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Mal-Adaptation of Adaptive At High Altitude

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Abstract: ***Hypoxia or Oxygen deficiency, contributes significantly to the pathophysiology of many human diseases. High altitude is one such kind of environment where hypoxia is a major stress. The changes in the physiology at high altitude, whether short term or long term, help the successful survival of people from thousands of years. This suggests their adaptation to the adverse environment of high altitude. However the course of adaptation for one trait might be ill-intentioned for another but in term of disease acquisition adaptation is more poisonous. A better understanding of the fundamental physiological, molecular and genetic basis for adaptation to low-oxygen environments of high altitude will help us pointing out the maladaptiveness of adaptive traits to high-altitude hypoxia in humans which arise during the course of adaptation to high altitude. The current review is pointing out few of the adaptive traits at high altitude which also has maladaptive effects as an inherent aspect of adaptation.***

Keywords: Hypoxia, Adaptation, Mal-adaptation,

1. Introduction

Oxygen is indispensable for life progression. Oxygen deficiency alters number of pathways and contributes significantly to the pathophysiology of many human diseases. High altitude induced hypoxia is one of the major stresses which is not subjected to any kind of behavioral buffering and technicality. In this fraction of adaptation physiological alteration is the most important factor. However the adjustment to hypoxia, like any other new environmental condition, is via short term acclimatization or long term adaptation. Adaptation is gradual alteration in the body systems and made adjustment more pronounced and permanent. There were number of studies on high altitude natives devoted for adaptive aspect, but the maladaptive perspectives of these adaptive traits are still unknown. A better understanding of the fundamental molecular and genetic basis for adaptation to low-oxygen environments will help us develop therapeutic strategies to prevent or treat diseases that have hypoxia as a major part of their pathogenesis. The current revolution of genomic technology has advanced our understanding of the genetic basis of many diseases and conditions, including hypoxia tolerance and susceptibility. In this perspective, we point out the maladaptiveness of adaptive traits to high-altitude hypoxia in humans which arise during the course of adaptation to high altitude.

2. Maladaptation of Adaptive

For acclimatization and/or adaptation to hypoxia, physiological alteration is the most important factor. The changes in the physiology at high altitude, whether short term or long term, help the successful survival of people from thousands of years [1]. This suggests their adaptation to the adverse environment of high altitude. However the course of adaptation for one trait might be ill-intentioned for another hence in term of disease acquisition adaptation is more poisonous (Fig.1).

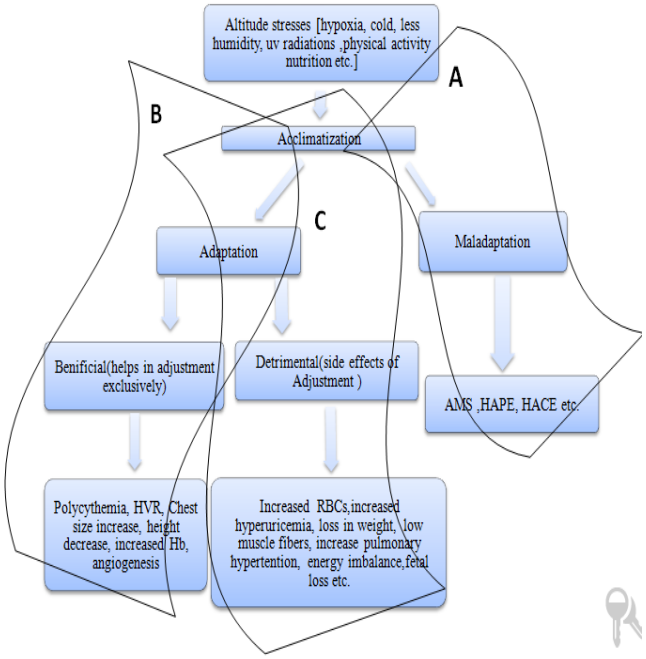

Figure 1

This figure indicating the process of adaptation via acclimatization with example of high altitude stresses. Acclimatization is short term adjustment to any noble environment and is either adaptive or maladaptive. **A**. represent the maladaptive aspect of high altitude encounter via acclimatization **B**. representing the obvious beneficial aspect of adaptation proceeding acclimatization at high altitude and **C**. representing the most important and most neglected aspects; the non beneficial aspects or side effects of adaptation. Before assigning a trait the status of completely adaptive, it is essential to observe its side effects.

Let's start with example of Oxygen transport cascade. At high altitude the atmospheric Partial pressure of Oxygen is lower and falls at each consecutive step in the O_2 transport cascade. The first physiological adjustment to compensate this reduced pressure gradient at HA is the increase in depth and rate of breathing, which results in an increased alveolar ventilation. Although hyperventilation is adaptive since it increases the arterial O_2 levels, it is also maladaptive because

the hypoxia induced decrease in $PaCO_2$ at the alveolar level induces blood alkalization. Prolonged alkalosis is not compatible with normal body homeostasis, as it impairs several functions, including those of the CNS [2]. Prolonging alkalosis also induces sleep disorder [3]. The reduced oxygen content of the blood (hypoxemia) induces breathing instability and high-altitude sleep disturbances [4].

