DEVELOPMENT AT HIGH ALTITUDE: INTRAUTERINE AND EXTRAUTERINE

HIGH ALTITUDE, HYPOXEMIC-INDUCED RESPONSES IN ADULT AND FETAL CEREBRAL BLOOD VESSELS

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RESUMEN: Respuestas de Vasos Sanguíneos Cerebrales Fetales y Adultos Inducidas por Hipoxemia de Altura

En respuesta a la hipoxemia de altura prolongada, las arterias cerebrales de fetos de ovejas y de ovejas adultas muestran respuestas contáctiles disminuidas a la noradrenalina y a otros agonistas. En esta revisión examinamos los mecanismos contráctiles pre-sinápticos y post-sinápticos que podrían explicar estos cambios. Además, examinamos la relajación de los vasos cerebrales y el rol del embarazo en la alteración de estas respuestas. Los resultados revelan la profundas diferencias de respuesta de las arterias carótidas común e intracraneal, así como las diferencias significativas existentes en las respuestas del feto y del adulto. Dichos resultados también enfatizan el rol de la hipoxemia de altura prolongada en la modulación del acoplamiento farmaco-mecánico a nivel de la microcirculación cerebral.

Palabras claves : Aclimatación; Hipoxia; Sistema nervioso simpático; Noradrenalina; Desarrollo

RÉSUMÉ: Réponses des vaisseaux sanguins cérébraux foetaux et adultes, induites par hypoxémie d'altitude.

En réaction à l'hypoxémie prolongée d'altitude, les artères cérébrales de foetus de brebis et de brebis adultes présentent des réponses contractiles amoindries à la noradrénaline et à d'autres agonistes. Dans cette étude de révision nous examinons les mécanismes contractiles pré-synaptiques et post-synaptiques qui pourraient expliquer ces changements. Nous étudions également la relaxation des vaisseaux cérébraux et le rôle de la gestation dans l'altération de ces réponses. Les résultats révèlent de profondes différences entre les réponses des artères carotide commune et intracrânienne, ainsi que des différences significatives entre les réponses du foetus et celles de l'adulte. Ces résultats mettent aussi en relief le rôle de l'hypoxémie prolongée d'altitude dans la modulation de l'accouplement pharmaco-mécanique au niveau de la microcirculation cérébrale.

Mots-clés : Acclimatation, Hypoxie, Système nerveux sympathique, Noradrénaline, Développement.

SUMMARY: In response to high altitude long-term hypoxemia, the cerebral arteries of adult and fetal sheep show decreased contractile responses to norepinephrine and other agonists. In this review we examine the pre-synaptic and post-synaptic contractile mechanisms which might account for these changes. In addition, we examine cerebral vessel relaxation and the role of pregnancy in altering these responses. The results highlight the profound differences in response of common carotid and intracranial arteries, as well as the significant differences in responses of fetus and adult. They also emphasize the role of high altitude, long-term hypoxemia in modulating pharmaco-mechanical coupling in the cerebrovasculature .

Key Words: Acclimatization, Hypoxia, Sympathetic nervous system, Norepinephrine, Development

INTRODUCTION

In the late 1920s and the 1930s several investigators determined that in man and other mammals, fetal umbilical blood had low oxyhemoglobin saturation and high O_2 capacity, as compared to adults. This led to the concept of

the fetus, as a mountaineer at high altitude, being exposed to a low O_2 tension, and thus being at "Mt. Everest in Utero" (1, 2). The question arose, if the fetus carried by a mother at sea level is in effect living at simulated high altitude, how does a fetus survive which is borne by a mother at high altitude in whose arterial blood the O_2 tension is much lower than that at sea level? What are the mechanisms, both maternal and fetal, which enable man and many mammals to reproduce at altitudes up to 4,500 to 4,880 m (15,000 to 16,000 ft)? In addition to women at high-altitude, fetuses of a large number of other pregnant women may experience prolonged hypoxemic stress. Thus, the problem of long-term hypoxemia, and the mechanisms whereby mother and fetus attempt to maintain tissue and cellular oxygenation, is of great physiologic importance and clinical relevance.

