Significance of Renin Angiotensin Aldosterone System (RAAS) pathway in High Altitude Pulmonary Edema (HAPE) susceptibility

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Abstract

People living in plains often travel to high altitude regions for trekking, expedition, pilgrimage and deployment. Hypobaric hypoxia is one of the major challenges at high altitude. Since the people living at plains are not accustomed to oxygen scarcity prevailing at high altitude (HA), they often suffer from various high altitude maladies such as acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), high-altitude cerebral edema (HACE) or chronic mountain sickness (CMS). Amongst these, HAPE and HACE are the life threatening diseases are variable and cannot be predicted. The occurrences of these maladies also depend on the rate of ascent and the altitude attained. Study of genetic variations amongst individuals can explain the inter-individual variations in susceptibility to hypoxia and HAPE. The rennin-angiotensin-aldosterone system (RAAS) pathway, which is a major endocrine system, plays a key role in maintaining physiological homeostasis of blood pressure and electrolyte balance in the body. Since HAPE is commonly associated with pulmonary hypertension and elevated capillary pressure, the genetic variations in RAAS pathway could be playing a significant role in susceptibility of an individual towards HAPE. This brief review focuses on the functional relevance of polymorphisms in genes of RAAS pathway as revealed in several genetic studies, in susceptibility towards HAPE.

Keywords
RAAS; HAPE; High Altitude; Polymorphism

Abbreviations
HA: High Altitude, HAPE: High Altitude Pulmonary Edema, HACE: High Altitude Cerebral, Edema, CMS: Chronic Mountain Sickness, RAAS: Renin Angiotensin Aldosterone System, NP: Single nucleotide polymorphism

Challenges at High altitude

Mountains cover approximately one fifth of earth’s surface. These regions are not only a home for millions of peoples but also are very popular tourist attractions. With the improvements in transportation system, access to moderate (2,000 to 4,000 m) and even very high altitudes (5,500 m) has become increasingly convenient. The high altitude region possesses several physiological challenges such as cold chilly winds, dryness, intense solar radiations and oxygen depleted environment known as hypoxia. Majority of people can acclimatize to the inevitable, hypoxic conditions through the process of acclimatization. The acclimatizing mechanisms mainly comprise of short-term hyperventilation and long-term compensation by increased oxygen uptake, transport and increased red blood cell mass, myoglobin, and mitochondria and also hypoxic pulmonary vasoconstriction. Those individuals who cannot acclimatize to HA, may suffer from different forms of high altitude maladies, such AMS, CMS, HAPE, or HACE, collectively known as “Altitude sickness”. The HAPE and HACE are potentially fatal conditions, if the immediate treatment or evacuation is not done. HAPE is the cause of most deaths due to high altitude illness [1]. Some individuals are more susceptible to HA diseases compared to others due to differences in genetic make-up [2], the incidences and severity of these medical complications are highly variable and cannot be predicted. Although numerous studies have been performed to investigate specific genes involved in the patho-physiology of HAPE and variations in multiple genes have been predicted can contribute to the occurrence of HAPE, the genes of RAAS pathway have gained special attention and significance as they are responsible for maintaining the homeostatic balance of our body.
Significance of RAAS pathway

The hypothalamus in brain can sense the concentration of sodium ion and extracellular fluid osmolarity through ion channels. Glomerular filtration rate, the sympathetic nervous system, and the renin–angiotensin–aldosterone system (RAAS) are the major volume effectors in the body. Thirst stimulation, release of the anti-diuretic hormone ADH), vasopressin and the placement of aquaporin water channels in the renal collecting duct to concentrate urine are amongst the major osmolarity effectors. Since RAAS is the major regulator of blood pressure within the human body and HAPE is primarily associated with pulmonary hypertension and elevated capillary pressure [3], RAAS polymorphism study have gained special importance in study of pathogenicity of HAPE. Also, study of RAAS has gained importance in study of hypertension and other cardiovascular diseases [4]. The key effector molecule of RAAS is angiotensinogen, a protein which is produced primarily in liver. In a chain of reactions, angiotensinogen is cleaved by renin (REN), a aspartyl protease, produced by the juxtaglomerular apparatus in the kidney into a 10 amino-acid molecule, angiotensin I. Angiotensin converting enzyme (ACE) cleaves Ang I into a eight amino acid peptide, angiotensin II (Ang II). Ang II acts on the adrenal cortex resulting in release of aldosterone (ALD). ALD in turn acts on the kidneys, primarily on collecting duct cells facilitating the reabsorption of sodium (and chloride). Ang II also has its own independent sodium re-absorptive effects in the kidney and it also acts in brain to stimulate thirst and salt appetite, as well as increases sympathetic tone and acts directly on the vessel wall thus affecting vasconstriction and increasing blood pressure [7].

Renin, a protease synthesized and stored in kidney until released in blood, has a direct effect on the conversion of angiotensinogen to Ang I which is then converted to its active form Ang II by ACE. Angiotensinogen is secreted by the liver whereas ACE is produced by many organs including the lungs, heart and kidneys. Biological activity of Ang II makes it a strong vasoconstrictor. The vasoconstrictor activity of Ang II is several times stronger than that of adrenaline and it can also stimulate aldosterone synthesis which is regulated by aldosterone synthetic enzyme (CYP11B2) to further stimulate water and sodium retention.

