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REVIEW PAPER

Nutritional Requirement at High-altitude with Special Emphasis to Behaviour of Gastro-intestinal Tract and Hormonal Changes

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ABSTRACT

When people are exposed to the extreme environmental conditions, such as high altitude where there is decrease in temperature and partial pressure of oxygen induces fatigue, insomnia, loss of appetite and increased cardiac output. Hence there is need to improve the appetite through the diet and digestion clout of the individual. In the present review paper the efficiency of digestion is compromised at high altitude is discussed. Also about, Hypoxia, resulting by decreased partial pressure of oxygen can be classified into acute hypoxia and chronic hypoxia based on the exposure time. There is increased formation of reactive oxygen species due to less oxygen available in the air at high altitude which leads to oxidative stress. Lipid peroxidation caused by oxidative stress. Hypoxia is mediated through hypoxia inducible factors which maintain oxygen haemostasis in the body. At high altitude diet rich in carbohydrates have been found to be beneficial as it increases glucose metabolism. Requirement of nutrients such as vitamin A, vitamin E and vitamin C as well as micronutrients such as zinc, iron, selenium, copper and manganese will be required at high altitude. Hypoxia effect on the intestine leads to malabsorption and the lipid storage is stimulated and lipid catabolism is inhibited through β-oxidation.

Keywords: High faltitude; Hypoxia; Oxidative stress; Acute mountain sickness; Hypoxia-inducible factors; Normoxia; Nutrition

1. INTRODUCTION

Humans are able to survive in almost all the environmental extremes of Earth due to their physiological adaptability and/or by modification of environment itself. Some of the extreme environments are deserts, humid forests, hot humid coastal regions and high altitude (HA). High-altitude presents an extreme environment with hypoxia, cold, high solar radiation as physical stresses beside the psychological stress[1]. HA is defined to begin at 2,400 m above sea level. The air pressure decreases as the altitude increases which leads to hypoxia or oxygen deprivation (Fig. 1).

The human body can adapt to high altitude through short-term and long-term acclimatisation. Acute mountain sickness (AMS) occurs on short-term exposure to high-altitude due to low partial pressure. AMS can further lead to high altitude pulmonary edema (HAPE) and High altitude cerebral edema (HACE)[2]. Chronic mountain sickness (CMS) occurs after prolong stay at high altitude which leads to polycythemia[3] and hypoxemia[4]. Some of the common problem faced by people ascending high altitude are loss of appetite, fatigue, breathlessness, insomnia, abdominal pain, constipation, nausea, blisters in hands and feet[5] as shown in Fig. 2.

Hypoxia is a condition which occurs on oxygen depletion. Due to the lack of oxygen there is an increase in the breathing rate and sleep cycle is affected[6]. In addition, the heart rate increases and digestive efficiency of food is reduced, as the body suppresses the digestive system in favour of increasing its cardiopulmonary reserves; there is a decrease in the amount of blood flowing to digestive organs and increased blood to the brain, heart and lungs[7].The glucose is metabolised by liver cells but is not able to utilise it. Associated with the depression of liver function will be a significant decrease in its ability to rid the body of metabolites or conjugate steroids. Very little work has been done on the effect of hypoxia on digestive system in a person ascending high altitude.

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2. TYPES OF HYPOXIA

Hypoxia is a condition which arises by low oxygen tension (PO_2) created either by environmental conditions like exposure to high altitude, or by pathological conditions such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea or severe anemia[8]. The traditional classification of hypoxia has only two subgroups based on empirical observations i.e., chronic and acute hypoxia (Fig. 3). Acute hypoxia response occurs within minutes of exposure to a hypoxic environment i.e., symptoms occur in first few hours–days. Some of the symptoms are hyperventilation, insomnia, fatigue, dizziness and gastrointestinal disturbances. In chronic hypoxia, the term 'chronic' is used to indicate the time interval which ranges over weeks and months. However long term adaptation to hypoxia has been studied in human populations in Himalayas, Ethiopian and Andes over generation[9].