The cerebral vasculature is richly innervated by sympathetic nerves (3, 4), and the neurotransmitter norepinephrine acts post-synaptically on smooth muscle adrenergic receptors as a principle determinant of vascular contractility (5, 6, 7). The reactivity of vascular smooth muscle to adrenergic agonists has been shown to be modulated by a number of factors including hypoxia (8, 9, 10). In the adult, high altitude, long-term hypoxia is associated with a number of cerebrovascular, cardiovascular, metabolic, and other adaptations (11), the cellular bases of which are poorly understood. For the fetus, which at sea level thrives at an arterial PO_2 value comparable to an adult at high altitude, almost nothing is known of its cerebrovascular acclimatization responses when its mother is at high altitude.

Here we review what is known of cerebrovascular acclimatization responses to prolonged hypoxemic stress in the adult and the developing fetus. Most of the data is derived from studies in sheep. Because it is outside the scope of this presentation, we will not attempt to review pulmonary, cardiovascular, hematologic, and other responses to high-altitude (>3000 m), long-term hypoxemia in the adult or fetus.

Several definitions are in order. Generally speaking "hypoxia" refers to a relative lack of oxygen (e.g., low O_2 content or tension) in the ambient air and/or tissues. Strictly speaking, "hypoxia" or "dysoxia" is O_2 limited energy flux and electron transfer in the mitochondrial cytochrome oxidase system rather than a low O_2 content or tension, *per se* (12). "Hypoxemia" is a state of less than normal O_2 in the arterial blood. "Acclimatization" to high altitude is the process of becoming accustomed to an environment with a relatively low O_2 tension, as ambient PO_2 is inversely related to altitude. The process of acclimatization occurs over a period of days to weeks, but is believed to be essentially complete within five to six weeks (13). This is to be distinguished from "adaptation" which occurs over a period of decades or generations.

High Altitude, Long-Term Hypoxemia "Model"

During the past decade, we have explored a number of facets of the process whereby the fetus, pregnant mother, and nonpregnant adult acclimatize successfully to the stress of high-altitude, long-term hypoxemia. The high-altitude "model" which we have used is as follows. Western grade Suffolk ewes (both 30 days pregnant and nonpregnant) are transported to the White Mountain Research Station (WMRS), White Mountain, California, where they are maintained, at 3,820 m (12,470 ft). After three to four months of acclimatization, the near-term (~140 of 147 days gestation), and nonpregnant ewes are transported to our laboratories for study. In addition, some pregnant ewes are returned to our laboratories at ~115 to 120 days gestation for chronic catheterization and in vivo studies. After arrival at LLU, the maternal arterial O_2 tension of all long-term hypoxemic ewes is maintained at that level which they experienced at high-altitude, e.g., ~60 Torr.

Table 1. Maternal and Fetal Physiologic Responses to High Altitude, Long-Term Hypoxemia

Physiologic Response	Normoxia	High Altitude	% Change
Mother			
PO_2 (Torr)	102±2	64+2*	-37.1
PCO_2 (Torr)	35±1	29_1*	-17.9
pH	7.44±0.01	7.46_0.01	0.3
[Hb] (g/dl)	8.7±0.3	10.5_0.4*	20.7
BP (mm Hg)	81±3	88_4	8.6
Fetus			
Weight (g) (at 140 days gestation)	4640±180	862±300	-
PO_2 (Torr)	23±1	19±1*	-17.2
[HbO_2] (%)	59±3	50±3♦	-15.9
[Hb] (g/dl)	10.1±0.7	12.6±_0.6*	24.7
O_2 content (mUdl)	7 7±0.5	7.8±0.5	1.0
PCO_2 (Torr)	48±1	4±1 *	-18 4
pH	7.36±0.01	7.37±0.0l	0.1
Lactate (mg/dl)	13 1±07	14 4±1	9.9
Heart Rate (beats/min)	168±5	165±5	-1.6
Arterial Pressure (mmHg)	44±1	52±1*	17.1
Right Ventricular Output(ml min^{-1} kg^{-1})	276±10	183±10*	-33.6
Left Ventricular Output(ml min^{-1} kg^{-1})	166±16	142±16	-14.5
Right Stroke Volume (ml/kg)	1.66±0.05	1.11±0.05*	-33.1
Left Stroke Volume (ml/kg)	0.97±0.09	0.84±0.08	-13.4
Combined Ventricular Output (ml min^{-1} kg^{-1})	441±23	335±28♦	-24.1
Breathing Incidence (min/h)	25	25	-
Norepinephrine (pg/ml)	553±55	635±65	14.8
Epinephrine (pg/ml)	81±19	113±12	39.5
ACTH (pg/ml)	66±8	60±9	-10
Cortisol (ng/ml)	47±3	50±1	6.4
Erythropoietin (mU/ml)	23±2	31±17	35

