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ACCLIMATIZATION TO HIGH ALTITUDE HYPOXIA: ROLE OF HYPOXIA MIMETIC COBALT CHLORIDE

Hypobaric hypoxia becomes progressively more severe with increasing altitude which stresses biological systems because of non-availability of a steady, uninterrupted supply of oxygen for mitochondrial metabolism. High-altitude illness is the collective term for the syndromes that can affect unacclimatised individuals shortly after ascent to high altitude, acute mountain sickness, high-altitude cerebral edema, and high-altitude pulmonary edema. The hypoxia preconditioning has potential clinical usefulness and can be mimicked by many divalent metals as cobalt, nickel, cadmium and zinc that act as hypoxic mimetics by stabilizing HIF-1á even under hypoxia.

Keywords: hypoxia, cobalt, preconditioning, hypoxia induced factor.

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Oxygen is a fundamental requirement for cellular respiration and any deficiency in oxygen concentration in the body as a whole (generalized hypoxia) or a region (tissue hypoxia) is sufficient to cause an impairment of function. Hypoxia is caused by: (i) the reduction in partial pressure of oxygen, (ii) inadequate oxygen transport, (iii) the inability of the tissue to use oxygen [1]. The lowered barometric pressure of the atmosphere (760 mm Hg at sea level to ~250 mm Hg at Everest) results in diminished alveolar oxygen tension (hypobaric hypoxia) and as a consequence, arterial partial pressure of oxygen (PaO_2) drops dramatically with increase in altitude. While normal PaO_2 at sea level is about 90-95 mm Hg, it plummets to 35 mm Hg at 20,140 feet above sea level. In addition to dramatic decreases in PaO_2, higher altitudes also trigger a greater decrease in oxygen saturation (PO_2) (150 mm Hg at sea level to ~ 40 mm Hg at Everest), thus putting the body in further jeopardy. Hypobaric hypoxia becomes progressively more severe with increasing altitude which stresses biological systems because of non-availability of a steady, uninterrupted supply of oxygen for mitochondrial metabolism. High-altitude illness is the collective term for the syndromes that can affect unacclimatised individuals shortly after ascent to high altitude, viz., acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). High-altitude illness is more likely to occur at altitudes higher than 2500 m but is being increasingly recognized at altitudes between 1500 m and 2500 m. However, in most cases it will result in mild AMS, the symptoms typically include headache, gastrointestinal symptoms (anorexia, nausea, or vomiting), insomnia, dizziness, and lassitude or fatigue but rarely it may progress to more severe forms, viz., HAPE and HACE, which can be life-threatening. The most important risk factors for the development of high-altitude illness are rate of ascent, altitude reached(especially the altitude where individual sleeps/rests), and individual susceptibility. HACE, clinically-defined as the onset of ataxia (loss of coordination), altered consciousness, severe headache, hallucinations and even seizures, has been considered as the end stage of AMS, eventually leading to death caused by brain herniation. Fluid accumulation in the brain may be caused by cytotoxic edema (cell swelling due to increased intracellular osmolarity), vasogenicoedema (leak of the blood-brain barrier with extravasation of proteins and fluid into the interstitial space), or both. HAPE, characterised by tightness in chest, cough, gurgling sound, difficulty in breathing, typically develops 2–4 days after arrival at high altitude and as the disease progresses frothy pink sputum develop which is the hallmark of HAPE. Although the exact mechanism underlying the development of HAPE remains unclear, clinical investigations suggest that HAPE is a form of non-cardiogenic pulmonary edema with increased pulmonary vascular permeability and pulmonary hypertension due to excessive hypoxic pulmonary vasoconstriction [1]. This leads to vascular leakage

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through overperfusion, capillary stress failure, or both, resulting in high concentration of vascular proteins and red blood cells in the alveolar fluid. Beside hypoxia induced damage to endothelial cells, activation of cytokines, chemokines and cell adhesion molecules may orchestrate the lung inflammatory response. It cannot be ruled out that reactive oxygen (ROS) and nitrogen species (RONS) are also involved and may even play a causative role in AMS, HAPE and HACE. ROS can contribute to 'opening up' of the blood-brain barrier, allowing neurotoxins, endotoxin and inflammatory cells to enter the brain. As millions of visitors as tourists, trekkers, mountaineers or defense personnel travel to high altitude locations each year, these high altitude maladies pose a public health problem and have severe economic consequences. Recovery occurs with descent, oxygen inhalation or bed rest but where descent is not possible and oxygen is not available, deaths continue to occur. Hypoxia is thus a life threatening stress that has to be dealt with at both cellular and systemic levels [2, 8].

