# IMPACT OF HYPOBARIC HYPOXIA ON THE PATHOPHYSIOLOGY OF GI SYSTEM : EVALUATION OF THE ROLES OF INDIGENOUS MICROBIOTA

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**High altitude expedition is characterized by a cluster of acute or chronic physiological complications including gastrointestinal hazards, and often called as high altitude sickness (HAS). This environment has an extraordinary stress by the assemblage of reduced air volume with low oxygen concentration, reflected solar light with radiation and increased air current with low temperature. The exclusive criterion, hypobaric hypoxia causes a mild to serious peril to nearly all lives. In spite, the interests of mountain tourism and the practice of sports are gaining massive importance at high altitude area recently. A range of symptomatic and asymptomatic gastrointestinal (GI) disorders are very common in such expeditions. The emerging and surprising consideration of recent time is that gut is our 'second brain' as its functions are reportedly entangled with the virtual brain. The cross talk between the flora and host are mediated via enteric nervous system and ultimately controlleds the physiological wellness of the host. This review mainly highlights about the impact of high altitude expeditions on the microbial structure of gut as well as the gut health. Therefore, the goal of the present report are: (1) to summarize the main adaptations of the body at high altitude, introducing the concepts of altitude sickness and oxygen free radicals and their relation; (2) to propose a mechanism of action in the development of the pathology due to alteration of indigenous gut microbiota at this environmental stressed condition.**

Modern science popularizes the term 'gut health', as it is evident by its more frequent use in the scientific literatures and popular health related articles. In Asian mythology, gut health is a central theme which recognizes the abdomen as the location of the soul. Japanese describe our largest organ as "Honored middle" (onaka) and "centre of the spiritual and physical strength" (hara), whereas Europeans describe it as a simple digestive system.

In 400 B.C., Hippocrates alleged that "...death sits in the bowels..." and "...bad digestion is the root of all evil....". The contribution and importance of the intestinal activities has long been recognized in human health and diseases (Sekirov *et al.*, 2010). In nineteenth century, Louis Kuhne theorized that specific food types are responsible for bacterial overgrowth and could initiate the diseases. Few years later, Elie Metchnikoff (1908) popularized the idea that fermented milk products could beneficially alter the microflora in the gut. He believed that many diseases, and even aging itself, took place due to putrefaction of protein in the bowel

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by the intestinal bacteria (Hawrelak and Myers, 2004). Present day research identifies the functional role of microbes on the dynamic gastrointestinal environment and also traced the path of pathogenesis of some diseases (Pimentel, 2012). A number of workers pointed out that microbial colonization in gastrointestinal tract affects animal behavior and central nervous system's (CNS) function via bidirectional neuronal circuits signaling mechanism (Collins and Bercik, 2009; Neufeld and Foster, 2009; Rhee *et al*., 2009; Heijtz *et al*., 2011; Lee and Chua, 2011).

It is well known that human gut contains vast and complex microbial consortia. Bacteria are the predominant habitat and this consortium is composed of 500 different species belonging to more than 50 genera. Estimated number of viable microorganisms that present in adult human gut is about 1014 per 200 – 400 $m^2$ area (epithelial surface) which is nearly ten times more than the number of eukaryotic cells present in the human body. Virtually, they are called as the 'microbial organ' – an organ similar in size to the liver (1.0-1.5 kg in weight) and functionally, too. They instruct the immune and physiological function throughout life (Rhee *et al*., 2009).

The dynamic microbial population inside the gut are tightly regulated and balanced in a steady state conditions. Breakdown of this stable microbial homeostasis leads to several gastrointestinal illness, like, diarrhea, inflammatory bowel diseases (IBD), Crohn's disease (CD), ulcerative colitis (UC), cholelithiasis, endotoxemia, liver cirrhosis, obesity, allergy, diabetes, familial mediterranean fever (FMF), autism, small intestine bacterial overgrowth (SIBO), fibromyalgia, pancreatitis, atherosclerosis, etc (Sekirov *et al*., 2010). There are many factors like host genetics, mood of birth delivery, age, sex, life style, sexual behavior, geographical location, diet and neutraceuticals, medications, steroid intake, antibiotic treatment, blood pH, hormonal level, etc. have the potentialities to dysregulate the microbial homeostasis in intestine. Besides, the environmental atmospheric pressure also plays an important role in changing their population steadiness. Availability of oxygen in atmosphere is also a discriminating factor of modification of microbial shape in intestine.