In order to compensate for the low ambient oxygen levels and inadequate tissue oxygenation, erythropoietin (EPO) secreted by the kidneys and liver is up-regulated to increase the red blood cell production **(Polycythemia)**. Polycythemia at high altitude normally reported in terms of increased hematocrit (greater than 48% in women and 52% in men) or hemoglobin (greater than 16.5g/dL in women or greater than18.5 g/dL in men) or red blood cell count above the normal limits. However this aspect of polycythemia is adaptive but there are also maladaptive aspects of polycythemia. Polycythemia leads to iron deficiency and also results in increased uric acid levels (hyperuricemia) caused by increased cell turnover [5]. Polycythemia also affects the reproductive system as a significant inverse relationship was observed between hemoglobin and progressive sperm motility [6]. The hyperviscous blood also lead to pulmonary hypertension, symptoms of cerebral hypoperfusion, and eventually right heart failure and death. Studies conducted in Peru and Tibetan revealed that uric acid levels tend to increase with rising hematocrit and are significantly greater at high altitude compared with those living at sea level [7,8]. Moreover, subjects living at high altitude have a low fractional excretion of uric acid despite the high serum levels of uric acid [8]. Hypoxemia generated lactate will compete with the excretion of urate at the proximal tubule, resulting in a decrease in urate clearance and cause frequent hyperuricemia at high altitude. This increased uric acid in blood is might be related to the disease especially, like joint pains or gout generally present in high altitude people. Interestingly, the higher prevalence of hyperuricemia associated with both the presence of microalbuminuria and systemic hypertension [7]. These findings expand on the laboratory finding that experimental hyperuricemia can induce systemic and glomerular hypertension and microalbuminuria in animals. Taken together, these observations at high altitude, polycythemia, hyperuricemia, systemic hypertension, and Microalbuminuria were suggesting a new clinical syndrome that is called high altitude renal syndrome.

Upon initial exposure to HA the reduced O_2 content of the blood, increases resting pulse rate rapidly. However with acclimatization, despite the increase in sympathetic nerve activity, heart rate and cardiac output tend to fall [9]. This decline in cardiac output appears to be associated with a decrease in heart rate which usually remains above sea level values and has been attributed to increased vagal input and down regulation of number of adrenergic receptors [9, 10]. However this decline in cardiac output is adaptive, but it causes pulmonary hypertension (**PH**). The reason might be hypoxic pulmonary artery vasoconstriction and loss of plasma volume which result in the reduction of this preload of less cardiac output [9, 11]. Studies in Tibetan and Andean highlander suggest that the prevalence of hypertension is similar, or higher than in people living at the sea level.**PH** is a different measurement altogether from systemic blood pressure. It reflects the pressure that heart must exert to pump blood from the heart through the arteries of the lungs. If exaggerated, however, it is associated with important morbidity and mortality. Recent mechanistic studies have provided insight into the importance of vascular and respiratory epithelial nitric oxide (NO) synthesis, increased endothelin-1 bioavailability, and over activation of the sympathetic nervous system in causing exaggerated hypoxic pulmonary hypertension in humans. **PH** might be considered another defining feature of high altitude renal syndrome, caused in part by uric acid–mediated suppression of pulmonary vascular endothelial cell NO production and breakdown of arginine, the nitrogenous substrate for NO formation. The fetal programming of pulmonary vascular dysfunction in children and offspring of preeclampsia represents a novel and frequent cause of pulmonary hypertension at high altitude. Epigenetic mechanisms are also operational in the fetal programming of pulmonary vascular dysfunction in humans.

At high altitude in hypoxic environment for the maintenance of all the vital processes of the body, more energy must be required. This energy expenditure or **Energy** balance could be maintained through **Basal Metabolic Rate (**BMR). BMR is the largest component of daily energy expenditures. After few days at high altitude BMR was elevated by about 10-17%. However increased BMR is the adaptive feature to counter the energy imbalance at high altitude but there are also number of maladaptive aspects. There is a negative energy balance due to a combination of decreased energy intake and increased energy expenditure. Increased basal metabolic rate is one of the proposed causes of **weight loss** at HA and having detrimental effects on muscle structure and leads to a marked decrease in muscle fiber density [12, 13, 14,15,16]. The cost of meeting tissue O2 requirement is competitive with other body functions that represent a compromise between the respiratory stimuli, which is aimed at increasing blood alkalosis in order to optimize the O_2 transport system and the metabolic adjustment.

3. Conclusion

All the evidences listed above suggest that while adaptations facilitate the survival, it also creates disadvantageous effects. The saying that “one pays a price for everything” is relevant to the process of adaptation. Till date, high altitude studies focused only for adaptive aspect both physiologically and/ or genetically. They found genetic and physiological basis for most of the adaptive traits. But there is a maladaptive aspect of these adaptive traits which is still unknown. The above listed situations are the some of the maladaptive aspects of adaptive traits at high altitude which questions the adaptation in terms of diseases acquisition. There might be more such conditions which in one aspect is adaptive but in other maladaptive. There is a need to explore such kind of situations because maladaptations seem to be an inherent aspect of adaptation.

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