HIF-1: Mediator of Hypoxic Response Hypoxia elicits variety of adaptive responses at different levels in the body that enhance cell survival. At the organism level there is increase in ventilation, increased erythropoeisis and neovascularisaton, which in combination lead to increased oxygen delivery from the atmosphere to the tissue [3]. At the cellular level, adaptation involves activated gycolysis, increased glucose uptake thus maintaining ATP despite low oxygen availability and the expression of cell survival and cell death related proteins. The regulation of the proteins required for hypoxic adaptation occur at gene level. Remarkably, the hypoxic induction of all these diverse genes appear to depend on a common mode of oxygen sensing and signal transduction mechanism mediated by activation of a critical transcription factor, hypoxia inducible factor (Hif1). It is a redox sensitive protein that binds to hypoxia responsive element in different hypoxia responsive genes including erythropoietin (Epo), vascular endothelial growth factor (VEGF), Nitric oxide synthase (NOS), hemeoxygenase (HO1), glucose transporter-1 (Glut-1), and several glycolytic enzymes, thus activating their transcription. HIF-1 is a heterodimer composed of two proteins called HIF-1á and HIF-1ß. HIF-1á is rapidly degraded under normoxia by hydroxylation of proline residue by prolyl hydroxylases within a highly conserved region in its oxygen dependent degradation domain (ODDD). The hydroxylated protein interacts with pVHL protein and is then degraded by proteasome pathway. Under hypoxic conditions, HIF-1á is not hydroxylated because of limitation of the major substrate oxygen. The unmodified protein escapes the pVHL-binding, ubiquitination and degradation and then dimerizes with HIF-1ß and stimulates the transcription of its target genes. Transition metals (Co, Ni, Mn) and iron chelators mimic hypoxia by causing the stabilization of HIF-1á, thus allowing its accumulation, nuclear translocation and binding to HIF-1ß to form the transcriptionally active HIF-1 complex [4].

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The hypoxia preconditioning has potential clinical usefulness and can be mimicked by many divalent metals as cobalt, nickel, cadmium and zinc that act as hypoxic mimetics by stabilizing HIF-1á even under hypoxia. Among all the metals reported, cobalt is one of the classic examples of a hypoxic mimetic. Cobalt (Co) is a silvery-white, hard metal with an atomic number of 27 and an atomic weight of 58.93. Common compounds of cobalt have an oxidation state of $^{+2}$ or $^{+3}$. The $^{+2}$ valence is stable in aqueous solution and is the major form of cobalt found in simple salts. Cobalt is as an essential component of vitamin B_{12} (cobalamin). Mammals lack the ability to synthesize vitamin B_{12}, and nonruminant animals require a dietary source of vitamin B_{12}. Absorbed cobalt is primarily excreted in urine with small amounts excreted via fecal endogenous routes. Cobalt concentrations in tissues is generally low (1mg/kg DM or less). The amount of cobalt normally stored in human body is around 1.5 mg[5]. Cobalt toxicosis in animals is very rare because concentrations of cobalt normally present in animal diets are much lower than those needed to cause toxicosis. Cobalt toxicosis is not likely to occur in nonruminants unless environmental contamination of feed or water occurs. Various hypotheses had been proposed to describe the mechanism of action of Co in stabilizing HIF-1á. (i) $CoCl_2$stabilises Hypoxia-inducible factor-1 (HIF-1á) by antagonizing Fe^{+2}, which is an essential cofactor along with oxygen for prolyl hydroxylases (PHDs) that degrade HIF-1á. (ii) Partial inhibition of PHDs, depletion of ascorbate, which is required to maintain the HIF-PHDs and FIH (factor inhibiting HIF) in an active state. (iii) Direct binding of cobalt to HIF-1á, which may prevent its degradation by VHL-dependent and VHL-independent pathways[6].

It has been known for a long time that cobalt increases erythropoietin production both in vitro and in vivo in normoxia. Cobalt had also been in use for the treatment of anaemia in infants and women. In the human hepatoma cell lines, production of erythropoietin mRNA was stimulated 6- to 12-fold in response to Co_2+ in the absence of hypoxia. Chronic oral administration of $CoCl_2$ has been reported to induce polycythemia without an effect on body or heart weight in animals as well as humans. Administration of $CoCl_2$ ($Co^{2+)}$ in 7 days old rats was shown to provide protection against ischemia reperfusion injury in brain. It has recently been reported that pretreatment with a low dose of cobalt in mice induced cardiac preconditioning and this protective effect of $CoCl_2$ is achieved through selective activation of HIF-1á signaling [3]. Also administration of cobalt resulted in a marked protection against ischemic renal injury. Cobalt was also shown to be cytoprotective against tert-butylhydroperoxide induced oxidative stress in $HepG_2$ cells in rats when $CoCl_2$ was given with drinking water for 13 days. Similarly it has been reported to improve cardiac contractile function in rats when administered with water containing 0.01% $CoCl_2$ for 6–7 weeks. Chemical preconditioning has the several advantages over

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physical preconditioning: (i) reduced acclimatization schedule at altitude, leading to decreased loss of man days (ii) number of people that can be preconditioned is not limited as compared to that of physical preconditioning in simulation chambers (iii) easy to implement and (iv) economical. However, most of the studies on hypoxia mimetics especially on cobalt are focused on ischemia/reperfusion injury and there is paucity of data on the efficacy of cobalt in facilitating acclimatization to high altitude (hypobaric hypoxia) and its efficacy in prevention of HA induced ailments [5, 7].

Cobalt chloride, thus has potential to be used in rapid acclimatization to hypoxia. Most importantly, supplementation of hypoxia mimetics is practical and feasible way of inducing hypoxia.

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