According to Best and Taylor[10] hypoxia is classified into four main type's i.e., Hypoxic hypoxia, anemic hypoxia, stagnant hypoxia and histotoxic hypoxia as shown in Fig. 4.

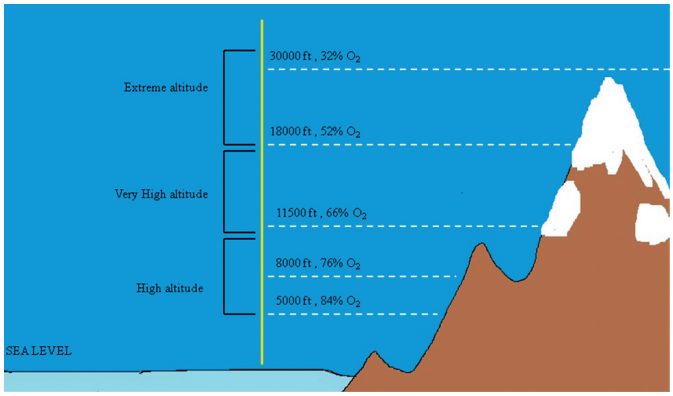

Figure 1. Classification of high altitude and percentage of oxygen available.

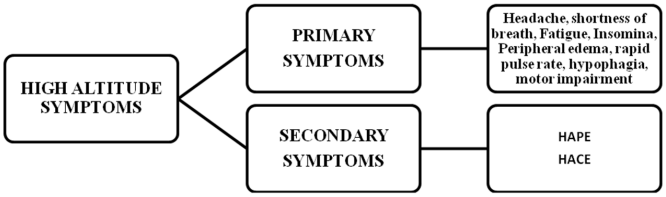

Figure 2. Symptoms experienced at high altitude.

Note: Symptoms experienced at HA can be classified into two types, i.e. primary symptoms or acute mountain sickness (AMS) such as headache, difficulty in breathing, fatigue, sleeplessness, peripheral edema i.e. swelling of hands, feet and face, rapid pulse rate and decreased food intake. The secondary symptoms are life threatening. High altitude pulmonary edema (HAPE) is accumulation of fluid in the lungs and high altitude cerebral edema (HACE) is swelling of the brain which if not treated leads to coma or death.

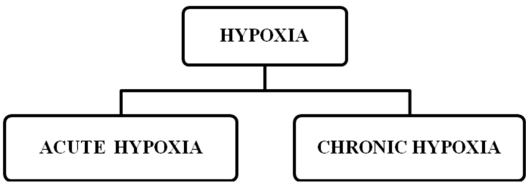

Figure 3. Types of hypoxia.

Hypoxic hypoxia is caused when there is low oxygen tension in the inhaled air as a result of which the haemoglobin present in the erythrocyte cannot saturate the fully saturate with oxygen leading to lack of oxygen in arterial blood. This is one of the most serious forms of hypoxia. Anemic hypoxia is a less serious condition than hypoxic hypoxia and it may be caused by an insufficient transport function of the haemoglobin. Stagnant/ Circulatory hypoxia arises when the amount of oxygen reaching the tissue is inadequate. This turn leads to reduced rate of blood circulation thereby allowing accumulation of carbon dioxide in the tissue. Histotoxic hypoxia is a condition where there is normal amount of oxygen in the blood and under normal tension but the cells are unable to accept oxygen from the capillaries. It may be produced by any agents that depress cellular respiration.

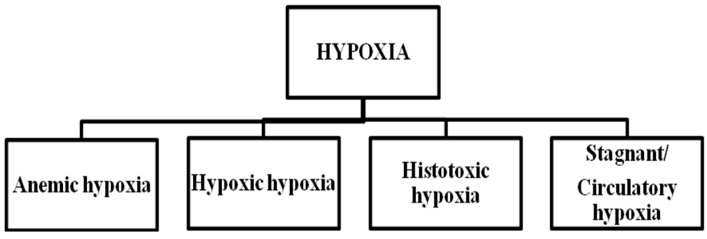

Figure 4. Classification of hypoxia based on exposure.