Data from References 19 and 20. Values are means ± SE; ** $p<0.01$; ♦ $p<0.05$ from control

General Fetal Responses/Adaptations to Long-Term Hypoxemia

In humans, newborn birth weight and perinatal mortality rate serve as fairly universal measures of the effects of high altitude on fetal growth and development. Over the past five decades, a number of studies on several continents and many ethnic groups have demonstrated lower mean birthweight, elevated placental to fetal weight ratios, and higher neonatal mortality and morbidity including intraventricular hemorrhage (14) in such infants (15, 16, 17, 18). Some specific physiologic responses to high altitude, long-term hypoxemia in chronically catheterized fetuses and adults are given in Table 1, with comparisons to normoxic control animals. The values are based on results in 10 to 40 adult or singleton fetuses in each group (19, 20).

Cerebrovascular Changes

General. In chronically catheterized near-term fetal sheep, cerebral blood flow (as measured with radioactive labeled microspheres) was not significantly different in the high altitude, acclimatized fetus (110±19 mUmin/100 g) as compared with sea level controls (139±12 mUmin/100 g). This, despite the fact that total cardiac output was 27% lower (351±55 mUmin/Kg) that in normoxic controls (483±12 ml/min/Kg) (20).

From a structural standpoint, the common carotid arteries of fetal and adult sheep showed ~50% increase in base soluble protein (percent of dry weight) as compared with normoxic controls (Fig. 1, upper panel). However, these vessels showed no significant differences in vessel resting inside diameter, wall thickness, or percent water (9). Fetal, but not adult, middle cerebral arteries

showed a less dramatic, 22% increase in base soluble protein (Fig. 1, lower panel). The reason for these large increases in protein is not clear.

Contractile Responses to Potassium and to Amines. In both common carotid and the cerebral arteries of adult and fetus, chronic hypoxemia depressed maximum contractile tension to depolarization by $1.2x10^{-1}$ M potassium. However, when these contractile responses to K^+ were normalized relative to vessel cross-sectional area, the responses of fetal and adult vessels differed. In the fetal arteries, the hypoxic-induced depression of response persisted. In contrast, adult arteries showed no significant changes in K^+-induced stress. When normalized to cross-sectional area, the potassium responses reveal not just the contractile capacity of the tissue, but also the relative proportion of contractile to noncontractile elements in the wall. That potassium-induced stresses decreases in the fetal common carotid suggests that either contractile protein synthesis decreased or that non-contractile elements increased, in response to hypoxia. That no other changes were noted suggests that hypoxia exerted few effects at the level of the contractile apparatus. As noted above, hypoxia generally increased protein content. If this occurred without a change in stress, then hypoxia must have exerted a parallel effect on both contractile and non-contractile elements in the adult common carotid, but may have preferentially stimulated noncontractile protein synthesis in the fetal common carotid.

Some may argue correctly that $1.2x10^{-1}$ M potassium is an unphysiologic stimulus. Thus, we repeated this comparison by the use of exogenous amines serotonin (10^{-5} M) and histamine ($2x10^{-5}$ M). In fetal common carotid and intracranial arteries, chronic hypoxemia depressed the maximal contractile response to a mixture of serotonin and histamine 37% and 26%, respectively. In contrast, the adult common carotid and cerebral arteries showed no significantly different responses. Of interest, when these maximum responses to serotonin and histamine were normalized relative to the maximum response to potassium, the changes in the fetal arteries became not significant, while the adult intracranial arteries showed significant 50 to 87% increases in the ratios (9). The amine-potassium ratio serves to normalize out any effects of changes in the basic contractile apparatus. Thus, changes in protein, thickness, and potassium-responses are all excluded from interpretation of these data. Instead, the data indicate the extent to which receptor effector coupling is changing as a consequence of hypoxia.