Activity of RAAS and HAPE susceptibility

Pathogenesis of HAPE is believed to be a result of interaction of a variety of biological pathways, suggesting a multi gene involvement in altitude. Hypoxic conditions prevailing at HA result in pulmonary vasconstriction which inturn leads to increase in pulmonary vascular resistance. These physiological conditions stimulate RAAS pathway. Common genetic variants in the genes of the RAAS such as renin (REN), angiotensin (AGT), angiotensin-converting enzyme (ACE), aldosterone synthase (CYP11B2) and angiotensin II receptor type 1 (AGTR1) have been investigated in various studies for their association with hypertension and cardiovascular diseases. The possible association of the polymorphisms of these genes with HAPE susceptibility has been suggested by several previous studies. Novel technological approaches, including genome-wide association studies (GWAS) and next-generation sequencing (NGS), are currently being used to identify biomarkers that can predict HAPE susceptibility. The review article is to summarize the current literature on the genetic variants of RAAS genes that have been predicted to be associated with HAPE susceptibility. Single nucleotide polymorphisms (SNPs) in particular which affects concentrations of RAAS enzymes disrupts body’s homeostasis could be contributing towards HAPE susceptibility. Although many studies have suggested that there is a close relationship between the susceptibility towards HAPE and the genetic variants of RAAS, there are few contradictory reports. One of them found that angiotensin converting enzyme activity was unchanged in subjects moving from 700 to 3,800 m [8]. Rapid ascent to HA causes hypoxemia and activates RAAS resulting in increase the activity of renin, Ang II and aldosterone in the plasma [9,10]. Increased production of Ang II in turn affects the systemic arteries and pulmonary vasoconstriction increases pulmonary artery pressure (PAP). Thus HA may directly damage the pulmonary vascular smooth-muscle-cells, which serves to close the membrane K+ channels and leads to cell depolarization. This stimulates the influx of extracellular Ca 2+ influx. Pulmonary vascular endothelial cells produce vasoactive substances that induce pulmonary vasoconstriction and leads to increased pulmonary hypertension [10,11]. Thus hypoxic conditions leading to increased blood pressure induces the renal artery to constrict, increase the aldosterone concentration which in turn causes sodium and water retention. As a result of this there occurs an increase in the pulmonary vascular hydrostatic pressure significantly greater than that of the fluid in the lung. Therefore HAPE occurs when fluid leakage exceeds non-lymphatic transport capacity.

Polymorphisms in RAAS pathway and HAPE

Rate of ascent, altitude reached, pre-acclimatization and individual susceptibility are the major determinants of susceptibility towards high altitude maladies. Human adaptations to HA problems involve a number of physiological changes that facilitate the uptake, transport and delivery of oxygen depending upon age, sex and health conditions. A number of studies have linked polymorphisms of RAAS pathway to HAPE in past two decades, however there have been few contradictory studies and results are different across different populations. In one of our previous studies, we found AGT T(174)M to be significantly associated with HAPE susceptibility in Indian population [12]. In this study, we also demonstrated that genetic polymorphism in RAAS genes in high altitude natives are different from that of HAPE sensitive lowlanders, which could be one of the major factors responsible for their resistance to high altitude hypoxic conditions [12]. Most commonly, a 287bp insertion/deletion (I/D) polymorphism in intron 16 of ACE gene has been identified for use as a genetic marker. ACE has been previously associated with regulation of blood pressure and maintenance of salt and water homeostasis in the body [13].To study the role of ACE I/D polymorphism in development of HAPE, a meta-analysis was conducted which
involved large data set comprising over 300 HAPE cases and over 600 controls in six different studies and the investigators found that the carriers of ACE D allele (associated with increased production of ACE molecule) have 1.55-fold increased risk for developing HAPE as compared to those with the II genotype [14]. Recently, positive association of D allele with HAPE has been recently demonstrated in Indian population [15]. In a contradictory finding by Dehnert and coworkers [16] ACE I/D polymorphism had no association with susceptibility to HAPE amongst the mountaineer population. Thus genotypes of ACE being associated with HAPE susceptibility have been reported but results have not been consistent. Hotta and co-workers evaluated the A1166C and G1517T SNPs of Ang type I receptor (AT1R) in HAPE patients compared to controls and found that the frequencies of the AT1R alleles 1517 G or 1517T were significantly different in HAPE patients group. They concluded that the AT1R polymorphisms causes increased pulmonary vascular resistance and pulmonary artery pressure and thus was related to HAPE susceptibility [17]. In a separate study 10 SNP loci of five RAAS pathway genes were analyzed for 144 healthy controls and 140 HAPE patients and the researchers found that the C-344T polymorphism of the CYP11B2 gene and the A240T and A2350G polymorphisms of the ACE gene were closely associated with HAPE susceptibility [18]. The other genetic profiles, 240A and 2350G polymorphisms of the ACE gene and the -344T polymorphism of the CYP11B2 gene were not found to be associated with susceptibility towards HAPE. The higher frequency wild-type –344T allele was positively associated with adaptation to HA in a study by Rajput and co-workers [19]. All of these above cited studies along with many others have been suggested to be associated with HAPE susceptibility significantly.

Conclusion

Travelers visiting HA climates are more susceptible to HA maladies compared to high altitude natives who are well adapted to the extreme hypoxic environment. However, the genetic susceptibility towards these HA diseases vary amongst different individuals across different populations, depending on the genetic makeup of the individuals. Several studies done over past few decades show that the polymorphisms in genes of RAAS pathway resulting in increased expression of different genes of RAAS pathway such as that of AGT, ACE, angiotensin receptors and CYP11B2. These polymorphisms could be considered as important determining factors for HAPE susceptibility. Although various studies support this hypothesis, however, integrating detailed information representing diverse genetic and molecular characteristics of RAAS gene expression profile amongst different individuals and ethnic groups, could help to build a detailed profile of susceptibility/resistance towards HAPE. Thus HAPE pathogenesis can be better understood and newer and quicker strategies to deal with it can be formulated in a better way.

References