3. HIGH ALTITUDE AND HYPOXIA

According to the observations made on humans a HA there is an initial weight loss and some of the factors that affects loss of weight are dysbarism, negative nitrogen balance, altered nutrient digestibility, increased water loss, increased energy expenditure, hypophagia, intestinal malabsorption[11] and change in hedonicity and taste perception[12]. There is an increase in metabolic rate at high altitude[7]. There are reports which confirmed by functional magnetic resonance imaging (fMRI) study that neural circuit for food craving on prolonged exposure to HA is reduced[13].

Exposing the lowlanders to HA is a useful model in getting insight into physiological responses in humans to hypoxia. In normoxic condition, the heart produces an abundant supply of ATP for fat oxidation. While in hypoxic condition, there is a decreased proportion of energy reliance on fat oxidation and the use of carbohydrate increases as the energy metabolism turns anaerobic[14]. Hypoxia under severe condition has shown to stimulate glucose transport across plasma membrane[15]. There are studies which report that high carbohydrate diets are beneficial at high altitude due to its high respiratory coefficient (RQ) compared to protein and fat. Diets high in carbohydrates have shown to enhance glucose metabolism[16]. Fat malabsorption[17] is significant only at altitudes below 5000 m.

At HA there is increased formation of reactive oxygen and nitrogen species (RONS) due to decrease in pressure which leads to increased oxidative damage to macromolecules. The oxidative stress can further be enhanced through physical exercise at high altitude for which supplementation of antioxidant seems to prevent or decrease high altitude associated oxidative stress[18]. On the contrary, there are studies which suggest that supplementation of antioxidant supplementation does not attenuate HA related oxidative stress[19-20]. The human body on ascent to HA oxygen consumption increases to generate energy to meet body requirements. Due to low oxygen availability, reactive oxygen species (ROS) accumulates in mitochondrion as oxygen available is less to be reduced to water. ROS together with nitric oxide (NO) in vasculature combine to form reactive oxygen and nitrogen species (RONS). Exposure to high-altitude also leads to imbalance in the levels of vasoactive modulators which leads to generation of more ROS/RONS. This in turn leads to vascular dysfunction i.e. narrowing of lumen, smooth muscle proliferation and vasoconstriction exaggeration, which aggravates imbalance in vasoactive modulators and ROS/ RONS. Thus, this vicious cycle of oxidative stress goes on until the subject receives medical help (Fig. 5).

4. HYPOXIA PATHWAY

When the level of oxygen in the air is low, the wall of Aorta (carry oxygenated blood) has chemoreceptor which detects oxygen level in the blood. There are sensory nerves

