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Review

Pharmacological approaches in either intermittent or permanent hypoxia: A tale of two exposures

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ABSTRACT

Hypoxia induces several responses at cardiovascular, pulmonary and reproductive levels, which may lead to chronic diseases. This is relevant in human populations exposed to high altitude (HA), in either chronic continuous (permanent inhabitants) or intermittent fashion (HA workers, tourists and mountaineers). In Chile, it is estimated that 1.000.000 people live at highlands and more than 55.000 work in HA shifts.

Initial responses to hypoxia are compensatory and induce activation of cardioprotective mechanisms, such as those seen under intermittent hypobaric (IH) hypoxia, events that could mediate preconditioning. However, whenever hypoxia is prolonged, the chronic activation of cellular responses induces long-lasting modifications that may result in acclimatization or produce maladaptive changes with increase in cardiovascular risk.

HA exposure during pregnancy induces hypoxia and oxidative stress, which in turn may promote cellular responses and epigenetic modifications resulting in severe impairment in growth and development. Sadly, this condition is accompanied with an increased fetal and neonatal morbi-mortality. Further, developmental hypoxia may program cardio-pulmonary circulations later in postnatal life, ending in vascular structural and functional alterations with augmented risk on pulmonary and cardiovascular failure.

Additionally, permanent HA inhabitants have augmented risk and prevalence of chronic hypoxic pulmonary hypertension, right ventricular hypertrophy and cardiopulmonary remodeling. Similar responses are seen in adults that are intermittently exposed to chronic hypoxia (CH) such as shift workers in HA areas. The mechanisms involved determining the immediate, short and long-lasting effects are still unclear. For several years, the study of the responses to hypoxic insults and pharmacological targets has been the motivation of our group. This review describes some of the mechanisms underlying hypoxic responses and potential therapeutic approaches with antioxidants such as melatonin, ascorbate, omega 3 (Ω3) or compounds that increase the nitric oxide (NO) bioavailability.

Contents

Abbreviations: HA, high altitude; NO, nitric oxide; O_2, oxygen; ICH, intermittent CH; IH, intermittent hypoxia; CH, chronic hypoxia; GSH, reduced glutathione; ROS, reactive oxygen species; LV, left ventricular; Ω3, omega 3; PVR, pulmonary vascular resistance; PDE5, phosphodiesterase 5; sGC, soluble guanylyl cyclase; 2-APB, 2-aminoethyldiphenylborinate; SOC, store-operated calcium; ROCK, rhoa-kinase; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; NADPH, nicotinamide adenine dinucleotide phosphate; CMS, chronic mountain sickness; PAP, pulmonary arterial pressure.

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1. Introduction

Hypoxia is defined as a deficient oxygen (O_2) supply for the physiological demands of a tissue, organ or organism. This is a restrictive condition frequently faced by environmental hypoxia as seen in the highlands at any stage of life. Hypoxia associated with reduced inspiratory oxygen pressure determines an pathophysiological response in living organisms. The lower partial pressure produces a decrease in the O_2 supply in the blood and tissues with various detrimental effects [1]. According United Nation Environment Programs (UNEP) report, approximately 12% of the human population lives in mountain regions, being a relevant public heath problem [2]. Further, in 1998 there were an estimated 140 million people permanently living above 2500 m worldwide and 35 million living in the Andean Mountains [3]. Considering the South American rate of population increase in the last 15 years, the total population living in the Andean cord should be around 41 million inhabitants. Indeed, there are others forms of hypobaric hypoxia such as acute (tourism people) to intermittent CH (ICH) (working shift, e.g., miners, observatory workers, and armed forces). This type of exposure to hypoxia determines intercalated periods of stay at HA with periods at sea level. The duration of these shifts as short as one day to several days [4]. Most of the different models of HA hypoxia are characterized by marked cardiovascular and pulmonary effect to offset a global decrease in tissue O_2 supply.