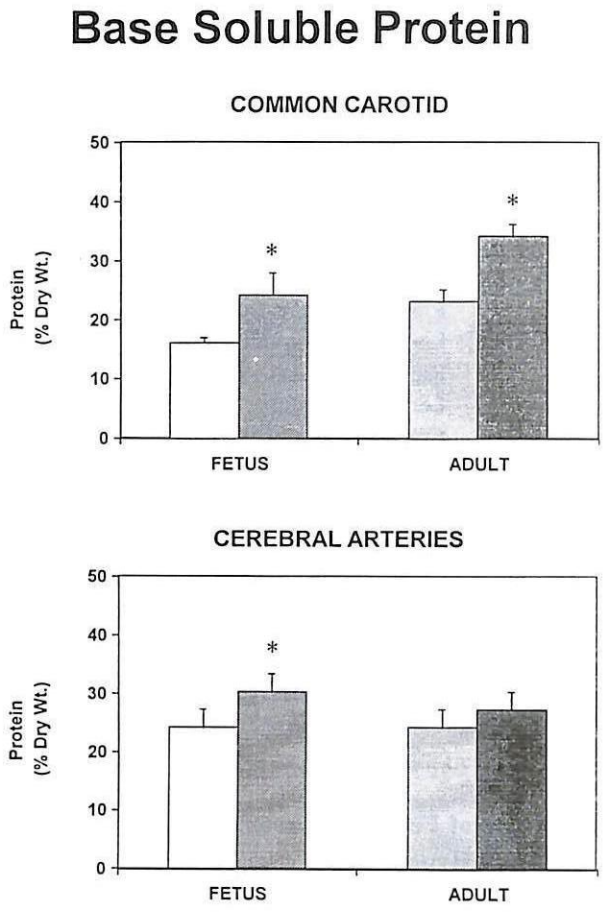

Figure 1. Upper Panel. Effects of long-term hypoxia on base-soluble cellular protein content, expressed as percent dry weight, in common carotid of fetal and non-pregnant adult sheep maintained at either sea level (open or lightly shaded bar) or at 3280 m (heavily shaded bar) for 110 days. Values are mean ± SEM; *p<0.05.

Lower Panel. Shown here are mean ± SEM, expressed as percent dry weight, measured in middle cerebral arteries of fetal and non-pregnant adult sheep maintained at either sea level or at 3280 m for 110 days (the last 110 days of gestation for the fetuses). Note that hypoxia was associated with significantly elevated protein levels in arteries of both age groups. *p<0.05.

Contractile Responses to Endogenous Norepinephrine. To examine adrenergic-mediated contractile mechanisms, the arterial nerves were directly and selectively stimulated at physiological frequencies resulting in norepinephrine (NE) release with contractile effect (21, 22). For all arteries, the contractile response of normoxic arteries were significantly greater in adult than in fetus (21). In the adult comrnon carotid and intracranial arteries, long-term hypoxemia was associated with significant depression of contractile response. In contrast, in fetal common carotid and intracranial arteries, long-term hypoxemia was associated with a markedly greater contractile response (21). We emphasize that these responses were to endogenous norepinephrine, and that all normal uptake systems were intact and not blocked. Thus, the data reflect the true functioning of the adrenergic receptors in these arteries. If the blood brain barrier is intact, circulating norepinephrine would never reach the α-receptors on cerebral arteries and only NE from sympathetic neurons would activate these receptors. As the adrenergic neuroeffector pathway is not completely developed in the fetus, hypoxia appears to accelerate development of this system in the fetus, but retard it in the adult.

Pre-Synaptic Noradrenergic Function. In a series of studies, we have attempted to dissect the hypoxic-mediated NE-induced responses in terms of pre-synaptic (e.g., neuronal neurotransmitter release) versus post-synaptic (e.g., factors which determine contractile response) components. One measure of pre-synaptic noradrenergic functional capacity is NE content. In fetal intracranial arteries, but not common carotid, long-term hypoxemia was associated with a slight decrease in NE content. In contrast, both common carotid and cerebral arteries of the adult showed significant increase in NE content (21). These changes may appear paradoxical in light of the depression of neurogenic vasoconstriction in adult arteries, and its augmentation in fetal arteries. However, NE content is the product of both nerve number and the mean NE content per nerve fiber. In addition, NE content may be less in those nerves which fire often, as compared with those that are more quiescent. Thus, these results suggest that in comparison with normoxic, control fetal arteries, hypoxic vessels· have fewer adrenergic nerve terminals or less NE per nerve. The opposite would be expected in the adult arteries, e.g., increased adrenergic nerve density or greater NE content per nerve. These results emphasize the contrasting effects of long-term hypoxia on fetal and adult common carotid and cerebral arteries.

