do not venture out 500 m per day. During ascension, staging refers to stopping for a period of time and at a specific altitude. Both of these processes of acclimatization are used in mountaineering as well as in trekking at HA. There are several protocols used for acclimatization like some exercise after resting at HA. Pre-acclimatization and intermittent hypoxia exposure strategies have worked well for high altitude sickness (Luks et al. 2017). Recently, members of the union international des association's d'Alpinisme medical commission (UIIA Med Com) claimed that high altitude climbers didn't found to be symptomatic of AMS as compared to the other ones. Pre-acclimatization strategies are also included in the carrying of drugs that minimize the effect of high altitude sicknesses such as Acetazolamide and Dexamethasone. These drugs along with some natural extracts such as a nasal cannula, *Biloba* also helped to decrease the deleterious effect of HA (Karinen 2013).

1.3.1 Acute Mountain Sickness

Acute mountain sickness is often known as "Mountain sickness" and "Altitude sickness," which is a clinical condition that can occur if people move or climb to a

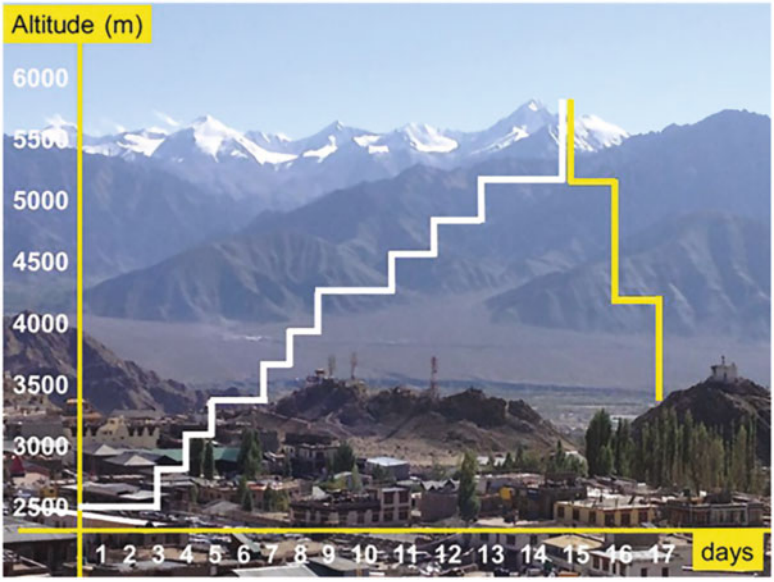

Fig. 1.3 Example of a safe (traditional) ascent from 2500 m to 6121 m (Stok Kangri, Ladakh). 300–500 m per day and one rest day for every 1000 m gain in altitude (Burtscher et al. 2021)

greater height or altitude too rapidly. This condition rise because of less oxygen availability like if someone went to a greater height the pressure dropped and oxygen availability dropped. This sickness can begin at any elevation above 8000 ft. AMS is characterized by headaches, dizziness, shortness of breath, drowsiness, poor appetite (often associated with nausea), exhaustion, fatigue, and irritability these symptoms may develop within 12–24 h after reaching high elevation and disappear within 2 days as the body adjusts to change in higher altitude (Wilson et al. 2009). In the case of mild altitude sickness symptoms may be more severe and will not improve with time and medicine, as time passes by instead of feeling good, a person will begin to feel bad and will have increased tiredness and breathlessness. HAPE (high altitude pulmonary oedema) and HACE (high altitude cerebral oedema) both are considered as a severe form of altitude sickness, induration, patients may acquire symptoms such as shortness of breath even when resting, inability to move, while coughing a white or pink substance foam, coma, and so on. Altitude sickness may affect anyone, no matter how strong, young, or physically fit they are, it can even affect athletes too. Various factors involved that can influence the risk of altitude illness include how rapidly people climb to a greater height, how high they go up and the altitude at which they sleep, it also depends upon where a person belongs (where to live) age and if they ever had altitude illness before. Some health issues also make it more severe to the people who suffer from these such as diabetes and lung disease, genes also play a role in the ability of the body to handle HA. The symptoms regarding HA sickness will assist in seeking treatment as soon as possible. The basic

