AN INTEGRATIVE APPROACH FOR HIGH ALTITUDE STUDIES

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In general, the effects of hypoxia or high altitude are divided into different categories which correspond more or less to different entities with a specific symptomatology. Among these entities it is worth mentioning, acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), high altitude cerebral edema (HACE), and chronic mountain sickness or Monge's Disease (CMS). Thus, the effects of hypoxia are classified according to respiratory, hematological, cardiovascular and/or brain effects. The cause is one and common, the decrease in the ambient oxygen pressure (PO2), but the tendency is to order its effect as if there were many different and independent causes.

Usually, we try to apply rigorous rules to the classification of high altitude diseases, but when we become aware of features, which prevent the definition of the exact clinical limits of these conditions, we have particular problems. For example, a decreased ventilatory response and relative hypoventilation are common findings in AMS and CMS; pulmonary hypertension is present in HAPE and CMS, and disorders in vascular permeability are present in AMS, HAPE and HACE (1). Moreover, these characteristics may have been acquired in the prenatal period due to an exposure to excessive hypoxia (2,3).

Another important issue that should be taken into account in the understanding of the process of adaptation to hypoxia is the concept of "normality" and "abnormality". At high altitude, where the organism is compelled to respond to the decreased PO2, any minor physiological impairment or abnormality (excess or defect) of a certain function will produce an inadequate physiological response. For example, it is worthwhile mentioning hypoventilation and excessive erythrocytosis in CMS, and pulmonary hypertension, decreased oxygen saturation and vascular disorders in acute and chronic high altitude diseases (1,4). Are CMS patients, persons basically intolerant of high altitude in whom its intolerance only becomes apparent with age, or after an associated impairment?

THINKING IN TERMS OF COMPARATIVE PHYSIOLOGY

Comparative physiology of adaptation to high altitude has shown that high altitude diseases affect humans and domestic animals, but not genetically adapted animals (5). It seems that the absence of high altitude diseases in genetically adapted native animals is related to several adaptations which allow adapted animals to regulate their responses to high altitude more efficiently at lower values of PO2 than sea level animals. For example, in regard to ventilatory function, acclimatised humans and domestics animals hyperventilate around an arterial PO2 of 60 torr, adapted high altitude animals start to hyperventilate only around an arterial PO2 of 30 torr. Additionally, acclimatised humans and domestics animals, show attenuation of respiratory sensitivity to acute hypoxia when compared with sea level controls.

In contrast, this has not been found in genetically adapted high altitude native animals. Peripheral chemoreceptors, which mediate the hypoxic ventilatory

response, have been found enlarged in acclimatised humans and domestics animals, however, no enlargement has been found in llamas or alpacas suggesting an association between anatomical and functional findings. Domestic mammals introduced in the mountains after the Spanish Conquest all show variable degrees of erythrocytosis when exposed to hypoxia. In contrast, animals genetically adapted to high altitude exhibit a modest increase or no increase in hematocrit at the same level of hypoxia. The absence of erythrocytic response avoids the concomitant burden on the circulatory system. At the same level of PO2, native high-altitude mammals do not respond (as a sea level animal normally would) with pulmonary vasoconstriction. This fact avoids a sustained elevated pulmonary arterial pressure and the consequent right ventricular hypertrophy that is present in humans and in the domestics mammals and birds introduced into the mountains (6,7). The hypoxic pulmonary vasoconstrictor response to hypoxia, which might be beneficial in the first phase of exposure, becomes deleterious when excessive and constitutes a charge to the myocardium for life at high altitude. Additionally, genotypically adapted high-altitude animals have a higher hemoglobin-oxygen affinity than acclimatised humans and domestics animals. This characteristic, which does not favour the release of oxygen to the tissues at sea level, facilitates the oxygen supply, at the tissue level, in conditions of severe hypoxia.

In summary, the absence of high altitude diseases in the genotypically adapted animals suggests that, in order to be considered adapted, a different physiological design may be needed besides a distinctive capacity to regulate the response to hypoxia (4,8). Conversely, the diseases of acclimatisation show the incapacity of men and domestic animals to obtain complete adaptation to hypoxia. The lack of an accurate regulation of their responses to acute and chronic hypoxia are an indication of the limited use of their phenotypic capacity beyond the limits of tolerance to life at high altitude.

The great challenge is to determine, at the organ and/or at the cellular level, by what anatomical and physiological advantages some animals are adapted to high altitude while others are not (including man). The actual tendency to try to explain the process of adaptation to hypoxia from the field of molecular biology should not make us forget that the control of the process is at least as important (if not more) as the identification of the organic molecules which participate in the process of adaptation. If the logic of successful adaptation to high altitude is to be made clear, an integral approach is required. This approach should include the conventional disciplines, but also ought to incorporate fields such as epidemiology and population genetics, as well as the fortuitous neonatal history of the organism.

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