Another index of pre-synaptic noradrenergic function is nerve density. This can be determined indirectly by quantifying cocaine-sensitive NE uptake, a selective measure of NE containing nerve terminals. As shown in Figure 2, upper panel, in adult and fetal common carotid arteries exposed to 10^{-7} M cocaine, long-term hypoxia was associated with elevated NE uptake of 86% and 132%, respectively (i.e., greater adrenergic nerve density). Other intracranial arteries except the middle cerebral also showed a similar increase (21). Importantly, long-term hypoxia had a similar effect in both fetus and adult. Thus, nerve density changes alone cannot explain the age related differences in NE content (hypoxemic-induced decrease in fetus and increase in adult). Thus, it would appear that long-term hypoxemia is associated with decreased NE content per nerve, possibly resulting from increased nerve recruitment in fetal arteries. Adult arteries show the opposite response, e.g., increased NE content per nerve, due possibly from decreased nerve recruitment (21).

An additional factor that may account, in part, for the hypoxic-induced alterations in contractile response to nerve stimulation, is the co-release with NE from adrenergic nerve terminals of neuropeptide Y (NPY). Following NE depletion from adrenergic nerves by pretreatment with guanethidine (10^{-6} M), the remaining tetrodotoxin-sensitive neurogenic responses can be attributed to NPY release. In response to long-term hypoxemia, both adult common carotid and middle cerebral artery showed significant decreases in maximum response to stimulation at 8 Hz. In contrast, fetal arteries showed enhanced responses. That is, long-term hypoxemia decreased the NPY component in adult common carotid and intracranial arteries, while enhancing it in the fetal vessels (21). Thus, the pre-synaptic effects of long-term hypoxemia were similar for NE and NPY, but are opposite for adult and fetus. In the adult, long-term hypoxemia appears to increase neurotransmitter content per nerve, possibly due to increased adrenergic nerve activity. In contrast, long-term hypoxia decreases neurotransmitter content per nerve in the fetus, possibly as a result of increased neuronal activity

(21).

Post-Synaptic Noradrenergic Function. Post-synaptic mechanisms in adrenergic-mediated vascular contractility include a multitude of factors, some of which are: vascular smooth muscle plasma membrane α_1-,α_2-, and ,ß-adrenergic receptors (AR), their density and binding affinity, the second messengers (inositol 1,4,5-trisphosphate ans(1,4,5)P_3) for α_1-AR, and cyclic adenosine monophosphate (cAMP) for α_2- and ß-AR), the Ins(1,4,5)P_3 receptor (Ins(1,4,5)P_3-R) on endoplasmic reticulum, intracellular calcium, several enzymes and their state of activation, and so forth.