treatment for any altitude sickness is to descend as quickly as possible with staying safe, in case of severe altitude sickness person must be transferred to a lower height immediately. It should be less than 4000 ft, in the case of HACE steroid prescribe for the patient and in HAPE, the individual should be given oxygen and lowered as soon as possible. The other way to reduce high altitude illness is acclimatization; it might help to reduce the chances of experiencing altitude sickness as a person climb to HA they should gradually acclimatize their body to the variations in atmospheric pressure. Another way is to wear loose clothing to allow easy release of gastrointestinal gases similarly; some other recommendation is given to person going for high elevation like less utilization of milk and milk derivatives either switch to lactose-free diet on first of arrival good oral hydration is necessary at this time (Zubieta-Calleja and Zubieta-DeUrioste 2021). HAPE and in extreme instances HACE, both followed by AMS, can arise on the day of arrival and around 3 to 4 days later. The identification of mountain sickness is clinical because the patient is new to a higher altitude or not.

1.3.2 High Altitude Cerebral Oedema (HACE)

HACE (high altitude cerebral oedema) is a life-threatening neurological disease that develops in people with AMS or HAPE over hours to days. It is characterized by variable levels of disorientation, behavioural problems, paralysis, and cerebral oedema on neuroimaging. If it is not treated promptly, it can quickly progress to stupor, which can be deadly. Unlike HACE, AMS is characterized by vague symptoms and these two are generally linked with non-acclimatized persons who abruptly climb over 2500 m as a result, it is considered as the last stage of AMS (Hultgren 1997; Yarnell et al. 2000; Hackett 1999a, b). HACE could emerge 3 to 5 days upon arriving at elevations as low as 2700 m (9020 ft), although it is more commonly observed in isolated places higher than this range when the symptoms appear much more rapidly within an hour. Usually, it affects individuals of different ages and genders; however, youngsters may be more vulnerable due to continued rise despite AMS symptoms and a faster pace of ascension that lead to caused hypoxia (Jacob et al. 2020). HACE is diagnosed clinically, but the symptoms associated from mild to moderate. AMS can appear soon after the rise and typically worsen over 24 to 72 h. Notably, the peak period of AMS appearance often corresponds with the onset of HACE symptoms indicate a possible continuity from AMS to HACE (Sutton 1992).

The diagnosis of cerebral oedema is routinely done by neuroimaging investigations. The intracranial pressure, cerebrovascular, and MRI investigations have provided a better knowledge of the macroscopic changes associated with cerebral oedema. However, the forms of oedema may differ in different parts of the brain, in different individuals and it is not always evident in imaging through the processes. The mechanism of these changes at the vascular and cellular levels remain unclear (Jacob et al. 2020). The aetiology behind cerebral oedema includes an excessive build up of water in the parenchyma of the brain including various

compartments such as interstitial and intracellular. Some of the evidence recommended that this type of oedema occurs when AMS develops. AMS and HACE both share a common pathological process include increasing cerebral blood volume and early formation of intracellular oedema, which is dependent on the osmotic gradient and further take part in the formation of ionic oedema alongside vasogenic oedema. Furthermore, several types of physiological processes have been recognized that take part in altered brain water regulation (Turner et al. 2021).

1.3.2.1 Intracellular Oedema

Intracellular oedema is osmotically dependent on the cellular movement of water and ions from cerebral extracellular to intracellular space. It is occurred due to the failure of an energy-dependent mechanism of transport, as a result, the intracellular space swell but there is no initial brain swelling was observed. It is shown that no additional volume was introduced into the intracranial section. This condition is also common in the periventricular white matter of those who have just moderate hypoxia. It is shown that energy-dependent pathways become impaired even at a moderate level of hypoxia (Turner et al. 2021).

1.3.2.2 Ionic Oedema

Intracellular oedema is reduced Na^+ Cl^- and water in the cerebral extracellular space and create an osmotic pressure gradient for this molecule across the capillary blood-brain barrier. As Na^+Cl^- homeostasis is restored in the cerebral extracellular space, water is pulled into the brain and developed extracellular /ionic oedema and this kind of oedema develop without changes or disruption of the blood–brain barrier (BBB) (Turner et al. 2021).

