Placenta 32, Supplement B, Trophoblast Research, Vol. 25 (2011) S100–S103

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Current Topic

Fetal and postnatal pulmonary circulation in the Alto Andino

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ARTICLE INFO

Article history:
Accepted 5 January 2011

Keywords:
Fetus
Neonate
Pulmonary circulation
High altitude
Llama
Sheep

ABSTRACT

Lowland mammals at high altitude constrict the pulmonary vessels, augmenting vascular resistance and developing pulmonary arterial hypertension. In contrast, highland mammals, like the llama, do not present pulmonary arterial hypertension. Using wire myography, we studied the sensitivity to norepinephrine (NE) and NO of small pulmonary arteries of fetal llamas and sheep at high altitudes. The sensitivity of the contractile responses to NE was decreased whereas the relaxation sensitivity to NO was augmented in the llama fetus compared to the sheep fetus. Altogether these data show that the fetal llama has a lower sensitivity to a vasoconstrictor (NE) and a higher sensitivity to a vasodilator (NO), than the fetal sheep, consistent with a lower pulmonary arterial pressure found in the neonatal llama in the Andean *altiplano*. Additionally, we investigated carbon monoxide (CO) in the pulmonary circulation in lowland and highland newborn sheep and llamas. Pulmonary arterial pressure was augmented in neonatal sheep but not in llamas. These sheep had reduced soluble guanylate cyclase and heme oxygenase expression and CO production than at lowland. In contrast, neonatal llamas increased markedly pulmonary CO production and HO expression at high altitude. Thus, enhanced pulmonary CO protects against pulmonary hypertension in the highland neonate. Further, we compared pulmonary vascular responses to acute hypoxia in the adult llama versus the adult sheep. The rise in pulmonary arterial pressure was more marked in the sheep than in the llama. The llama pulmonary dilator strategy may provide insights into new treatments for pulmonary arterial hypertension of the neonate and adult.

1. Introduction

Von Euler and Liljestrand described the pulmonary hypertension induced by hypoxia more than 64 years ago [1]. Since then, there have been numerous advances in establishing the mechanisms by which this pathology occurs. Pulmonary hypertension is particularly frequent in neonatal life due to the changes that take place in the pulmonary circulation in the transition from fetus to newborn. The pulmonary circulation switches to a condition of low resistance and high blood flow in the neonate [2]. The initiation of alveolar ventilation, with the substantial increase in PO_2 and the shear stress produced by the passage of the total cardiac output through the pulmonary circulation, liberates a myriad of mediators that finally reduce the pulmonary vascular resistance [2–4].

Chronic hypoxia during gestation is one of the causes that may produce a failure in the transition of the fetal to neonatal circulation resulting in the syndrome of persistent pulmonary hypertension of the neonate. The prevalence is 1.9 per 1000 live births at lowland [5], with no data available at high altitude. High altitude babies have a greater occurrence of intrauterine growth restriction [6], fetal hypoxia and newborn respiratory distress [7], conditions producing neonatal pulmonary hypertension, with a further increase in pulmonary arterial pressure when superimposed acute

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0143-4004/$ – see front matter © 2011 Published by IFPA and Elsevier Ltd.
doi:10.1016/j.placenta.2011.01.001

hypoxia is added [8–10]. Chronic fetal hypoxia causes pulmonary vasoconstriction and remodeling of the pulmonary vessels, thereby increasing the postnatal pulmonary vascular resistance and pulmonary arterial blood pressure [3,9,11,12].

Most of the lowland mammals have a modest tolerance to hypoxia, whereas some species whose evolution took place at high altitude, such as one of the South American Camelidae, the Llama, has developed a particular tolerance to hypoxia [13].

2. Fetal llamas and sheep

The llama fetus has several physiological adaptations to live in the Andean *altiplano*, among them a marked alpha-adrenergic function [14–17]. It has a high peripheral vascular resistance that is mainly due to alpha-adrenergic receptors, particularly alpha-1-adrenergic receptors [18]. The fetal llama plasma catecholamine concentrations are higher compared to those found in the fetal sheep [19], highlighting the crucial role that the sympathetic system plays in the regulation of the fetal llama systemic circulation [18].

