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Evolving in thin air—Lessons from the llama fetus in the *altiplano*

Aníbal J. Llanos [a,b,c,*], Raquel A. Riquelme [d], Emilio A. Herrera [a,b], Germán Ebensperger [a], Bernardo Krause [a], Roberto V. Reyes [a], Emilia M. Sanhueza [a], Víctor M. Pulgar [a,1], Claus Behn [b,e,f,g], Gertrudis Cabello [c,h], Julian T. Parer [i], Dino A. Giussani [j], Carlos E. Blanco [k], Mark A. Hanson [l]

[a] *Laboratorio de Fisiología y Fisiopatología del Desarrollo, Programa de Fisiopatología, Instituto de Ciencias Biomédicas (ICBM), Facultad de Medicina, Universidad de Chile, Santiago, Chile*
[b] *International Center for Andean Studies (INCAS), Universidad de Chile, Santiago-Arica-Putre, Chile*
[c] *Universidad de Tarapacá and Centro de Investigaciones del Hombre en el Desierto (CIHDE), Arica, Chile*
[d] *Departamento de Bioquímica y Biología Molecular, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile*
[e] *Programa de Fisiología y Biofísica, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile*
[f] *Escuela de Medicina, Facultad de Medicina, Universidad Mayor, Santiago, Chile*
[g] *Facultad de Medicina, Universidad de Valparaíso, Valparaíso, Chile*
[h] *Departamento de Biología, Facultad de Ciencias, Universidad de Tarapacá, Arica, Chile*
[i] *University of California San Francisco, San Francisco, CA, USA*
[j] *Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK*
[k] *Department of Pediatrics, Academic Hospital University of Maastricht, Maastricht, The Netherlands*
[l] *Centre for Developmental Origins of Health and Disease, University of Southampton, Southampton, UK*

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Abstract

Compared with lowland species, fetal life for mammalian species whose mothers live in high altitude is demanding. For instance, fetal llamas have to cope with the low fetal arterial P_{O_2} of all species, but also the likely superimposition of hypoxia as a result of the decreased oxygen environment in which the mother lives in the Andean *altiplano*. When subjected to acute hypoxia the llama fetus responds with an intense peripheral vasoconstriction mediated by alpha-adrenergic mechanisms plus high plasma concentrations of catecholamines and neuropeptide Y (NPY). Endothelial factors such as NO and endothelin-1 also play a role in the regulation of local blood flows. Unlike fetuses of lowland species such as the sheep, the llama fetus shows a profound cerebral hypometabolic response to hypoxia, decreasing cerebral oxygen consumption, Na–K-ATPase activity and temperature, and resulting in an absence of seizures and apoptosis in neural cells. These strategies may have evolved to prevent hypoxic injury to the brain or other organs in the face of the persistent hypobaric hypoxia of life in the Andean *altiplano*.

Keywords: Hypoxia; High altitude; Hypometabolism; Vasoconstriction; Adrenergic; Cardiovascular

1. Introduction

Hypoxia during fetal development or shortly after birth induces abnormal growth and development. It can cause short (death, pulmonary hypertension) and long-term consequences such as abnormal neurodevelopment and an increase in risk for diseases later in life (Fowden et al., 2006). Causes for hypoxia are found in placental pathology, umbilical cord abnormalities, asphyxia during delivery or neonatal pathologies such as metabolic diseases, lung pathology (immaturity, pulmonary hypertension, aspiration of meconium or infection (Alonso-Spilsbury et al., 2005). Its treatment is often very invasive where the neonate is artificially ventilated, a practice that can produce inflammation, lung injury and infection. Moreover, powerful pharmaceutical adrenergic drugs are administered to increase the function of the heart and thus move more oxygen to the organs and tissues. The use of such drugs may damage the heart. A more informed approach to prevent hypoxia in seriously ill newborns is required. A great deal can be learnt from

* Corresponding author at: Programa de Fisiopatología, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Casilla 16038, Santiago 9, Chile. Tel.: +56 2 341 9147; fax: +56 2 274 1628.
E-mail address: allanos@med.uchile.cl (A.J. Llanos).
[1] Present address: Department of Obstetrics and Gynecology, Wake Forest University, Winston, Salem, NC 27157, USA.

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nature in this respect by studying appropriate animal models. In this review we concentrate on ideas derived from the South American camelids and particularly the domestic species, the llama (*Lama glama*), which develops, resides and reproduces in chronic environmental hypoxia.

Most mammalian species live and develop in an environment close to sea level, with an atmospheric pressure near to 760 mmHg and a partial pressure of 150 mmHg of O_2 in the air. Although most mammals are very susceptible to even modest oxygen shortages, some species have developed a particular tolerance to hypoxia, since their evolution has taken place in an environment of low oxygen availability. Among these species are seals and other diving mammals, animals that live in burrows, and those which live and develop in the hypobaric hypoxia of high altitudes. The latter comprises the South American *Camelidae*, which includes the domestic species, llama (*L. glama*) and alpaca (*Lama pacos*), and, the wild species, vicuña (*Vicugna vicugna*) and guanaco (*Lama guanicoe*).