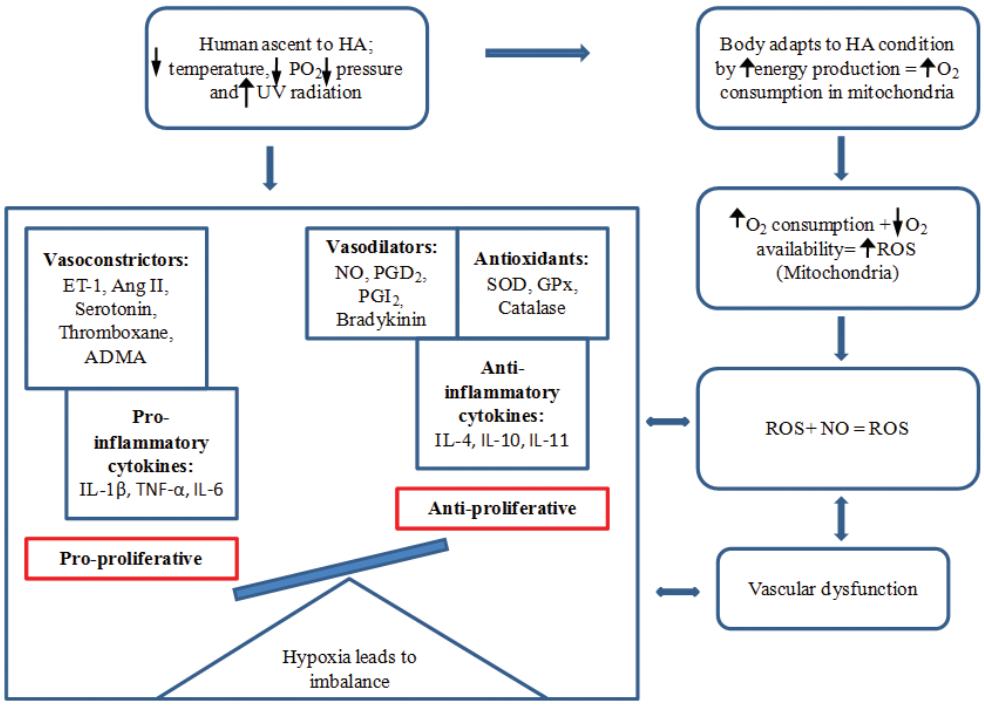

Figure 5. Oxidative stress at high-altitude.

which connect the aorta to the brain stem in medulla oblongata and carry information about the arterial blood. The carotid artery branches into internal and external carotid artery. The internal carotid artery carries blood to the brain while external carotid artery supplies blood to the neck and face. The carotid body receives blood from external carotid artery and detects the oxygen level. Internal carotid artery has chemoreceptors in carotid sinus which is more sensitive than aorta. The carotid sinus and the carotid body together sense the amount of oxygen and send the signal to medulla oblongata. The medulla oblongata contain sensors i.e., cardiac sensors, respiratory sensors and pulmonary vasculature which in increases the sympathetic outflow leading to increased heart rate, increased cardiac output and increased breath rate and constriction of peripheral vessels[21].

The critical mediators of adaptive responses to hypoxia have been identified as the hypoxia-inducible factors (HIFs), which regulates the expression of genes responsible for growth, vascular development and metabolism. HIF-1 belongs to family of oxygen-sensitive transcription factors[22]. HIF-1 is found in all nucleated cells which are highly conserved and it is regulated by the oxygen available. HIF-1 is a heterodimer, composed of HIF-1α and HIF-1β (Fig. 6(a)). It belongs to the PER-ARNT-SIM (PAS) subfamily of the basic helix-loop-helix (bHLH) family of transcription factor. Under normoxic/ normal condition, HIF-1 dimer does not exist as the HIF-1α produced has a half life of less than 5 min. The HIF-1β is constitutively present and HIF-1α level is very low. HIF-1α is degraded by proteosome system only in the presence of oxygen. In the absence of oxygen it cannot be degraded. HIF-1α (826 amino acids) at the N-terminal consists of bHLH and PAS for heterodimerisation and DNA binding. It also has oxygen dependent degradation domain (ODDD) which contains two sub domains N-ODDD and C-ODDD. They have two proline residues i.e. Pro 402 and Pro 564 which are hydroxylated in normoxia. At the C-terminal it has two terminal-transactivation domains (TAD) i.e. N-TAD and C-TAD which are involved in transcriptional activation during hypoxic condition (Fig. 6(b)). The hydroxylation of proline is catalysed by Prolyl hydroxylase domain (PHD) or hypoxia inducible factor –prolyl hydroxylase (HPH). To the hydroxylated proline residue von Hippel-Lindau (pVHL or VHL) tumor suppressor protein binds. VHL protein comprises of E3 ubiquitin ligase, which targets protein for proteosome degradation[23].

Under hypoxic condition, the HIF-1α is not degraded. HIF-1α translocate to the nucleus to form a dimer with HIF-1β. In association with p300/ CBP (cAMP –response element- binding protein), it binds to hypoxia response elements (HREs) in their upstream regulator region up regulating the expression of HIF-target genes such as vascular endothelial growth factor (VEGF), erythropoietin (EPO), and glucose transporters (GLUT) and key glycolytic enzymes, including hexokinase[24] as shown in Fig. 6(c).