Since the alpha-adrenergic mechanisms are upregulated in the fetal llama systemic circulation, we studied the contractile responses of small pulmonary arteries to norepinephrine (NE) of fetal llamas and fetal sheep at high altitudes [20]. In contrast to the systemic circulation, the sensitivity of the contractile responses to NE was decreased in the llama fetus compared to the sheep fetus, with an increase in the maximal response at very high NE concentration (Fig. 1). The sensitivity to the relaxation due to NO (SNP) was greater in fetal llama than in fetal sheep small pulmonary arteries (Fig. 2). Altogether these data show that the fetal llama has a higher sensitivity to a vasodilator (NO), and a lower sensitivity to a vasoconstrictor (NE) than the fetal sheep, consistent with a lower pulmonary arterial pressure found in the neonatal llama in the Andean *altiplano* [8]. Compared to the fetal llama, the high altitude adult llama has even lesser small pulmonary artery contractility and relaxation [13].

3. Neonatal llamas and sheep

Chronic hypoxia can produce rises in pulmonary vascular resistance and high-altitude pulmonary hypertension and pulmonary edema [3,21]. This is the case with high altitude sheep neonates, which present pulmonary hypertension when compared with their lowland counterparts (Fig. 3) [22]. Furthermore, they have stronger pulmonary vascular responses to acute hypoxia associated with higher arterial contractile status and an increased wall thickness in the small pulmonary arteries compared to low altitude controls [9]. The higher pulmonary arterial pressure at high altitude could be due in part to a higher activity and/or expression

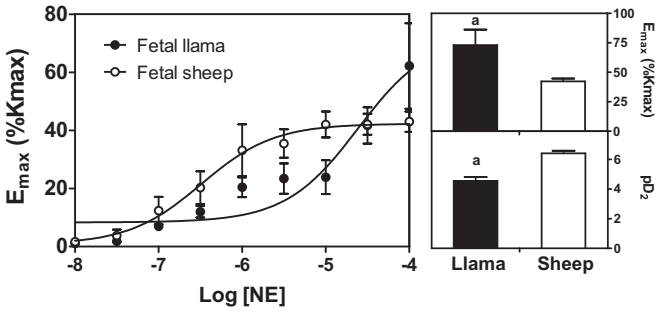

Fig. 1. Response to norepinephrine (NE) in small pulmonary arteries from fetal llamas and sheep. Each point represents the mean ± S.E.M. of 6 llamas and 6 sheep. Maximal responses and sensitivity are presented as histograms for llamas (black) and sheep (white). Significant differences $p < 0.05$ (*t*-test): a vs. sheep.

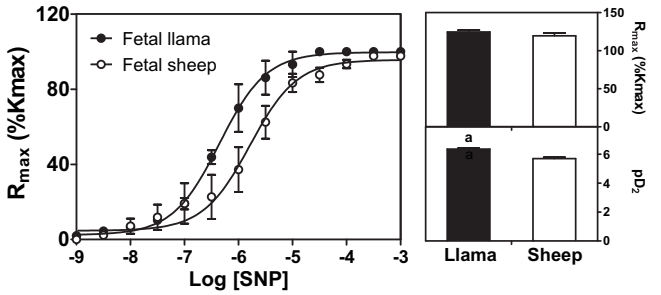

Fig. 2. Response to sodium nitroprusside (SNP) in small pulmonary arteries from fetal llamas and sheep. Each point represents the mean ± S.E.M. of 6 fetal llamas and 6 fetal sheep. Maximal responses and sensitivity are presented as histograms for llamas (black) and sheep (white). Significant differences $p < 0.05$ (*t*-test): a vs. sheep.

of phosphodiesterase 5 (PDE5), decreasing the intracellular concentration of cGMP, and this apparently takes place in highland newborn lambs, since they are more sensitive to sildenafil, a PDE5 antagonist [9]. In contrast, species evolved at high altitude appear to have enhanced pulmonary vasodilator function, for example, Tibetans and Bolivian Aymaras exhibit an increase in pulmonary nitric oxide (NO) synthesis compared to lowland individuals [23,24]. Another potential pulmonary vasodilator is carbon monoxide (CO), synthesized by hemoxygenase (HO) [25]. Like NO, carbon monoxide activates soluble guanylate cyclase and potassium channels in the pulmonary vessels [12,26,27] and also contributes to a decrease in cardiovascular remodeling induced by hypoxia [25,28].

Consequently, we studied whether the HO–CO system was enhanced in the newborn llama, protecting its pulmonary vasculature against the deleterious effects of chronic hypoxia. In the Andean *altiplano*, the basal pulmonary arterial pressure was higher in newborn sheep compared to newborn llamas (Fig. 3). Furthermore, there was reduced CO production and HO-1 expression in high altitude sheep neonates. In contrast, newborn llamas showed a marked increase in pulmonary CO production and HO-1 expression at high altitude compared with sea level llama neonates [8]. The pulmonary HO–CO system may protect not only against the development of hypoxic pulmonary vasoconstriction, but also by preventing vascular remodeling [29,30]. CO action is mediated by cGMP and BKCa channels, resulting in an effective mechanism in the regulation of this vascular bed [25].