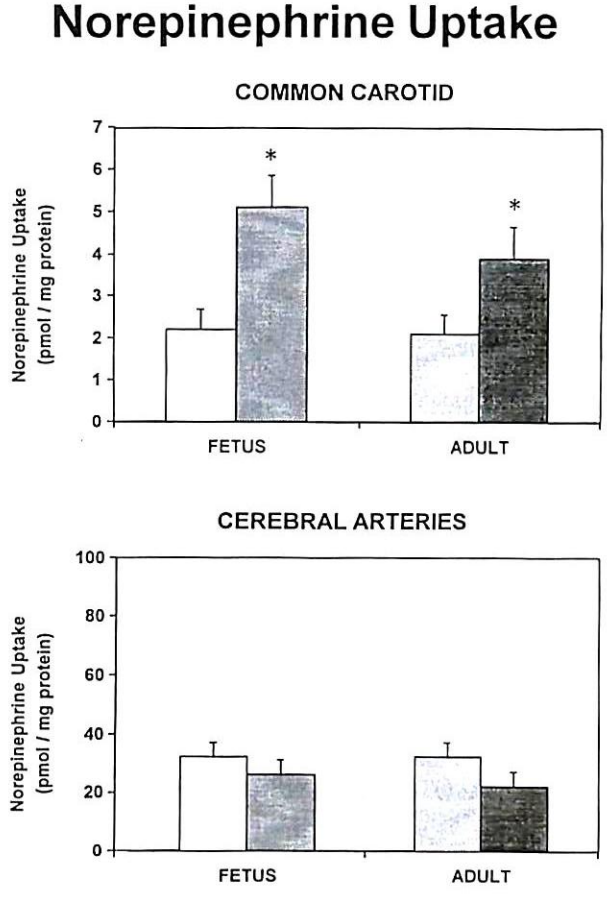

Figure 2. Upper Panel. Effects of long-term hypoxia on norepinephrine uptake in fetal and adult common carotid artery. Paired arteries were exposed to [^{3}H]-norepinephrine with and without the presence of 10^{-7} M cocaine. The differences between control and cocainetreated arteries are shown. Note that in the common carotid hypoxia appears to increase nerve density in both fetal and adult arteries. Values are mean ± SEM; *p<0.05 Lower Panel. Effects of long-term hypoxia on norepinephrine uptake in fetal and adult middle cerebral arteries. Paired arteries were exposed to [^{3}H]-norepinephrine with and without the presence of 10^{-7} M cocaine. *p<0.05.

To examine the role of α_1-adrenergic receptors and their alteration with long-term hypoxia, we quantified these receptors in common carotid and anterior, middle, and posterior (AMP) cerebral arteries of fetuses and adult sheep acclimatized to high altitude. Figure 3, upper panel, shows the α_1-adrenergic receptor density values (B_{max},in fmol/mg protein), as measured with saturation binding of the α_1-AR antagonist [^{3}H]prazosin, for normoxic control and high altitude, hypoxemic fetal and adult common carotid artery. In the fetus and adult, in response to long-term hypoxemia, α_1-AR density decreased 75% and 66% from normoxic control values, respectively. For both the hypoxemic fetus and adult, these receptor density values were significantly different from normoxic controls (p<0.01). Figure 3, lower panel, shows •$_1$-AR density values in fetal and adult combined anterior, middle, and posterior cerebral arteries. High altitude, long-term hypoxemia was associated with decreases of 76% and 61% from control values, respectively (p<0.01). [3H]prazosin binding affinity values (K_D) of both common carotid and AMP cerebral arteries averaged 0.13±0.07 nM, and did not vary significantly as a function of hypoxemia, developmental age, or vessel type (23).

To examine the effect of long-term hypoxemia on the NE dose--Ins(1,4,5)P_3 response relationship for cerebral arteries, we quantified Ins(1,4,5)P_3 (maximal response at 45 sec) as NE varied from 10^{-7} to 104 M in both adult and fetal AMP cerebral arteries. For normoxic fetal AMP cerebral arteries, 10^{-3} M NE-induced Ins(1,4,5)P_3 increased 212% from the basal value. In hypoxic arteries the basal value was similar to normoxic control, increasing only 96% with 10^{-3} M NE. The EC_{50} values for hypoxic adult and fetal AMP cerebral vessels did not differ significantly from normoxic control. Figure 4, upper panel, shows these responses, expressed as percent of basal value, for the common carotid artery of the fetus and adult. The normoxic fetal common carotid showed essentially no response to NE, and this was not altered by hypoxemia. In contrast, in adult common carotid, long-term hypoxemia was associated with a decrease of NE-induced Ins(1,4,5)P_3 response of 51% from control. In fetal and adult AMP cerebral arteries aFig. 4, lower panel), long-term hypoxemia was associated with decreases in Ins(1,4,5)P_3 response

of 35% and 44%, respectively, from normoxic NE-induced values (23).

To examine inositol 1,4,5 trisphosphate receptor binding in hypoxic vessels, we quantified the Ins(1,4,5)P_3-R in the hypoxemic fetal and adult common carotid and AMP cerebral arteries, and compared these values with normoxic controls. In the common carotid artery of the fetus and adult, Ins(1,4,5)P_3-R density fell 32% and 70% from normoxic control values, respectively. Ins(1,4,5)P_3-R density decreased 80% and 47% from control values for fetal and adult AMP cerebral arteries, respectively. In the hypoxic vessels Ins(1,4,5)P_3-R affinity did not change significantly from control (23).