The other pathway that affects the HIF-1 transcriptional activity is through the phosphatidylinositol 3-kinase/AKT pathway which influences HIF-1α levels through transcriptional regulation (in contrast to the proteasome degradation pathway) via the downstream effector mammalian target of rapamycin which inhibits FKBP12 rapamycin associated protein (FRAP)[25]. Genes that are up-regulates the increase of HIF-1α production and/or stability are cobalt chloride ($CoCl_2$), Human epidermal growth factor receptor 2 (HRE2), Insulin like growth factor (IGFR), Epidermal growth factor receptor (EGFR) and Proto-oncogene tyrosine-protein kinase (SRC). Genes that down-regulate factors HIF-1α production and/or stability include Phosphatase and tensin homolog (PTEN) which inhibits Atk (Protein kinase B) , Factor inhibiting HIF-1 (FIH-1) which inhibits HIF-1 transcription factor and specific drugs such as LY294002 which inhibits PI3K[26] as shown in Fig. 7.

5. NUTRITION AT HIGH ALTITUDE

The human habitation goes up to an altitude of 4300 m and the Indian soldiers are deployed to an altitude of 5800 m for fixed tenure. High altitude presents physical and psychological stress. The availability of drinking water is scarce and at the high altitude the vegetation is sparse. The boiling point of water is decreased due to reduced barometric pressure there by making preparation of food difficult. Studies have reported that there is reduction in meal size with increase in meal frequency and rapid satiety[27]. The diet rich carbohydrate are found to be beneficial at high altitude as they have a respiratory co-efficient

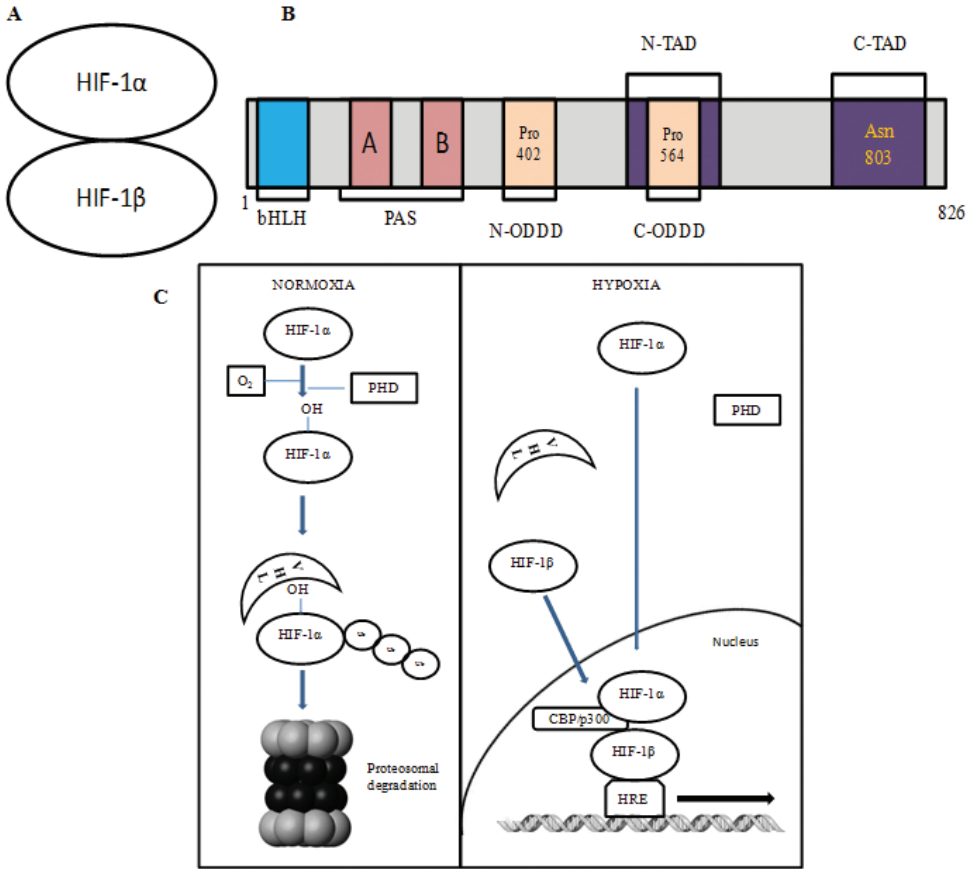

Figure 6. (a) Hypoxia inducible factor 1 (HIF-1) (b) Structure of HIF-1α (c) Effect of hypoxia.