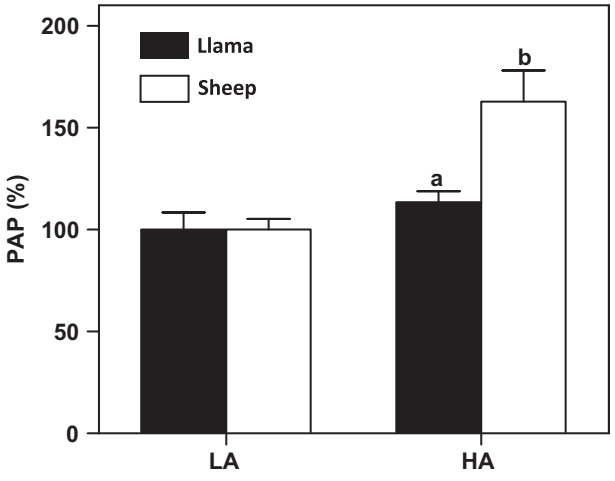

Fig. 3. Pulmonary arterial pressure (PAP) in neonatal llama ($n = 7$, black bars) and sheep ($n = 7$, white bars) from low- (LA) and high altitude (HA). Data are expressed as percentage of change relative to LA (LA sheep: 11.3 ± 0.6 mmHg; LA llama: 13.7 ± 1.1 mmHg). Means ± S.E.M., $p < 0.05$, a vs. sheep, b vs. LA, (ANOVA and Newman–Keuls).

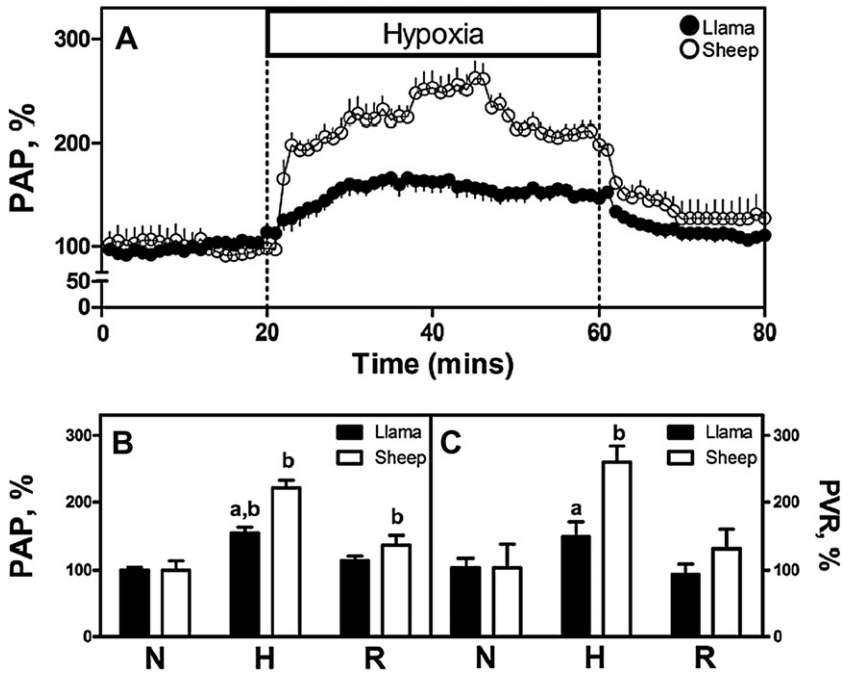

Fig. 4. Pulmonary arterial pressure (PAP) and vascular resistance (PVR) in adult llama ($n = 5$, black circles-bars) and sheep ($n = 5$, white circles-bars) during acute hypoxia. (A) PAP was recorded continuously during 20 min of normoxia, 40 min of hypoxia and 20 min of recovery; (B) Average PAP during 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., $p < 0.05$, a vs. sheep, b vs. normoxia, (ANOVA and Newman–Keuls). Modified from Llanos et al., 2007.

