Role of Genomics, Proteomics, and Antioxidant Interventions in Preventing High Altitude Sickness

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Abstract

Some individuals become sick on spending some time at low atmospheric pressure which is above 1500 m (5000 feet), i.e. flying in a plane or climbing a mountain at high altitude. One of the three forms of high altitude sickness, i.e. AMS (acute mountain sickness having life frightening complications), HAPE (high altitude pulmonary edema, a non-cardiogenic form of pulmonary edema occurs due to excessive hypoxic pulmonary vasoconstriction which can be fatal if not recognized and treated promptly), and HACE (high altitude cerebral edema, a potentially fatal sickness characterized by ataxia, decreased consciousness, and characteristic changes on magnetic resonance imaging) may develop in an individual when they spend 1–5 days to altitudes ⩾2500 m. Nowadays, there is an increasing population of visitors to ski resorts and mountains because of which milder forms of illness may occur at more moderate altitude. Problems experienced by a passenger when they fly in newer planes at 2440 m (8000 feet) which is higher equivalent cabin altitude than the earlier designs, can also be understood due to these research. In this chapter, the role of genomics, proteomics, and antibiotics interventions towards high altitude sickness is briefly discussed.

Keywords

High altitude · Acute mountain sickness · High altitude pulmonary edema · High altitude cerebral edema

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11.1 Introduction

The condition hypobaric hypoxia which in some cases accelerates the chain of some physiological responses that will help the individual to adapt and tolerate the low availability of oxygen at high altitude but in other cases maladaptive responses takes place which in return causes AMS, HAPE or HACE (Luks et al. 2017). Among millions of people who visit high altitude every year, many of them suffer from AMS (acute mountain sickness), HACE (high altitude cerebral edema), and HAPE (high altitude pulmonary edema) which are all life threatening sickness with varying symptoms (Moore 1987).

The ambient pressure is higher at lower latitudes, and lower in summer as compared to winter. AMS (acute mountain sickness) increases with the low pressure weather because temporary weather patterns also affect pressure (Zafren and Honigman 1997). The heart rate is much higher with the faster climbing as compared to planes take off (McFarland 1953). Heart rates are related with higher altitude on mountains, i.e. the heart rate will increase by 52% at 9000 feet (2700 m) and 72% at 12,000 feet (3700 m) (Saito et al. 2000). The rate of breathing is increased continuously on climbing and it remains upraised (Zafren and Honigman 1997). There is also an increase in blood flow within the eye and the blood vessels present in the retina of eye also swell (Botella de Maglia and Martinez-Costa 1998; Frayser et al. 1970).

There are some changes that are not considered as pathological, i.e. disturbed breathing during sleep, increased urination even at night, shortness of breath during excretion, quick breathing, weird dreams are all normal at altitude but changed patterns of sleep can overtire the climbers (Dietz 2001). The person feels suffocated or awakes suddenly due to restlessness within the period when breathing ceases (Curtis 1995).

Oxygen shortage imputes decline in night vision which can further be restored within some minutes by inbreathing pure oxygen (Heath and Williams 1995). When people reach 8200–10,000 feet (2500–3000 m), they got fainted and they recover quickly and stand up immediately after eating without any further complications (Bezruchka 1994). On flights, fainting is most common medical incidents which contain 15–35% medical problems on boarding (Donaldson and Pearnt 1996; Harding and Mills 1993).

At 6500 feet (2000 m) altitude, the penetration of ultra-violet irradiation is 50% higher than at sea level which will ultimately increase the problems of eye damage and sunburns (Heath and Williams 1995). At 10,000 feet (3000 m) altitude faster climbing shows a remarkable effect in difficult mental tasks (McFarland 1953). At 5000 feet (1500 m), the reaction time was noteworthy high (22%) on investigation (Ernsting 1978). At 11,500 feet (3500 m), latency becomes high in the sounded invoke potential (Mukhopadhyay et al. 2000).

Above 2500 m altitude individuals get affected from AMS (acute mountain sickness). Figure 11.1 shows various symptoms of acute mountain sickness such as excessive flatulating, headache, loss of appetite, nose bleeds, palpitations, peripheral edema, persistent rapid pulse, pins and needles, shortness of breath, etc. (Roach