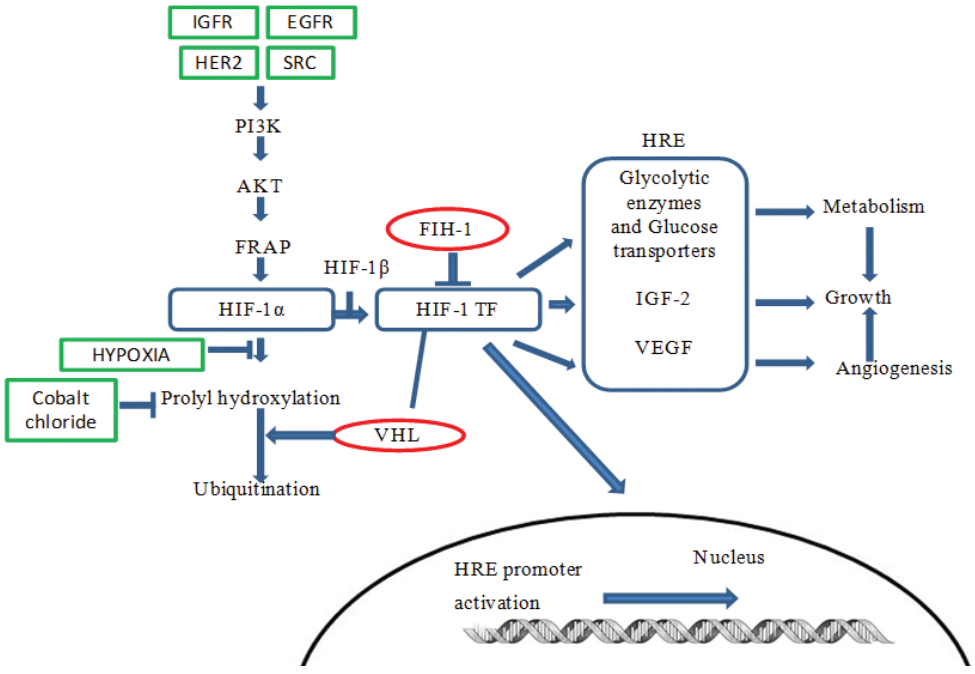

Figure 7. Regulation of HIF-1α.

around 1 compared to fat (0.7) and protein (0.8-0.9).The diet rich in carbohydrate are found to enhance glucose metabolism and it serves as fuel for thermogenesis. The intake of food may decrease due to anorexia but it does not affect absorption[28]. The diet rich in fat have been observed to increase cold endurance and tolerance in experimental animals[29]. At the initial stages of acclimatisation there is weight loss i.e. loss of body water due to decrease in food intake which causes a drastic reduction in lean body mass[30-32] and reduction of body fat due to the mobilisation of fatty acids from triglycerides pool of adipose tissue and it is measured by reduction in skin fold thickness[33].

Exposure to altitude causes hypohydration, caused by increased diuresis and decreased water intake. Negative nitrogen balance have been reported at high altitude but this report is not reliable as the calorie intake was less[34]. To achieve a positive nitrogen balance the minimum intake of protein should be 0.96 g/kg for exercising men but there is increased excretion of protein and nitrogen at high altitude hypoxia[35]. During prolonged stay at an altitude of 3500 m - 4000 m, positive nitrogen balance was maintained with decreased amino acid excretion. The entry of amino acids into neural tissues and brain is modulated by the relative concentration of specific amino acids in the blood. So it would be ideal to design food with high tryptophan food to alleviate sleep disturbance, higher glutamic acid food for deterioration in cognitive function and higher phenylalanine/ tyrosine for hindering mood depression for high performance at high altitude[36]. Supplementation of branched chain amino acids such as leucine, isoleucine and valine have been reported to prevent muscle loss during trekking at high altitude[37]. In order to reduce lipid peroxidation caused by oxidative stress the supply of nutrients such as vitamin A, vitamin E and vitamin C as well as micronutrients such as zinc, iron, selenium, copper and manganese may be required in a greater amount at HA[1].