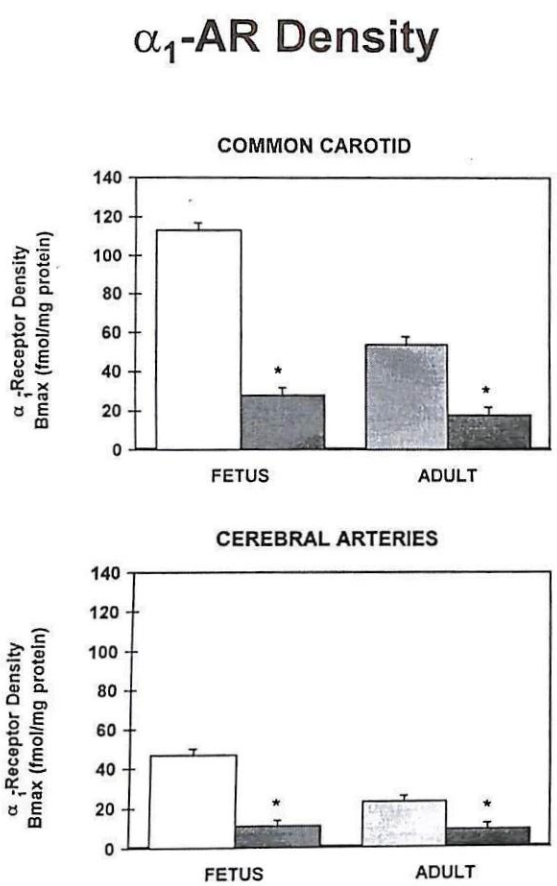

Figure 3. Upper Panel. α_1-adrenergic receptor density (B_{max}) values (fmol/mg protein) as determined with ^{3}H-prazosin, in the common carotid artery of normoxic control (open or lightly shaded bar) and high altitude, hypoxemic (heavily shaded bar) fetal and adult sheep. Data are mean values ± SEM. For both fetal (n=4) and adult (n=5) COM the receptor density values for hypoxemic vessels were significantly different from normoxic controls. *p <0.01

Lower Panel. α_1-adrenergic receptor density of combined anterior, middle, and posterior cerebral arteries for the normoxic control and hypoxemic fetus and adult. Data are mean values ± SEM. The receptor density values of both fetus (n=4) and adult (n=4)were significantly different from the values for the normoxic controls. *p<0.01.

Relaxation Responses. In response to the endothelium-dependent, receptor-independent, vasodilator (by release of endothelium-derived relaxation factor) A23187, chronically hypoxemic fetal common carotid and middle cerebral arteries showed less relaxation than normoxic controls. In contrast, adult common carotid (and to a less extent other cerebral arteries) showed enhanced responses to A23187. By comparison, both hypoxemic fetus and adult showed decreased relaxation responses to the endothelium-independent relaxant nitrosothiol SNAP (s-nitroso-N-acetylpenicillamine). Thus, the ratios of A23187 to SNAP were lower in hypoxemic fetal arteries, while they were higher in the adult vessels (9).

Pregnancy-Associated Effects on Contraction and Relaxation Responses. In the normoxic adult, pregnancy is associated with profound alterations of vascular structure and function, including the cerebrovasculature (24, 25, 26). These changes are believed to be mediated in part by the marked increases in circulating estrogen, progesterone, and other hormones (27, 28). To examine the combined challenge of hypoxia and pregnancy, we examined contractile and relaxation responses in pregnant and nonpregnant adult sheep acclimatized to high altitude hypoxemia. Although both pregnancy and high altitude produced significant alterations in cerebrovascular function, these were not simply the sum of responses in the two groups. Both hypoxic pregnant and hypoxic nonpregnant common carotid and middle cerebral arteries showed increased contractility to potassium depolarization, compared with normoxic pregnant or nonpregnant controls (29). For common carotid (but not middle cerebral) these changes were similar when corrected for vessel thickness (e.g., stress). We observed no significant difference in α_1-AR density or affinity, NE-induced Ins(1,4,5)P_3 response, or Ins(1,4,5)P_3-R density or affinity between pregnant and nonpregnant common carotid or AMP cerebral arteries. For

common carotid from pregnant animals, endothelial function, as measured by relaxation response to A23187, was decreased. However, this was markedly enhanced by hypoxia. Such changes were not notable in middle cerebral or other intercranial arteries (29). Clearly, cerebral vascular responses and dynamics of hypoxemia and pregnancy affect vessels in an artery specific manner.

