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Review article

Diagnosis and prophylaxis for high-altitude acclimatization: Adherence to molecular rationale to evade high-altitude illnesses

Subhojit Paul, Anamika Gangwar, Kalpana Bhargava, Pankaj Khurana, Yasmin Ahmad*

Peptide & Proteomics Division, Defence Institute of Physiology & Allied Sciences (DIPAS), Defence R&D Organization (DRDO), Timarpur, New Delhi 110054, India

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ABSTRACT

Lack of zero side-effect, prescription-less prophylactics and diagnostic markers of acclimatization status lead to many suffering from high altitude illnesses. Although not fully translated to the clinical setting, many strategies and interventions are being developed that are aimed at providing an objective and tangible answer regarding the acclimatization status of an individual as well as zero side-effect prophylaxis that is cost-effective and does not require medical supervision. This short review brings together the twin problems associated with high-altitude acclimatization, i.e. acclimatization status and zero side-effect, easy-to-use prophylaxis, for the reader to comprehend as cogs of the same phenomenon. We describe current research aimed at preventing all the high-altitude illnesses by considering them an assault on redox and energy homeostasis at the molecular level. This review also entails some proteins capable of diagnosing either acclimatization or high-altitude illnesses. The future strategies based on bioinformatics and systems biology is also discussed.

1. Introduction

High altitude areas have become focal for both leisure and adventure travel, attracting millions of visitors each year. Both the leisure and adventure travelers, as well as the deployed security forces in these areas, seek out uncharted pristine territory which requires high levels of cognitive and physical function. High-altitude areas are inversely related to high-level cognitive and physical performance [1,2]. High altitude areas, apart from the difficult terrain and uncomfortable weather conditions, also expose one to hypobaric hypoxia (HH). HH, on its own, can cause notable decreases in cognitive and physical functions. If unattended, these decreases become severe enough to cause maladies like Acute mountain sickness (AMS) and High altitude pulmonary/cerebral edema (HACE/HAPE), collectively referred to as High altitude illnesses (HAI).

The preferred treatment for HAI is either immediate descent, supplemental oxygen or both [3,4]. But in practical life and death situations, both can be difficult to administer. Thus, to prevent such a situation from occurring many pharmacological interventions like nifedipine, dexamethasone and tadalafil have been advocated and marketed. Such interventions, although useful for most of the high-altitude visitors, are contra-indicated for individuals suffering from cardiac, renal and hepatic issues. Also, all such interventions require proper medical supervision for prescription and dosing with both over and under dosing causing harm [5]. Over the years, many solutions have been proposed which circumvent the issues related to both faster acclimatization and better side-effect free prophylaxis.

The treatment options mentioned above are useful only when there is quick and accurate detection of HAI, preferably before descent and oxygen are essential. As an aside, the incidence rates for AMS are reported to be 75% (Finnish Kilimanjaro trekkers, altitude attained 4730 m)-10% (Nepali Himalayas, 3000–4000 m group); with most studies showing AMS incidence increases with both high rate of ascent and the altitude obtained [6–12]. Mt. Kilimanjaro trekkers are reported to have a high incidence of AMS, with most researchers concurring that rapid ascent in this region due to socio-economic reasons is the culprit [6,9]. Basnyat has compiled various studies to give the range of HAPE/HACE incidence as between 2% to 31% [13]. Currently, diagnosis is based generally on consensus clinical parameters, which maybe subjective to some extent, e.g. Lake Louise self-scoring criteria for AMS. The current impetus, thus, is also towards ensuring a more objective assessment of HAI and acclimatization, before clinical symptoms like pulmonary and cerebral edema manifest themselves. In this regard also, the authors' lab has made considerable progress towards blood plasma based diagnosis of acclimatization/HAI as well as providing a novel method for faster acclimatization [14]. This short review aims to present the notable advances made in the twin areas of biomarker discovery and prophylaxis/therapy for high-altitude. We first introduce the various HAI concisely, discussing their current diagnosis and treatment options. To conclude, we present the newer advances

* Corresponding author.
E-mail address: yasminchem@gmail.com (Y. Ahmad).

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towards faster diagnosis based on molecular perturbations and side-effect free methods of prophylaxis with smaller doses and shorter dosing regimens. An overriding insight across the various aspects of HAI and acclimatization is that managing redox and energy homeostasis is sufficient to prevent HAI and assure acclimatization.

2. Acute mountain sickness

Acute mountain sickness (AMS) affects individuals above 2500 m elevation. Its symptoms include general fatigue, headache, nausea, vomiting, palpitations, persistent rapid pulse, loss of appetite, excessive flatulating, insomnia, dizziness, peripheral edema, pins and needles, nose bleeds and shortness of breath [15]. The pathophysiology of AMS remains unclear [16] and according to a popular theory of tight-fit hypothesis which suggests that increased brain volume with hypobaric hypoxia elevates intracranial pressure and, when accompanied by impaired or diminished intracranial buffering capacity, contributes to the development of the symptoms that define AMS [17]. The incidence and severity of AMS can be measured by Environmental Symptoms Questionnaire and the Lake Louise AMS symptom score [18]. Different individuals have different susceptibility to AMS. Some may not be highly affected by the primary symptoms while others may develop HAPE and HACE if left untreated.