6. GASTROINTESTINAL TRACT AT HIGH ALTITUDE

The primary functions of the gastrointestinal tract are

the absorption of ingested nutrients, removal of waste, fluid homeostasis and protection from pathogens[38]. The barrier function and the absorptive function of the epithelium of intestine is regulated based on oxygen availability as regulators of hypoxia i.e PHD and factor inhibiting HIF1 (FIH1) are expressed in the intestinal mucosal tissue[39]. At high altitude, as the core body temperature decreases the gastrointestinal smooth muscle motility decreases which further leads to distension of colon, reduced gastrointestinal secretion and free acid production. Hypothermic condition leads to decreased splanchnic blood flow and causes a catecholamine-induced vasoconstriction of blood vessels. As the catecholamine secretion decreases leading to vasodialation it results in reperfusion and extravasation of blood. The reperfusion and associated changes alter the gastric mucosa's protective mechanism, resulting in cellular damage induced by hydrochloric acid. The liver cells cannot utilise glucose but they continue to metabolise them. The depression of liver function leads to decrease in its ability to rid the body of metabolites, drugs, or conjugate steroids[40].

There are reports which suggest that hypoxia effect on the intestine which leads to malabsorption[41] and there is no change in fat utilisation[42] up to an altitude of 4700 m. Up to an altitude of 3500 m the concentration of gastric acid, and total acid output, is reduced significantly in basal conditions. However; there is no change in maximal levels, using pentagastrin stimulation. The gastrointestinal function is not altered in terms of digestion and absorption of food components[43]. Reports on the gastrointestinal function on an altitude above 5000 m are sparse.

7. HORMONAL LEVEL AT HIGH ALTITUDE

The hypoxic effect at cellular level are thought to be mediated by the hypoxia inducible factor-1 (HIF-1) pathway[44], and hypoxia-response elements (HRE) have been identified for erythropoietin (EPO), vascular endothelial growth factor-A (VEGF) and leptin[45]. Hypoxia-inducible factor is regulated through oxygen-dependent proteasomal degradation and it responds to variations in oxygen availability. VEGF expression in skeletal muscle increases after exercise and it is a potent stimulus for angiogenesis. Its expression at HA is crucial to promote muscle capillarity during training[46]. Leptin is produced by adipose tissue and is a major regulator of satiety and food intake[47-48]. Studies in humans at HA or mice exposed to hypobaric hypoxia have reported increased, unchanged or decreased leptin levels[49]. Little is known about changes in leptin after acute exercise at HA[45]. Literature on ghrelin in high altitude is sparse and inconsistent, with reports of both decreased ghrelin levels and no change in ghrelin at high altitude[50]. Studies report increased level of cholecystokinin (CCK) at high altitude[51].

In most studies there have been increased level of thyroid hormones at high altitude, although report suggest that TSH secretion is not modified but the mechanisms involved in this process are still unclear[52]. The insulin level is increased during elevated glucose circulation and it functions to suppress the hepatic glucose output. The insulin level was found to be elevated in hypoxic condition[53]. Glucagon levels have been reported to be unaltered at HA[54]. Corticosteroids, have a well documented immunosuppressive effect which are released during cold stress, hypothermia, or both[55].

