Hypoxic sensing in the lung: mitochondria and reactive oxygen species

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The ability to sense changes in oxygen tension is shared by a variety of tissues, though there is evidence to suggest that the same mechanisms and transduction pathways are not employed by all. The carotid body glomus cell, neuroepithelial cells of the lung and pulmonary vascular smooth muscle all respond to an acute fall in oxygen with a rapid rise in intracellular calcium, with a consequent increase in efferent nerve activity or hypoxic pulmonary vasoconstriction (HPV) respectively. These mechanisms are primarily focused on matching and optimising gas exchange in the lung to metabolism. More prolonged hypoxia affects gene transcription in many tissues, often mediated via HIF, leading in the lung to metabolism. More prolonged hypoxia affects gene transcription in many tissues, often mediated via HIF, leading to adaptive alterations in protein expression and often modulation of cell proliferation and tissue remodelling.

ROS have also been implicated in the effects of changes in oxygen tension on proliferation of human fetal airway smooth muscle. Changes in oxygen tension from the norm, either up or down, may therefore have profound effects on development of the fetus. For example, the relative hyperoxia suffered by ventilated premature neonates is believed to contribute to the development of bronchopulmonary dysplasia. In the adult, chronic hypoxic lung disease can lead to pulmonary vascular remodelling and pulmonary hypertension.

Despite numerous studies, the cellular mechanisms responsible for oxygen sensing remain elusive, although a consensus is emerging that electron transport chain (ETC) of the mitochondrion plays a central role, at least in the carotid body and pulmonary vasculature. However both the location and mechanism of the ETC sensor, and the signal transduction pathways linking the mitochondria to the rise in intracellular calcium, remain highly controversial. There are three main competing hypotheses, all essentially based on an hypoxia-induced reduction in electron flux through the ETC: the first hypothesis is that during hypoxia there is a fall in production of reactive oxygen species by the ETC and a reduced cytosolic redox state; potassium channels are therefore reduced and inhibited, leading to depolarisation (e.g. Michelakis et al., 2002). In direct contrast, the second hypothesis proposes that hypoxia causes an increase in generation of ROS from complex III of the ETC, which then acts as the signalling moiety (e.g. Waypa et al., 2002). Although the precise cellular targets of the latter are unclear, several potential candidates have been suggested (Ward et al., 2004). The third hypothesis essentially proposes that signalling is related, either directly or indirectly, to a fall in activity of the ATP F1F0 synthase and ATP production (e.g. Wyatt & Buckler, 2004). This last hypothesis is largely based on studies of the glomus cell, which may well differ from pulmonary vascular smooth muscle. Different predictions can be made for each hypothesis, in particular concerning the effects of mitochondrial inhibitors acting at different points in the ETC. Our own data on HPV in isolated small pulmonary arteries would largely tend to support hypothesis 2, with signalling derived from complex III of the ETC (Ward et al., 2004). ROS have also been implicated in the effects of changes in oxygen tension on proliferation of human fetal airway smooth muscle, but here the relationship may be even more complicated.

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Developmental regulation of oxygen sensing in the
pulmonary circulation.

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At birth, the pulmonary circulation dilates in response to an increase in O2 tension and nitric oxide (NO). Both pulmonary artery smooth muscle cells (PA SMC) and endothelial cells directly sense an acute increase in O2 tension. In PA SMC, the capacity to respond to an acute increase in O2 tension is developmentally regulated. In fetal PA SMC, the ion channel that determines resting membrane potential is the large-conductance calcium-sensitive K+ (KCa) channel. The signaling pathway that results in pulmonary artery smooth muscle (PA SMC) relaxation in response to an acute increase in O2 tension includes an increase in cytosolic cGMP, cGMP dependent kinase-mediated release of calcium (Ca2+) sparks from ryanodine-sensitive intracellular stores, KCa activation and membrane hyperpolarization. With maturation, concomitant with loss of the capacity to respond to an acute increase in O2 tension, the ion channel that determines PA SMC resting membrane potential changes to a voltage-sensitive K+ (Kv) channel, as KCa channel expression decreases, Kv 2.1 expression and the sensitivity to acute hypoxia increases.

If the perinatal pulmonary circulation responds incompletely to vasodilator stimuli a syndrome termed persistent pulmonary hypertension of the newborn (PPHN) results. PPHN is characterized by severe central hypoxemia as blood shunts away from the lung via the ductus arteriosus and the patent foramen ovale. PPHN is a significant cause of neonatal morbidity and mortality. PPHN is associated with perinatal infection, bleeding, asphyxia, and intrauterine exposure to cyclooxygenase inhibitors. PA SMC oxygen sensing is compromised in an ovine model of PPHN, as an acute increase in oxygen tension has no effect on cytosolic calcium. PA SMC KCa channel expression is decreased, the ion channel that determines resting membrane potential changes to a Kv channel, and intracellular Ca2+ homeostasis is compromised. Recent data indicates that in PA SMC from fetal...
lambs with chronic intrauterine pulmonary hypertension, capacitive calcium entry is increased and the expression of transient receptor protein channel 6 is increased, providing evidence that augmented capacitative Ca^{2+} entry may play an etiologic role in PPHN.