4. Adult llamas and sheep

Adult lowland species such as sheep and humans, submitted to high altitude, have augmented pulmonary vascular resistance and pulmonary arterial pressure [12,21]. In contrast, the adult llama avoids pulmonary arterial hypertension, among other mechanisms, by having less muscularized pulmonary arterioles [31]. To study further this issue, we measured the pulmonary vascular responses to

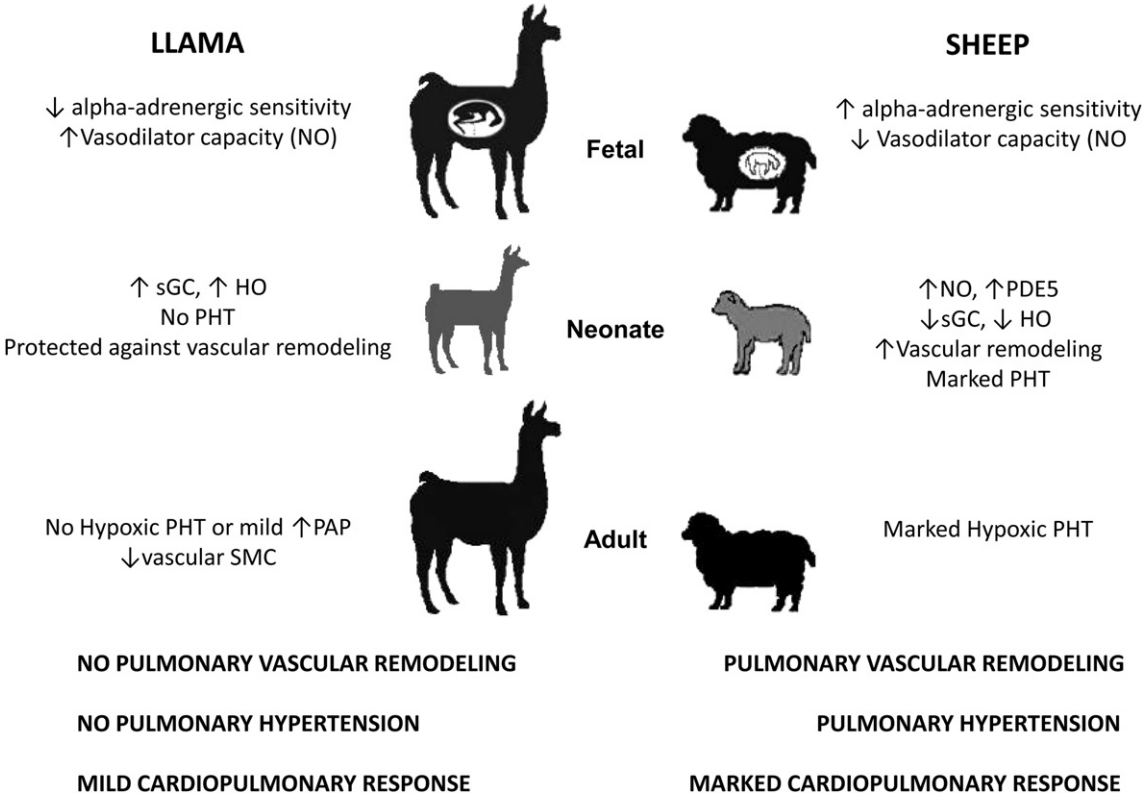

Fig. 5. Pulmonary characteristics of the llama and the sheep. Summary diagram showing the comparison of the pulmonary circulation characteristics between the highland sheep and llama at different stages of development.

acute hypoxia in adult llamas and sheep raised at lowland. There was a rise in pulmonary arterial pressure and vascular resistance in the sheep, while these variations were attenuated in llamas (Fig. 4). These data show that the llama responds to acute hypoxia with blunted cardiovascular responses, displaying only a mild pulmonary hypertension relative to the sheep. Decreased cardiopulmonary responses to acute hypoxia may be a beneficial adaptation in the Andean llamas to the chronic hypoxia of life at high altitude [13].

Nature gives us some clues from animals living in hypoxic environments, such as the llama, dwelling in the *Alto Andino* without suffering pulmonary arterial hypertension (Fig. 5). The challenge is now to investigate the several mechanisms by which this remarkable feat is achieved. The shift of the pulmonary circulation dilator strategy to efficient mediators, i.e. the HO–CO system, could help us to understand further the biological basis of this pathological condition in humans and help to design new treatments of this syndrome of great scientific, medical and social impact.

Ethics

The Faculty of Medicine Ethics Committee of the University of Chile approved all experimental procedures. The studies on animals were performed according with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and adhered to APS's Guiding Principles in the Care and Use of Animals.

Conflict of interest

The authors do not have any potential or actual personal, political, or financial interest in the material, information, or techniques described in this paper.

Acknowledgements

This work was funded by the Fondo Nacional de Ciencia y Tecnología (FONDECYT), Chile, Grants 1090355, 1080663, 1050479, 1010636; The Wellcome Trust Collaborative Research Initiative (CRIG), UK, Grant 072256.

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