2.1. Current prescribed treatment

Although immediate descent, supplemental oxygen and rest are still considered the best treatment, acetazolamide at 125 mg–250 mg twice daily starting from 24 h before ascent till few hours after descent to either prevent AMS is the most recommended [19]. Acetazolamide 750 mg has been proven effective for treating AMS. Also, 500 mg acetazolamide was categorically rejected as ineffective for treating AMS. Some reports suggest dexamethasone to be better at treating AMS. In the same study, dexamethasone 8–16 mg was found to be equally effective as 750 mg acetazolamide in treating AMS above 4000 m [20].

3. High altitude cerebral edema

High altitude cerebral edema (HACE) is considered the extreme escalation of pathological events that began during AMS. Extravascular fluid accumulation in the brain begins during AMS. Further ascent causes greater fluid accumulation leading to coma, ataxia, convulsions and death. Thus, apart from pharmacological interventions, the primary focus for anyone diagnosed with AMS should be either rest at that altitude or descent of at least 1000 m. Once HACE occurs, the only true treatment is rapid descent [21]. Maximal HACE incidence is reported to be 31%(Gosainkund, Nepal, 4300 m) by Basnyat et al. [10]. The pharmacological alternatives are just to help the person survive. Nonetheless, pharmacological alternatives should be provided immediately to either prevent or delay HACE symptoms, with focus being on prevention.

3.1. Current prescribed treatment

The primary rescue medicine for HACE beyond 3000–4000 m is dexamethasone [22], when rapid descent is a difficulty due to weather and terrain during long excursions. Acetazolamide and nifedipine both are useful in preventing HACE, at concentrations similar to those taken for preventing AMS. Hyperbaric therapy, immediate descent and supplemental oxygen remain the mainstay in treating and resolving HACE cases.

4. High altitude pulmonary edema

High altitude pulmonary edema (HAPE) is the extravascular fluid accumulation in alveolar airspaces of lung. Pink frothy sputum combined with labored breathing are the hallmarks of HAPE accompanied by cough, dyspnea at rest, tachycardia and tachypnea. It usually occurs above 2500 m upon 1–3 days of arrival. Cold ambient temperatures, rapid ascent rate (> 500 m/day), vigorous physical exertion, hampered pulmonary system (due to pulmonary infection and hypertension) and being male with previous history of high altitude illness are considered pre-disposing factors for HAPE incidence [23]. HAPE incidence is reported to be between 6.4%–0.4% (based on individual's age being over or below 20 years) by none other than Hultgren himself [24]. Other authors have stated the same to be 5% [10]–1.9% [12]. Although descent, supplemental oxygen and rest thereafter are critical for resolving HAPE, the adjunctive interventions cannot be left out.

4.1. Current prescribed treatment

Nifedipine (30 mg PO every 12 h during ascent) is the most widely used intervention for preventing HAPE. Phosphodiesterase inhibitors like sildenafil and tadalafil are also used extensively and they are quite recent additions. Tadalafil with a longer half-life is more commonly used. Salmeterol, a new inhalable drug, is also being prescribed nowadays [25].

5. From physiological to molecular: changing perspectives

Physiologists approached high altitude illnesses via categorizing them between lung or brain. When viewed from the prism of molecular events, it is obvious that all these diseases may be linked to each other more than expected previously. All acute high-altitude illnesses show extravasation of fluids into the extracellular spaces, whether in brain or lung. Bao et al. reported that some Chronic Mountain Sickness (CMS) patients have deranged cerebral hemodynamics and cerebral edema linking CMS and HACE [26]. Bailey et al. report that AMS and HACE are better explained by the interactions between free radicals and the trigeminal system rather than classical edema of the brain [27]. Also, there is offset redox balance in above mentioned tissues evident from the increased levels of oxidative damage products (TBARS, 8-OHdG) and free radicals (ROS) upon exposure to hypobaric hypoxia [28–30]. Hultgren et al. reviewed the medical records of 150 HAPE patients in Colorado Rocky Mountain ski area and found that 14% had symptoms of cerebral edema [31]. Lt. Col. A. Chawla reported that 41% of HAPE patients in Western Himalayas had mild to severe AMS symptoms and though the two don't share a common pathophysiology, Lake Louise scores showed AMS co-existed with HAPE in these patients [32]. Further, oblique evidence can be derived from the efficacy of a common drug (e.g. dexamethasone) for all high-altitude illnesses [33]. Thus, future interventions will be targeted at overcoming the systemic molecular events that result in such pathophysiologies summarily rather than categorizing medicines to be effective against a single illness. The future may view AMS, HACE and HAPE through the lens of molecular/omics data as branches of the same tree, i.e. systemic redox imbalance due to hypobaric hypoxia exposure.

Notable advances have been made in providing proof-of-concept regarding agents and modalities for treating the redox imbalance caused due to hypobaric hypoxia. These may become future prescriptions for faster, safer acclimatization to high altitude. The next two sections will focus on: a) the probable biomarkers for hypobaric hypoxia and b) the prophylactics and therapeutics with potential to prevent HAI.

6. Biomarkers reflecting high-altitude maladies and acclimatization status for high-altitude hypoxia

The term biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (NIH Biomarkers Definitions Working Group, 1998) [34].