Generally, people face various physiological problems when they move above the sea level (hypobaric hypoxic conditions), these are collectively called as acute mountain sickness (AMS). Cardiac, respiratory and neurologic symptoms are more common among high altitude climbers. Besides, gastrointestinal disorders, like, indigestion, nausea, gastric acidity, acute diarrhoea with or without vomiting, excessive bowel and flatus formation, colon inflammation, epigastric pain, constipation, occult blood in stool, peptic ulcers, dyspepsia, haematemesis, mareo, puna, soroche, acosta's disease, piles, etc are also very common (MacInnis *et al*., 2011).

Microbes are the predominant mentor of patho-mechanical status of gut. Apprantly, continuous border line of gut epithilia makes a boundary beween eukaryotic and prokaryotic horode. Microbes normally reside over this boundary line and control the health and diseased conditions of gut in an intricate utmost way. The functional aspects are greatly influenced by the temporal and spatial compositions of microbiota. The specific lack is that we know very little on this functional facets which are under the control of numerous host dependent and independent physic-chemical factors. The present review thus concentrate on the impact of hypoxia on the gastrointestinal pathomechanism created during high altitude climbing.

***High altitude climbing and physiological disorders***

Mountains cover one-fifth of the earth's surface; 38 million people live permanently at altitudes ≥2400 m, and 100 million people travel to high-altitude locations each year. High altitude environment is characterized by extreme stresses with the assimilation of reduced air volume with low oxygen concentration, reflected solar light with radiation, increased air current with poor temperature. All these conditions make the environment inhabitable for long term staying at high altitude. In spite of this extra-terrestrial uniqueness, people executed these high lands for the long term tenancy and become more common for recreation and adventure purposes. Astronauts, skiers, fliers, rope divers, religious pilgrims, trekkers and climbers, military personnel, dwellers deployed to high-altitude and are all at risk of developing different types of symptomatic and non-symptomatic high altitude sickness. Barometric pressure declines exponentially on ascent. As pressure declines, gas volumes increase and so a fixed volume of gas contains fewer molecules. Thus, although the percentage of oxygen in air remains constant at 20.9%, the partial pressureof oxygen in inspired air falls progressively. This causes a reductionin the pressure gradient for oxygen from the inspired gas to the tissues and hence into mixed venous blood.Therefore, ascent to altitude is a specific, hypobaric, cause of hypobaric hypoxia (Bailey *et al.*, 2004).

The high altitude sickness (HAS) can be broadly categorized into - (i) acute mountain sickness (AMS), characterized by varying degrees of headache, sleep disturbance, fatigue, shortness of breath, dizziness, and GI disturbances; (ii) high-altitude cerebral edema (HACE), characterized by a change in neural and mental status and/or ataxia; (iii) high-altitude pulmonary edema (HAPE), characterized by dyspnea, bronchitis, cough, and decreased exercise tolerance; and (iv) other high altitude - related symptoms (HARS) including multiple organ dysfunction syndrome (MODS) (Kayser *et al*., 2010). Altitude illness is likely to occur above 2500 m but has been documented even at 1500–2500 m. Of the thousands of high altitude travellers trekking in the Himalayas each year, approximately 50% develop symptoms of AMS when travelling to elevations greater than 4000 m. As one ascends from sea level the principal challenges to traveler arise from an exponential fall in atmospheric pressure and a drop in temperature. The four key physiological challenges during acute exposure to altitude are: hypoxia (and hyperventilation), gas volume changes, decompression sickness and cold. The environmental stress of high altitude is hypoxia that, in turn, creates the conditions for physiological hypoxia (less than the normal amount of oxygen in the organism). The severity of high-altitude hypobaric hypoxia is also associated with low temperature and dehydration (Reeves *et al*., 1993). Hypoxaemia is a common consequence of critical illness, may be caused by low fractional inspired oxygen tension, hypoventilation, ventilation/ perfusion mismatch, limitation of diffusion of oxygen across the alveolar–capillary membrane, respiratory alkalosis (Semenza, 2000; LaManna *et al*., 2004). Hypoxaemia may also occur due to decreased tissue oxygen delivery associated with microcirculatory dysfunction, or may occur via alterations in cellular energy pathways and mitochondrial function, resulting in a decreased ability to utilize the available oxygen (classical oxygen cascade) – a phenomenon termed cellular dysoxia (Reeves *et al*., 2001). In tissue level, hypoxia may act through a variety of pathways in signal transduction, in particular through the excessive activation of reactive oxygen species (ROS) (Schoene, 2000), which can also increase the expression

level of several cytokines and amplifying their inflammatory effects (Grover and Bartsch, 2001). Due to the imbalance between the pro-inflammatory and anti-inflammatory media and the release of a large number of oxygen-derived free radicals and lysosomal enzymes, alteration of buffering capacity of cell (due to insufficiency of oxygen), the endothelial cells (fast growing cells) and parenchymal organs in mucosal and sub-mucosal layers are mostly affected and damaged by hypoxic shock (Wagner, 2001; Schoene, 2000). For this reason, acute mountain sickness is generally regarded as non-infectious inflammatory disease (Schoene, 2008).