1.3.2.3 Vasogenic Oedema

In vasogenic oedema, cerebral extracellular fluid accumulation has occurred. It contains plasma proteins, that are largely linked to dysfunction of endothelial, vascular damage, and disrupt the integrity of the blood–brain barrier (BBB). It is found that the blood–brain barrier lost integrity in several cases of HACE (Turner et al. 2021).

Several processes are involved to understand the mechanism of action during HACE; it is started with cell progression in which the transition from artery to a vein occurred (left to right) and this progression is further increased intravascular pressure caused vasogenic oedema and arterial wall damage. Specific alterations have been found in the artery and vein, with increased hydrostatic pressure in the artery and venous outflow blockage in the vein. These partial pressures of oxygen and carbon dioxide have been thought to have direct vasoactive properties with hypoxemia producing vasodilation and hypocarbia causing vasoconstriction. The hypoxic ventilatory response has mediated a balance between hypoxemia and hypocarbia. Direct hypoxia may further induce Na^+/K^+ ATPase failure that caused cytotoxic oedema. Besides various chemical mediators that have been linked to the disease progression, free radical production is one of them that could cause vasogenic oedema by directly damaging vessel basement membranes. In addition to HIF-1 accumulation and

consequent VEGF, overexpression could lead to more damage of the basal membrane and cerebral oedema. The limited hyperkalemia may also produce nitric oxide that is calcium-dependent and may further be caused vasodilation by acting on vascular smooth muscle. The vasodilation may also be caused by neuronally mediated adenosine release and activation of vasodilation is linked to the trigeminovascular system, which is caused the headache. In the complete scenario, micro-haemorrhage development is a key component of HACE, which can be generated by damage of vessels caused by cytokines or various other chemical mediators or by elevation of hydrostatic pressure (Wilson et al. 2009).

1.3.3 High Altitude Pulmonary Oedema (HAPE)

High altitude pulmonary oedema is a fatal disease; defined by the accumulation of fluid in the lungs as a result of acute high altitude hypoxic exposure. These clinical categories are also included AMS, which is more frequent and HACE. HACE is uncommon at HA and the complication of high altitude illness is occurred after above 3000 m. There are two main causes for the development of HAPE. First is pulmonary artery vasoconstriction which caused an increase in pulmonary circulation pressure and the second is an increase in capillary permeability that lead fluid to flow into the alveoli in patients who are prone to HAPE. It is generally followed by symptoms of AMS though the most common symptoms associated that are included shortness of breath, cough, dizziness, dyspnea, fatigue, and cyanosis.

Early symptoms of HAPE are included mild nonproductive cough, dyspnea with effort and reduced physical performance. These symptoms are often ignored by patient's that resulted in increased cough and severe dyspnea even at rest conditions. These extreme cases are distinguished by bubbling in the chest and pink foam of sputum. Although the exact prevalence is still not fully explained (Paralikar 2012), it is responsible for the majority of fatalities associated with high altitude disease and cases have been reported as low as 8500 ft approximately (3000 m) (Yarnell et al. 2000). The lack of early detection methods for HAPE also contributed to the complications at HA. This pulmonary oedema at high altitude is developed within a day to 3 days of arriving at HA, and then hardly after a day (Hackett and Roach 2001), it turns into HAPE. For this reason, hypoxia-induced extensive pulmonary vasoconstriction, capillary leak, and alternative diagnosis should be investigated. The imaging scans are also recommended by the hospitals after 4 days of arrival to HA. Various oxygen-sensing mechanisms such as nitric oxide syntheses, (VEGR) vascular endothelial growth factor, and hypoxia-inducible factors (HIF) are responsible for the activation of inflammatory, immunological, and physiological changes that cause HAPE.

HIF is a key transcriptional factor that stimulated the expression of various target genes that are responsible for the regulation of oxygen homeostasis (Woods and Alcock 2021). In recent years, the researchers are focused to study the signalling and biochemical processes in HAPE progression by emphasizing the fact that increased pulmonary hypertension on elevation leads to the development of HAPE. One

hypothesis has claimed that minimizing pulmonary hypertension would prevent HAPE (Paralikar 2012). It is found that glucocorticoids have been proven to be useful in reducing HAPE in a person when administered before climbing and during ascent to HA. It is activated the production of cGMP in hypoxia and increased the activity of nitric oxide syntheses by activation of epithelial Na^+ K^+ ATPase pump, however, extensive research is still needed to find the lowest effective dosage. The treatment for HAPE is included quick enhancement of oxygenation by supplementary oxygen, hyperbaric treatment, or fast decline.