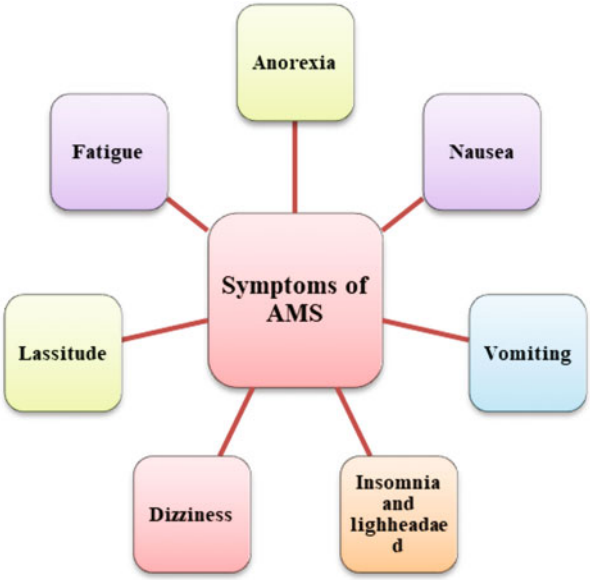

Fig. 11.1 Symptoms of acute mountain sickness

et al. 1996). The pathophysiology of AMS is uncertain (Kallenberg et al. 2007). The Lake Louise AMS symptom score and Environmental Symptoms Questionnaire help in measuring the severity and incidence of AMS (Roach et al. 1993). Every individual has different susceptibility towards AMS, few people may develop HACE and HAPE it is left untreated and some of them may not be highly affected by the primary symptoms.

It is recommended that acetazolamide (125–250 mg), two times a day starting from 24 h before climbing till few hours after subsiding to prevent AMS; although rest, immediate dropping and supplemental oxygen are known for best cure of AMS (Queiroz and Rapoport 2007). 750 mg of acetazolamide is most effective in treating AMS but acetazolamide (500 mg) was rejected for the treatment of AMS as it is ineffective. According to some researchers' dexamethasone is considered better for treating AMS, 8–16 mg of dexamethasone is equally effective as 750 mg of acetazolamide for treating AMS above 4000 m altitude (Dumont et al. 2000).

The maximum growth of pathological incidents that starts during AMS is known as HACE (high altitude cerebral edema). During AMS, there is an accumulation of extravascular fluid in brain which further increases due to climbing causing various symptoms (as shown in Fig. 11.2) like ataxia, coma, convulsions, and death. The major precaution to cure from AMS is taking rest at that altitude or immediate descent of at least 1000 m other than the pharmacological treatments.

The accumulation of extravascular fluid in alveolar airspaces of lung is known as HAPE (high altitude pulmonary edema). There are various symptoms of HAPE (as shown in Fig. 11.3) which includes tachycardia, dyspnea, tachypnea, cough, and pink frothy sputum associated with heavy breathing are the major stamp of HAPE. 30 mg PO of nifedipine every 12 h during climbing is the most commonly utilized

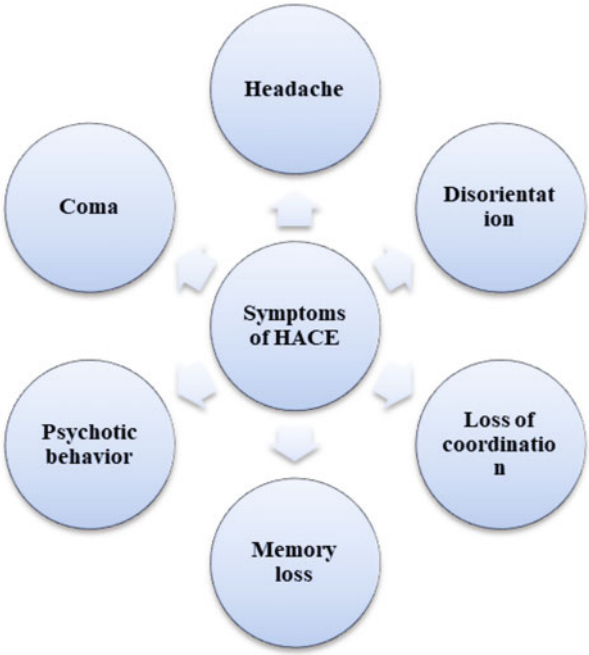

Fig. 11.2 Symptoms of high altitude cerebral edema

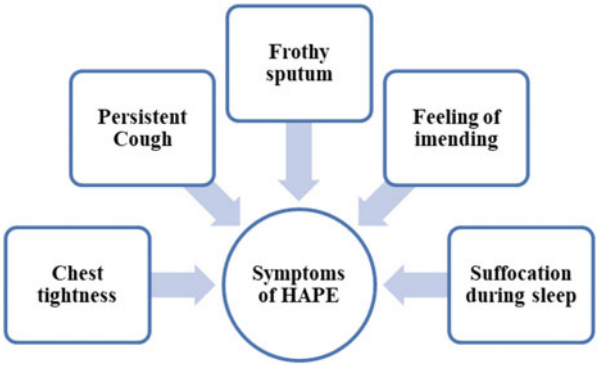

Fig. 11.3 Symptoms of high altitude pulmonary edema

intervention for treating HAPE. Recent additions like tadalafil, with a longer half-life and sildenafil (both are phosphodiesterase inhibitors) are also utilized extensively. Nowadays, a new inhalable medicine is prescribed, i.e. Salmeterol (Pennardt 2013).