High altitude induced hypoxia plays a critical role in regulating many important signalling molecules and its functions in the physiological system (Beall, 2002; Vogeletal., 1986). Low barometric pressure at high altitude causes higher expression of hypoxia inducible factor (HIF). Hypoxia inhibits prolyl hydroxylation of HIF1a resulting in aggregation of a functional heterodimeric transcription factor (bothHIF1 and HIF1 subunits).One of the major proteins encoded by its target protein is a vascular endothelial growth factor (VEGF). A large volume of literature interprets, oxygen sensitive HIF1 subunit and VEGF are modulated in the hypoxic exposure; therefore, elevated level of HIF1 and VEGF is necessary to validate hypoxic animal models. Moreover, a well-known protein mechanism, chaperone systems are stress responsive and act as a stress sensor to link stress signalling process with protein homeostasis (Kumaretal., 2007). Hypoxia has also been reported to be accompanied by the behavioural deficits due to reduced motor activities. One of the earliest effects of hypoxia on neuronal function is to slow down of synaptic transmission, whereas chronic hypoxia results in neuronal death (Jonasetal., 2005; Niquet etal., 2003). MacInnis *et al*., 2011 have identified sixteen genes for association with AMS and variants in eight showed positive associations suggesting that AMS is an environmentally mediated polygenic disorder.

***Gastrointestinal disorders during hypobaric hypoxia***

Although cardiac, respiratory and neurological symptoms are more common among mountaineers and persons from lowland going to the high altitude, little work has been done on the effect of hypoxia on digestive system in either patients with altitude illness or in healthy individuals at high altitude (Ilavazhagan *et al*., 2001). Gastrointestinal problems at high altitude are commonplace for short-term visitors, long-term residents and native highlanders (Roche and Romero-Alvira, 1994; Suter and Kalra, 2011). In fact, symptoms of the digestive system such as anorexia, epigastric discomfort, epigastralgia, high altitude flatus expulsion (HAFE), heart burn, dyspepsia, nausea, severe acidity, vomiting, constipation, infectious diarrhea, haematemesis, piles and peptic ulcers are frequently found in mountaineers and altitude sojourners (Dallimore *et al*., 2002; Harris *et al*., 2003; Sadnicka *et al*., 2004; Skaiaa and Stave, 2006). High-altitude hypoxia causes not only gastrointestinal motility disorders and digestive secretion dysfunction but also pathological injury to the gastrointestinal mucosa. All these symptoms and mucosal damage are not only associated to the breakdown of physiological homeostasis, but also, to the altered metabolic activity at changed intestinal microenvironment. As, the intestinal homeostasis solely rely on the steady state microbial composition, thereby, the dysbiosis at reduced barometric pressure are believed to happen by them (Roach *et al*., 2000; Hackett, 2001; Ri-Li *et al*., 2003).

***Theorizedpath of cause-effect interrelations among brain, gut microbiome and host health at high altitude***

The interaction of microbial species with their host is becoming increasingly important in human health issues. The intestinal epithelium is covered by a wide mucus layer, which harbor an ecological niche of both commensal and pathogenic bacteria. Microbes are closely associated with this layer and can significantly influence the hosts normal health. The hypoxic conditions which are associated with the atmospheric pressure induced numerous gastrointestinal symptoms. These may be related to an imbalance in enteric microbiota could arise from alterations in gas induced gut distention and the modulation of gastrointestinal motility and secretion. The mechanisms that underlie the overgrowth or imbalanced ecology of enteric microbiota and their contribution in different gastrointestinal illness during hypobaric stresses are poorly understood. Several hypotheses could be put forward with the schematic model presented in Figure 1