1.4 Hypobaric Hypoxia and Brain

Hypobaric hypoxia (HH) is a phenomenon in which organisms lack an adequate supply of oxygen to various body tissue at HA. Due to a decrease in partial pressure at HA, the ability to transfer oxygen from the lungs to the bloodstream is adversely affected. The effects of HH are associated with the height of an altitude. The effect of HH is indistinguishable in the early phase and the body response of the different individuals are also different. The most common symptoms are included as breathing difficulty, rapid pulse rate, lethargy, headaches, inability to think, and tiredness. Most of the body organs got affected by the limited availability of oxygen including the lung, heart, brain, renal, and spleen. Among all, the brain is the most vulnerable organ affected and it is the first organ to be impaired in the HH (West 1996; West et al. 2007).

The brain is the most studied organ under HH since it uses 20% of inspired oxygen and has substantial energy expenditures that must not be reduced. The brain cells consumed half of the energy for charge transfer across cellular membranes to maintain cellular redox equilibrium (Stieg et al. 1999). As a result of that, in a few minutes of oxygen deprivation, the brain experiences energy failure. Several studies have discussed the differences between high altitude (HA) natives and low lenders in terms of altitude-related brain alterations. According to Zhang et al., HA natives had less grey matter than sea level controls, which resulted in lower blood pressure (Zhang et al. 2010).

Because of the diminished oxygen flow to the brain, higher altitude hypoxia lowers a person's mental abilities (Lieberman et al. 2005), and the effect varies depending on altitude height. The lower ability for continuous mental effort, memory problems, audio and visual difficulties, and irritation are all possible neurological and cerebral symptoms that occurred at HA. Adults may experience weight loss of 5–10 pounds if their appetite remains low. The symptoms of the high altitude associated sickness may be persisted until the stay there that hinder the normal functioning of the body. In some circumstances, patients' need to return to sea level too, however with the proper acclimatization, these issues can be minimized.

Mitochondria are the major sources of reactive oxygen and nitrogen species. The superoxide is reacted with nitric oxide radicals and produced peroxy-nitrites that is considered strong oxidant. Under hypobaric hypoxia, the NO_2^- pathway is activated that produced excess free radicals through the respiratory chain. The immediate

treatment for hypoxia is the supplementation of oxygen that can be given through an oxygen mask. HH has resulted in changes in blood flow to the brain, energy metabolism, and cognitive processes such as learning and memory. It is also responsible for cerebral damage but the molecular mechanism remains unknown yet.

Hypobaric hypoxia impairs cognitive function because of a variety of reasons including oxidative stress, neuronal damage, and neurotransmitter changes. Jayalakshmi et al. suggested that administration of N acetylcysteine improved the deleterious effects of hypoxia on spatial learning memory function. To diminish free radical production during hypobaric hypoxia, oxidative stress is reduced by increasing the antioxidant status (Jayalakshmi et al. 2007). Several other therapeutic agents are also reported to decrease cognitive impairment under hypobaric hypoxia such as acetyl-L-carnitine, L type calcium channel, and glutamate receptor (Barhwal et al. 2009), however, targeting single neural receptor, ion channels, and gene are unable to combat the enormous cascading of hypobaric hypoxia-induced alterations.