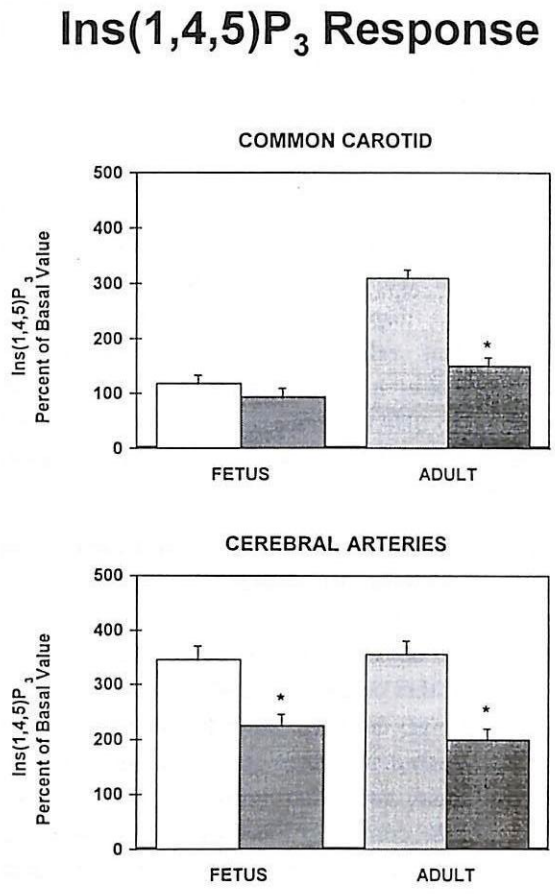

Figure 4. Upper Panel. Norepinephrine-stimulated (10^{-4} M) $Ins(1,4,5)P_3$ values (expressed as percent of basal value) in normoxic and hypoxemic term fetal and adult ovine common carotid artery. Values are expressed as mean ± SEM. The value for hypoxic adult COM (n=5) was significantly different from that of the normoxic control. **p <0.01.

Lower Panel. NE-induced $Ins(1,4,5)P_3$ values for AMP cerebral arteries of the normoxic (open bar) and hypoxemic (shaded bar) fetus and adult. The values for hypoxemic fetus (n=4) and adult (n=5) were both significantly different from normoxic controls, *p<0.01

COMMENT

For the adult, high altitude has served as a useful model of how the body's physiological mechanisms acclimatize over a period of days or weeks, or genetically adapt over the course of generations. For the fetus, because of its relatively low arterial PO_2values simulating "Mt. Everest *in utero*" under normoxic, control conditions, the question of how it can grow and develop in a mother at high altitude has posed a dilemma. Because of its obvious relevance to neuronal function, the regulation of cerebral blood flow is important.

Hopefully, the present studies will help to illuminate a rather obscure corner of regulatory physiology. That different elements of the adrenergic-mediated pre-synaptic and post-synaptic signal transduction cascade are independently regulated, both in the adult and in the fetus, should come as no surprise. Because in our studies of the fetus under conditions of long-term hypoxemia the circulating concentrations of epinephrine and norepinephrine were high normal to elevated (30), this chronic vasoconstrictor influence may down-regulate the several portions of the signal transduction cascade. Such a modified regulatory response may help insure that vessel contractility is decreased, so that cerebral oxygenation is not compromised. In addition, many of the hypoxic-induced changes observed in the fetal vessels are similar to those associated with developmental maturation. Nonetheless, the manner in which these changes serve to regulate cerebrovascular tone under these circumstances in vivo must await further studies. In addition, the present studies may provide useful leads to examine the critical issue of hypoxic-mediated gene transcription in modulating the adrenergic signal transduction pathway.

CONCLUSIONS

In adult common carotid and AMP cerebral arteries, acclimatization to high altitude, long-term hypoxemia was associated with significant alterations in pre-synaptic and post-synaptic adrenergicmediated mechanisms; however, these were not necessarily the same in the two vessel groups. Fetal common carotid and AMP cerebral arteries also showed considerable alterations in these mechanisms in response to long-term

hypoxemia. Nonetheless, there were significant differences in these responses between the two vessel groups in the fetus, and between adult and fetus. These findings illustrate the complexity of acclimatization responses to high altitude, and probably account, in part, for the significant hypoxic-induced differences in NE-induced contractility in adult and fetal cerebral vessels. Of course, other elements in the adrenergic-mediated signal transduction pathway may also differ under these conditions. Alterations in these or other signal transduction mechanisms may also play a key role in dysregulation of cerebral blood flow in the adult subjected to high altitude, long-term hypoxemia, as well as in the fetus or newborn subjected to prolonged hypoxemia.

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