(a) *Hypoxia induced inflammation in the gut mucosa –*

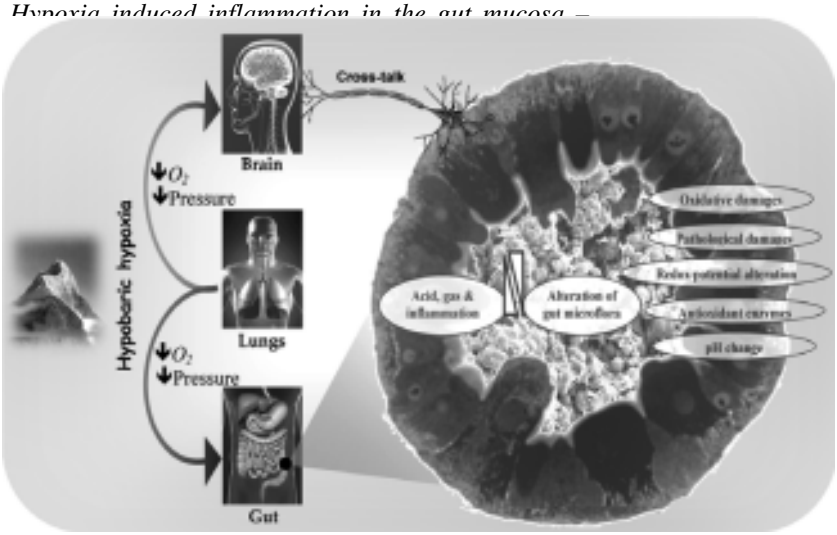


**Figure 1. Schematic diagram showing the multidirectional communication and probable role of hypobaric hypoxia on the modulation of gut pathophysiology.**

Hypoxia induced severe inflammation that leads to damage and necrosis on the mucosal layer of intestine. These affected host-microbes interaction and favours the microbial growth (Kubinak and Round, 2012; Chung *et al.*, 2012).

(b) *Alteration of patho-physiological conditions in the intestinal lumen –*

The prevalence of bacteria in different parts of the GI tract appears to be dependent on several factors, such as pH, peristalsis, redox potential, bacterial adhesion, bacterial cooperation, mucin secretion, nutrient availability, diet, and bacterial antagonism, etc. Evidences revealed that hypoxia suppressed gastrointestinal motility, gastric secretion,

absorption and overall digestive functions (Kleessen *et al*., 2005). This may lead to the breakdown the microbial ecology in the intestine.

(c) *Selection of microbial species and genetic exchange* –

Some microbial species are survived and multiplied in the gastrointestinal tract at hypobaric stresses by evading host and environment originated dual selection pressures. This is mainly achieved by the expression of stress-sensitive elegant proteins and development of extra-chromosomal genetic materials (Nelson *et al.*, 2010). Recipients usually receive these genetic materials from donors and from dead microbial cells via conjugation or transformation. This escorts the growth and/or conversion of other commensals and shapes the changed ecological profile (Jones and Curtiss, 1970; Bailey *et al*., 2006; Zhou *et al*., 2011).

(d) *Brain–gut–enteric microbiota axis* –

The brain can influence commensal organisms (enteric microbiota) indirectly, via changes in gastrointestinal motility and secretion, and intestinal permeability, or directly, via signaling molecules released into the gut lumen from cells in the lamina propria (enterochromaffin cells, neurons, immune cells) (Rhee *et al*., 2009; Grenham *et al.,* 2011). Enterochromaffin cells are important bidirectional transducers that regulate communication between the gut lumen and the nervous system. The brain is one of the most oxygen-sensitive organ of the body, and it is not surprising that neurologic dysfunction is a prominent manifestation of hypoxia associated hypobaric stresses. Both sympathetic and parasympathetic functions are also greatly affected by such conditions. Again both these autonomic nerves control overall activity of the gastrointestinal tract. These interactions may be one of the most influencing domain for alteration of functional aspects of gut microbes.

## CONCLUSION

Very few high quality researches have been documented particularly on the human health and diseases at high altitudes. Most of the studies are evidence andobservation based and relies upon personal experiences. The ‘dysbiosis’ during hypobaric hypoxia is not solely dependent on the physiological imbalances rather it is the outcome of complex entangle between central nervous system (CNS) and altered response of gastrointestinal microbiota. All these have impact about the physiological homeostasis and host health. More adaptive gut microbiota leads a stable microenvironment of gut which is the crucial to maintain the overall physiological homeostasis of hosts. The targeted preventive mechanism is essential to reduce the risks of mountain sickness. Detailed study on that will facilitate to design specific measures that could restore or help to maintain the steady state homeostasis of microbiota as well as good ‘gut health’.

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