1.4.1 Brain as a Vulnerable Site of Oxidative Stress

The brain is extremely vulnerable to oxidative stress because of its high oxygen demand and lipid-rich composition. The intake of oxygen, on the other hand, led in the development of free radicals, sometimes known as the "essential devils of the cell." In a healthy organism, the balance of pro-oxidants and anti-oxidants is crucial and if it is shifted towards pro-oxidants, oxidative stress may occur. It is widely established that high altitude increases the generation of reactive oxygen species (ROS), which is linked to the pathophysiology of hypoxia-induced changes. Oxidative stress causes inflammation in the brain, which compromises the integrity of the blood-brain barrier, a key component of CNS homeostasis, and leads to brain injury. It also triggered neuronal death in the cortical, subcortical, and hippocampal regions of the brain (Sharma et al. 2011, 2013; Ahmad et al. 2013). Oxygen plays an important role in energy production in mitochondria, when acted as a limiting factor, excess formation of ROS is generated during cellular respiration (Gandhi and Abramov 2012). The generation of free radicals and ROS is determined by analyzing the mitochondrial resting or active staus. In a cell, ROS production is ten times higher in mitochondria than in cytosol and nucleus. Cytochrome oxidase complex (Complex IV) is responsible for oxygen sensing in normal conditions. During cellular respiration, complex IV transfers electrons to molecular oxygen and reduced them to water. ROS and free radicals are served as intermediate and are attached to the complex until completely utilized to form water. HH induced oxidative stress that leads to the generation of excess ROS and free radicals which degrade or oxidized macromolecules in the cell (Schild et al. 2003; Maiti et al. 2006; Halliwell 1989). The above-discussed events can be seen in Fig. 1.4.

Due to increased ROS production on the outer side of the inner mitochondrial membrane in HH, cytosol or IMS oxidation increased, whereas mitochondrial matrix oxidation reduced. Mitochondrial DNA (mt DNA) is more vulnerable to oxidative stress than nuclear DNA due to poor DNA repair function and the continuous

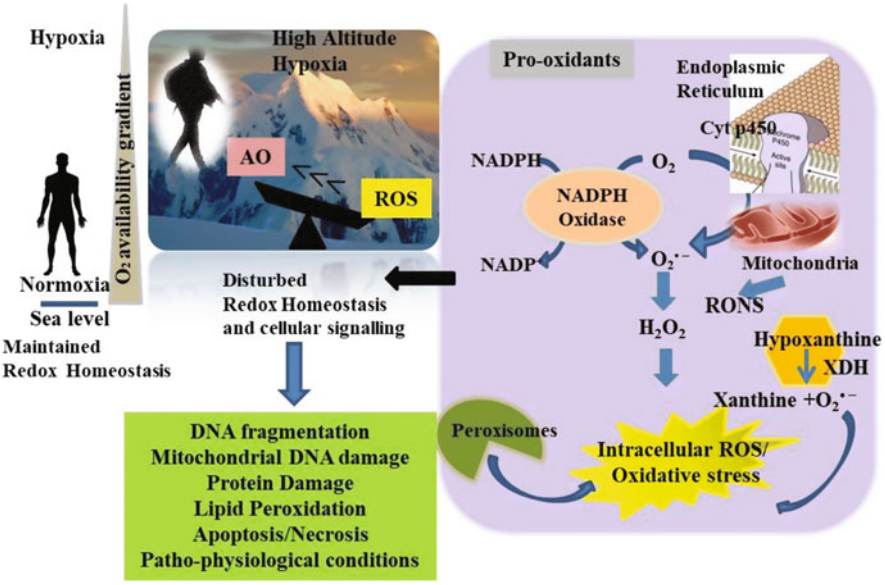

Fig. 1.4 Electron transport chain reaction showing oxygen as the terminal acceptor of electron and increases the level of ROS and the disturbance of redox homeostasis affects various biological reactions at the cellular level. (Adapted from Gaur et al. 2021)

production of free radicals which contributed to a highly reducing environment. Both the IMM and the IMS emit ROS during HH, which may lead to the activation of various transcription factors such as hypoxia-inducible factors (HIF1); additionally, FOXO-mediated transcription factors help to stabilize and influence a variety of biological responses in the body. Various studies revealed that a decreased level of GSH and elevated level of GSSG were also reported in humans to expose to high altitudes these are a good indicator of oxidative stress (Gaur et al. 2021). ROS are waste products of cellular oxidative metabolism (Halliwell 1989). They play critical roles as secondary messengers. However, increased ROS production overwhelms the antioxidant scavenging capability, resulting in oxidative damage to DNA, lipids, and proteins, as well as cellular damage (Bredesen 1995).

The brain also contains low to moderate levels of enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, which are involved in the metabolism of reactive oxygen species (ROS) (Kankofer 2001; Işlekel et al. 1999; Dringen et al. 2000). The presence of iron in the brain and particularly in areas such as globus-pallidus and substantia nigra may also be contributed to the production of ROS.