11.1.1 Role of Genetic Factors Towards High Altitude Sickness

There is no direct relation between susceptibility and gene polymorphisms till now and there is insubstantial data available about the role of genetic factors on high altitude sickness. Susceptibility of HAPE is linked with gene polymorphisms of

endothelial nitric acid synthase only in Japan (Droma et al. 2002) but not in Europe (Weiss et al. 2003). There is no direct relation between ACE (angiotensin-converting enzyme) genes polymorphisms with susceptibility to HAPE but ACE gene polymorphisms may give out performance significance at high altitude (Dehnert et al. 2002a). According to the preliminary data, diseases like primary pulmonary hypertension and HAPE have different genetic bases but both disease susceptibilities share some common physiological relationship (Dehnert et al. 2002b).

Genome is not just a constant blueprint for organismal and cellular structure, function, and development on comparing human proteome and metabolome. There are several processes that play a crucial role in production to regulate alternate mRNA splicing, histone modifications, microRNAs, modulation of transcription factor activity, single nucleotide polymorphisms (SNPs), and tissue and response specific gene expression including promoter methylation (Kirby et al. 2007). In order to investigate the genome, technologies are improving with the greatest level of sophistication. High resolution analysis of chromosomal abnormalities, location analyses (to measure transcription factor binding activity), microRNA activity, SNPs, splice variants, and targeted and global analyses of DNA methylation patterns are all allowed and investigated by bead-based and microarray platforms, expression analyses. Due to hypoxia, there are various changes in gene expression (Storey 2006). Because of hypoxia, the gene expression of several microRNAs is upregulated (Kulshreshtha et al. 2007). Several functional classes show impact on expression of genes by microRNAs, i.e. apoptotic signaling and cell cycle regulation. In the hypoxic pathways, traditionally hypoxic genes were examined but with the use of these techniques several other new genes were also identified which was not implicated previously. As per this study, strength of genomic mechanisms is illustrated like the potential of analyzing various related and non-related molecules at the same time with various conditions. Key components can easily be identified and biochemical processes can be explained. All such limitations will be undoubtedly resolved with the growth of these powerful technologies.

11.1.2 Role of Proteomics Towards High Altitude Sickness

Two basic workflows are being generally focused by the study of proteomics profiling: (1) to resolve and relatively quantitate proteins with mass spectrometry known as 2DE (two-dimensional gel electrophoresis) or (2) metabolic and post-metabolic labeling and non-labeling methods known as quantitative mass spectrometry (Bowler et al. 2006). Either a light tag which is hydrogen or a heavy tag which is deuterium are the two samples which are being used in labeling of peptides in one mode of post-metabolic labeling. Mass spectrometry is used to measure the amount of relative peptide and to detect the mass difference between these two peptides while proteins are also being identified simultaneously. Cells are cultured in media which contains variants of amino acid within the typical metabolic labeling, e.g. 13C/15N-labeled arginine, which is incorporated into the entire cell proteome. Three states of arginine can be compared and their three different masses can be

utilized such as Arg10 (13C6 15N4), Arg6 (13C6 14N4), and Arg0 (12C6 14N4). Several alternatives of these systems already existed which comprise the involvement of back end and front end fractionation/separation of proteins and peptides. Eventually, proteins are being identified with the help of mass analysis and upcoming database search. Significance of these workflows is that they have the strength to detect high amount of proteins without depending on gel-based methods which are discounted several protein classes, i.e. proteins found in membrane proteins and low abundance. Urine (low molecular weight and high salt protein) found in bio-fluids can make 2DE an unacceptable method. There are some consistent results which are observed between 2DE and labeling methods (Agarwal et al. 1995).

For clinical assays, there are several methodologies that have been used but there is no development of such method that can successfully analyze the whole proteome, i.e. urine proteome or human plasma and there is no validation of biomarkers for hypoxia till now. Focusing on the dynamic nature of human bio-fluid proteomes for more longitudinal studies, the available data on large-scale study of proteomics could be interpreted (Ommen 2005; Adachi et al. 2006). Only limitation related with proteomics is that there is a comprehensive shortage of sensitivity of the currently accepted analysis. Targeted analyses depending on antibodies which are sensitive but are difficult to develop into high yielding screens at the time of lack of antibodies and the selectivity of methods may sometimes not be appropriately examined (Anderson 2005). Analysis that depends on single biomarkers may not be as productive as those which contain panels of metabolites and proteins. Panels help in reducing the effect of normal variations between individuals but panels are also less vulnerable to noise than the single protein biomarkers.