Currently, living at HA is considered a health risk during development and adulthood [5,6] and it should be taken as a public health issue. Hence, establishing the impact of hypobaric O_2 restriction during prenatal and postnatal life would, represent a substantial advantage in understanding the role of hypoxia in determining cardiovascular diseases at HA populations. The latter shall help to introduce new pharmacologic approaches for hypoxia-related pathologic conditions.

For this reason, we and others scientists in Chile have developed lines of research related to the pathophysiological response in HA environments and studying potential pharmacological targets.

The International Center for Andean Studies (INCAS) was established 16 years ago, as an autonomous branch of the University of Chile, conceived as a place in which research on HA environment can be developed [7]. Most of our lines of research have been developed in this research station based at 3600 m in the Andean altiplano. Other experiments have been developed in hypobaric chambers located at near sea level. Here, we discuss some of the studies held by our group, the effects of intermittent and chronic exposure to hypobaric hypoxia and some potential pharmacological approaches.

2. Intermittent CH: high-altitudes shifts

In Chile due to job-related conditions, such as the mining industry, astronomers, army forces, border control staff, academics, and rural health officers, about 55,000 workers are subjected to an intermittent and chronic exposure to hypobaric hypoxia (above 3500 m) [8,9]. This population should grow as new mining and observatory projects are due to commence. Therefore, an increasing amount of people will be exposed to intermittent CH (ICH) [8,9,10]. Shift workers at HA must adjust to the requirements of hypobaric hypoxia for some days and then return to sea level, where, they lose some of the acclimatization to hypoxia, depending on the time in normoxia [9]. In this context, the adaptive or detrimental responses can be generally predicted by the frequency, severity, and duration of IH. Here, the two possible paradigms derived from IH in human and experimental animal approaches will be discussed.

2.1. Cardiovascular response & treatment

Cardiovascular manifestations in response to a decrease in tissue O_2 supply, including polycythemia and an increase sympathetic tone, determines the response to hypoxia. In a similar way to CH, there is a hypoxic pulmonary vasoconstriction, which leads to high pulmonary arterial pressure and the probable right ventricular hypertrophy, if the hypoxic exposure is too prolonged [11]. Currently, our understanding of the pathophysiological mechanisms linking IH and cardiovascular function is limited by the diversity of hypoxic phenomenon in human subjects and the multiple comorbidities, including obesity, insulin resistance and previous cardiac alterations [9,12]. Moreover, animals subjected to various acute IH become more resistant to tissue injury in subsequent exposures to severe hypoxic exposures [13]. This preconditioning effect has been demonstrated for example in mice treated with brief episodes of IH that survive longer when exposed to severe hypoxia [14]. Further, IH appears to provide a beneficial effect on coronary artery ligation-induced myocardial infarction by reducing the infarct size, myocardial fibrosis, and improve contractile dysfunction [15,16]. Interestingly, these effects involve the activation of pathways similar to those described in models of cardiac ischemic preconditioning [17]. It has been described antioxidant and anti-inflammatory mechanisms triggered in a short-term manner [18] and other related with genomic response [19]. Experimental approaches have shown that ICH attenuates the hypoxic damage in heart rat [16,20]. This cardioprotective mechanism was showed as an improvement in LV function associated with the higher antioxidant enzymes activity [21]. In a recent work, we showed that ICH (hypoxia-normoxia: 4×4 days) reduced myocardial injury, lipid peroxidation and IL-1 β levels [16]. These results are in agreement with other works that show an improvement of mitochondrial function and a reduced ROS-derived damage in rats exposed to ICH [22]. Understanding the ICH mechanisms, which can exert protective effects, may lead us to know relevant information for developing potential therapeutic approaches and a better management in clinical contexts [23]. A number of studies have been conducted using ICH-treated animal models to explore the effects of antioxidants, but the outcomes of these studies are controversial. Using an animal model of ICH in rats, it has been demonstrated that the use of allopurinol, a free radical scavenger was associated with a reduction in oxidative stress, myocardial dysfunction and apoptosis [24,25]. Also, It could be useful in the clinical treatment of chronic heart failure in humans as it is the only drug that has been proven able to lower O_2 consumption of the dysfunctioning myocardium [26]. In contrast, Kolár et al. demonstrated that the