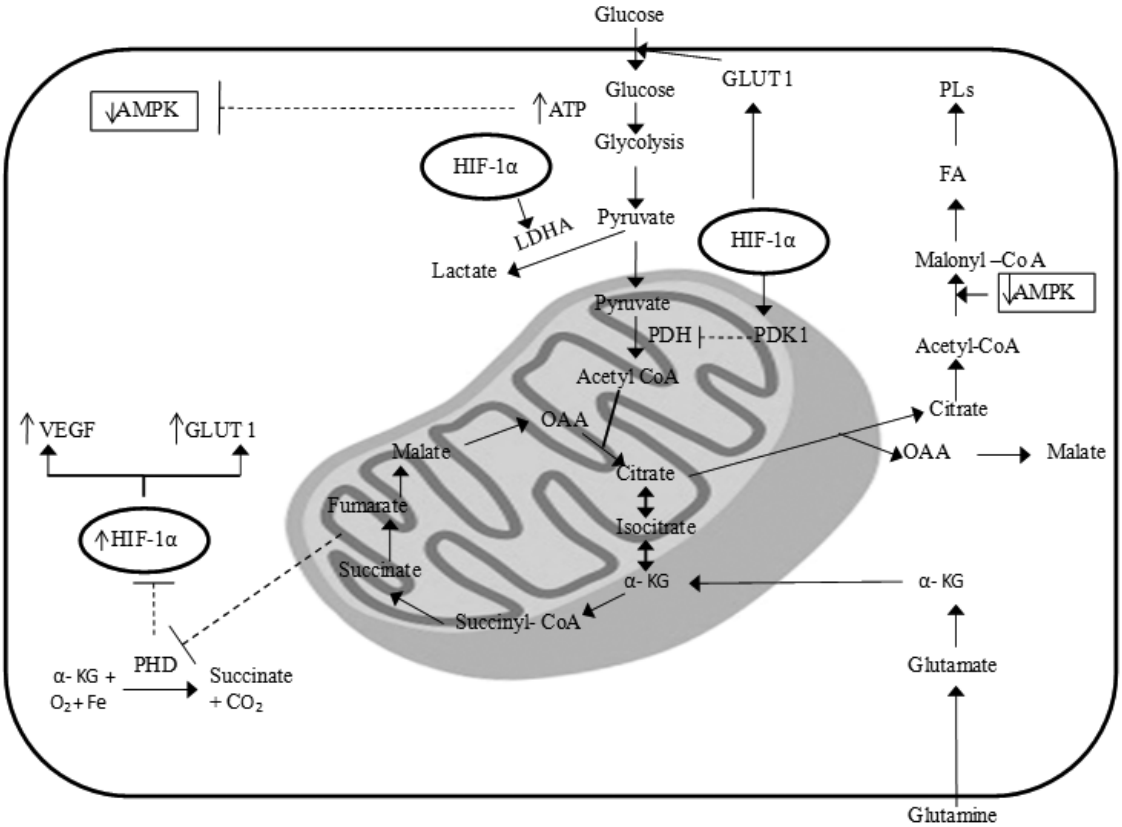

Figure 8. Enzymes at hypoxic condition.

8. ENZYMES AT HIGH-ALTITUDE

Hypoxia, in general results in an increased level of blood haemoglobin and increased hematocrit values leading to increased oxygen capacity. As oxidative pathways are limited at altitude, there is a shift toward anaerobic energy sources. At any given work level, lactic acid production is higher than at sea level. The HIF-1 have been proved to (a) induce a variety of glycolytic enzymes and glucose transporters such as aldolase A and pyruvate kinase M, which help produce energy in hypoxic condition[56-58] (b) reduce mitochondrial oxygen consumption by activating pyruvate dehydrogenase kinase I(PDK1) and halts citric acid cycle[59] as shown in Fig. 8. HIF 1α encodes PDK1 which suppress oxygen consumption[60]. I Disaccharidase activity (lactase, at least) is HIF-responsive, which may protect carbohydrate absorption at moderate altitudes. In hypoxic condition the level of 2, 3-bisphosphoglycerate is found to be increased due to anaerobic glycolysis. At hypoxic condition the lipid storage is stimulated and lipid catabolism is inhibited through β-oxidation[61].

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