There is a solution to overcome this problem is the use of mass spectrometry technique which is most used nowadays for analysis of small molecule known as multiple reaction monitoring (MRM). MRM consists of 13N and 15N stable isotope labeled artificial peptide as internal standards, quantitation of peptides, expected proteins, using mass spectrometry. The areas beneath peaks of endogenous and labeled peptides are analyzed, showing quantitative results and labeled and endogenous peptides are all analyzed by MRM. Antibody-based assays are not capable in differentiating between protein isoforms but MRM is more accurate method. Apo lipoprotein A1 with CV $<4\%$ is quantified by Barr et al. (1996); larger scale proteomics study has been done by (Gygi et al. 1999); and C-reactive protein in patients with rheumatoid arthritis was analyzed by Kuhn et al. (2004). A detailed review of MRM technique can be studied from Wright et al. (2005).

Immunoassays are highly specific and sensitive and antibody arrays (restricted by the quantity, quality, and availability of antibodies) which may be utilized for such high yielding screens (Hultschig et al. 2006). If it is unknown that either the proteins are capable biomarkers then it is restricted to develop antibody-based assays for large number of proteins in terms of money and time.

11.1.3 Role of Antioxidants Towards High Altitude Sickness

Phyto-extracts are most commonly used antioxidant against hypobaric hypoxia to enervate the oxidative stress caused by it at high altitude. Natural origins become favorite for the researchers because of their several qualities like biocompatibility without the need of much safety testing at high doses, easy availability, no need of medical supervision, and decreased requirement for synthesis. There are various phyto-extracts with significant effects on redox stress within the hypobaric hypoxia manifestation including, but are not restricted to, *Bacopa monniera* extracts (Hota et al. 2009), *Ginkgo biloba* extracts (Karcher et al. 1984; Oberpichler et al. 1988; Gertsch et al. 2004; Moraga et al. 2007; Hoyer et al. 1999), *quercetin* (Pandey et al. 2012), and *Withania somnifera* (Bhattacharya and Muruganandam 2003; Baitharu et al. 2013). Some other substances from natural or synthetic origin that are efficient against hypobaric hypoxia influenced oxidative stress are alphalipoic acid, alpha-ketoglutaric acid (Bailey and Davies 2001), acetyl-L-carnitine (Devi et al. 2007; Barhwal et al. 2009), ascorbic acid (Farias et al. 2010), Ceftriaxone (Hota et al. 2008), *Gabapentin* (Jafarian et al. 2008; Kumar and Goyal 2008), and 5-hydroxymethylfurfural (Gatterer et al. 2013; Zhang et al. 2015).

Problems with current pharmacological interventions like contra-indications in individuals with ongoing cardiac, hepatic, and renal conditions, cost, risks of over-dosing and medical supervision for use, and side effects are all can be controlled with the use of phyto-extracts. A novel stable aqueous suspension of micronized silymarin (SMN) is developed by all such efforts done. There are no side effects of SMN that are known and it has tolerance values reaching higher than 10 g/kg (oral; dogs) and 300 mg/kg (single IV bolus; dogs) (Arya et al. 2015). This dosage of SMN is reported safe for humans with 35 formulations (complex with higher cost) that are already marketed as a hepato-protective oral supplement having no problems related with cardiac and renal insufficiencies (Dixit et al. 2007). The rodent lung was protected from HH-induced oxidative stress with the usage of SMN and gets inflammated at 50 mg/kg/day with single oral doses repeated over 5 days (Paul et al. 2016). According to the previous study which shows several benefits and efficiency of SMN against HH-induced oxidative stress and inflammation, it is proven that SMN can be marketed in place of other current pharmacological interventions specifically in those individuals who are suffering from hepatic and renal problems.

11.2 Conclusion

Recently, development of powerful technologies takes place for inexpensive, large-scale producing, and widely utilized process for discovery. But according to the past research, the application and development of such process have been reported complicated for practical use which includes various reasons such as high variability seen in metabolomes of human populations, cost, and lack of comprehensive technical platforms which give amazing data sets. Modern analysis methods have

several limitations like high cost related with cutting-edge techniques, lack of validation, low sample numbers, poor reproducibility. Additionally, experimental variability effects have not been globally identified. In order to apply and integrate such technologies to relevant disease states that there is a need of well-characterized samples from specifically stratified patient cohorts, which in exchange requires strong association between the basic scientist and clinician. If all these things are in place, it is more challenging to perform bioinformatics and statistical analyses because of examining multiple data sets simultaneously.

The only treatment of high altitude sickness is immediate descent from the altitude, rest at that altitude, and supplemental oxygen to prevent from any form of HAI (high altitude illness). Undoubtedly, high altitude illness (HAI) is a present known danger to all the visitors who move towards high altitude. Interventions utilized to treat high altitude sickness are efficient but they remain mounted with side effects and contra-indications.

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