2. The adult llama

To thrive at the high altitudes of the Andean *altiplano*, the llama shows characteristics, which appear to have evolved in several physiological functions. These are now genetically determined, since they continue to be present in llamas born and living at low altitudes. These physiological changes include high hemoglobin oxygen affinity (low P_{50}), small elliptical red cells with high hemoglobin concentration, a small increase in blood hemoglobin concentration, high muscle myoglobin concentration, more efficient O_2 extraction at the tissue and high lactate dehydrogenase activity (Llanos et al., 2003). Lowland species such as the sheep, or indeed humans, develop pulmonary hypertension when they reside at high altitude. This produces structural changes in the pulmonary blood vessels (Harris et al., 1982). However, the llama prevents the occurrence of pulmonary arterial hypertension by having less highly muscularised pulmonary arterioles (Harris et al., 1982). To examine further such species differences, in adult llamas raised at sea level, we measured pulmonary vascular responses to acute hypoxia and compared them relative to those of lowland sheep. While pronounced increases in pulmonary arterial pressure and pulmonary vascular resistance occurred in sheep, these changes were markedly attenuated in llamas (Fig. 1). In both species cardiac output increased, systemic vascular resistance decreased and mean systemic arterial pressure was maintained during acute hypoxia. These data show that the llama responds to acute hypoxia with diminished cardiovascular responses, showing only a mild pulmonary hypertension relative to the sheep. Blunted cardiopulmonary responses to acute hypoxia may be a beneficial adaptation in the Andean camelid to the chronic hypobaric hypoxia of life at high altitude.

In contrast to pulmonary arterial pressure, systemic arterial blood pressure changes with the head position, since the llama is a long necked animal. Arterial blood pressure was higher when the head was above the heart level (Fig. 2). These results indicate a significant variation in the systemic arterial pressure with vertical variations in the head position as in the giraffe (Goetz et al., 1960; Mitchell et al., 2006). Nevertheless, in spite of a lower systemic arterial pressure when the llama's head was down, there was no tachycardia, suggesting a lower baroreflex threshold for eliciting an increase in heart rate (Fig. 2).

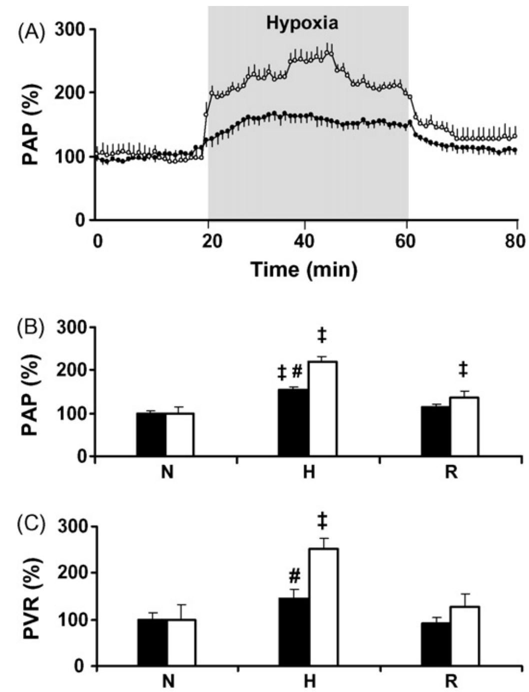

Fig. 1. Pulmonary arterial pressure (PAP) and vascular resistance (PVR) in adult llama ($n = 4$, solid circles-bars) and sheep ($n = 5$, open circles-bars) during acute hypoxia. (A) PAP was recorded continuously during 20 min of normoxia, 40 min of hypoxia and 20 min of recovery. (B) Average PAP during 20 min of normoxia, 40 min of hypoxia and 20 min of recovery. (C) Average PVR during 20 min of normoxia, 40 min of hypoxia and 20 min of recovery. Data are expressed as percentage of change for normoxic period. Means ± S.E.M., $p < 0.05$, ‡vs. normoxia, #vs. sheep (ANOVA and Newman-Keuls).

3. The fetal llama

Compared with lowland species, fetal life for mammalian species whose mothers live in an environment of oxygen shortage is demanding. For instance, fetal llamas have to cope with the low fetal arterial P_{O_2} of all species, plus the likely superimposition of low P_{O_2}, as a result of the decreased oxygen environment in which the mother lives in the Andean *altiplano* (Llanos et al., 2003). The fetal llama has a higher hemoglobin oxygen affinity compared with the adult llama, however the difference in hemoglobin oxygen affinity between mother and fetus is less that that between maternal and fetal sheep (Moraga et al., 1996). Basal cardiovascular function is characterized by lower cardiac output and organ blood flows and higher total peripheral vascular resistance than fetuses of lowland species such as the sheep, showing more efficient total O_2 extraction (Benavides et al., 1989; Llanos et al., 1995; Pérez et al., 1989).

Since the maternal llama can modify systemic arterial pressure and utero-placental blood flow by changes in the position of the head, we studied the influence of pregnancy on the variations of this cardiovascular variable. We also measured fetal oxygenation during such changes. As in the non-pregnant