Further data indicates that chronic intrauterine pulmonary hypertension effects not only the physiologic, but the molecular response of fetal PA SMC to an acute increase in O_{2}. In control fetal PA SMC, sustained exposure to room air concentrations of O_{2} tension decreases both KCa and voltage-operated calcium channel expression, while increasing cGMP-sensitive kinase I alpha (cGMP Kinase I α) expression. In contrast, in PA SMC derived from fetal lambs with chronic intrauterine pulmonary hypertension, the O_{2}-induced decreases in KCa and VOCC channel expression and the O_{2}-induced increase in cGMP Kinase I α are blocked. Since chronic intrauterine pulmonary hypertension has a long-term effect on the molecular response to sustained normoxia, the fetal experience of the pulmonary circulation may inform the response of pulmonary circulation well into adulthood.

Recent data from our laboratory suggests that the developmental regulation of hypoxic inducible factor-1 (HIF-1) genetic expression may render the fetal pulmonary circulation uniquely sensitive to an acute increase in O_{2} tension. In specific, HIF-1 mRNA expression is increased by hypoxia in fetal, but not adult, PA SMC. Conversely, normoxia decreases HIF-1 expression in adult, but not fetal PA SMC. From a teleologic perspective, relatively robust expression of hypoxia-sensitive genes can be rationalized by recognition that mammalian survival is absolutely contingent upon the capacity of the pulmonary circulation to vasodilate at parturition in response to an acute increase in O_{2} tension. Data indicating augmented HIF-1 mRNA and protein expression in the fetal, but not the adult, pulmonary circulation supports the notion that the low oxygen tension environment of the normal fetus increases expression of a transcription factor responsible for controlling expression of developmentally essential hypoxia-sensitive molecules.

Fetal PAEC respond to acute normoxia with an increase in cytosolic calcium. The O_{2}-induced increase in cytosolic calcium results from membrane depolarization, entry of extracellular calcium, and release of calcium from inositol triphosphate-sensitive stores. Interestingly, in PAEC from fetal lambs with chronic intrauterine pulmonary hypertension, cytosolic calcium does not increase in response to an increase in oxygen tension. In PAEC derived from control fetal lambs nitric oxide production increases in response to acute normoxia. However, in animals with chronic intrauterine pulmonary hypertension, PAEC cytosolic nitric oxide production does not increase in response to acute normoxia.

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**SA11**

**Genetic influences on pulmonary hypertension**

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Recent studies have identified key pathways involved in the development of pulmonary hypertension. In particular, heterozygous germline mutations in receptors of the transforming growth factor-β superfamily have been shown to underlie some cases of idiopathic pulmonary arterial hypertension. Thus mutations in the bone morphogenetic protein type II receptor (BMPR-II) are responsible for approximately 65% of cases of familial PAH, and 10-20% of sporadic cases. Mutations have been described in almost every exon of the BMPR-II coding sequence. 70% of these are predicted to cause premature truncation of the protein, with some mutations predicted to result in nonsense mediated mRNA decay and complete absence of protein product. Approximately 30% of mutations are missense mutations, resulting in a change in a highly conserved amino acid. Some of these cause disruption of the ligand binding or kinase domain of the receptor, while others lead to failure of receptor trafficking to the cell surface. Evidence is now emerging that dysfunction of these pathways may play an important role in patients in whom no mutation has been identified. Pulmonary artery smooth muscle cells isolated from patients with idiopathic PAH demonstrate abnormal growth responses to BMPs and TGF-β, whether or not a mutation can be identified in BMPR-II. Severe PAH can also occur in families with hereditary haemorrhagic telangiectasia, usually associated with mutations in the ALK-1 TGF-β receptor. BMPR-II and ALK-1 signal via the same restricted set of Smad proteins in endothelial cells. The molecular mechanism of the vascular occlusion seen in PAH may involve an imbalance between critical downstream mediators of TGF-β/BMP signalling, the Smad proteins, and upregulation of mitogen activated protein kinase pathways. The level of expression of the BMPR-II receptor and the phosphorylated isoforms of downstream Smads is reduced in the lung tissue of PAH patients whether or not a mutation is detected in the coding region of the gene. Studies of the BMPR-II promoter reveal powerful negative regulators of gene expression, which seem to be regulated by inflammatory stimuli. It is likely that other genetic or environmental stimuli are required for the clinical manifestation of PAH in patients carrying BMPR-II mutations, since it is estimated that only 15-20% of disease gene carriers eventually develop the disease. This “second hit” may involve further inherited or somatic mutations in related pathways, or exposure to other agents known to be associated with PAH, such as appetite suppressant drugs many of which influence the metabolism of serotonin. Recent genetic association studies have shown an increased frequency of polymorphisms regulating the expression of the serotonin transporter in PAH and in hypoxic pulmonary hypertension. This polymorphism affects the level of expression of the transporter. Interestingly, we have shown that serotonin potentiates the development of pulmonary hypertension in a mouse deficient in BMPR-II, providing a potential link between these two systems.

Fetal and neonatal adaptation of the cardiopulmonary systems to high altitude hypoxaemia

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The fetal llama has walked for millions of years by the thin oxygen trail of the Andean altiplano. We hypothesise that a pool of genes has been selected in the llama (Lama glama) that express very efficient mechanisms to withstand hypoxia. The fetal llama submitted to acute hypoxaemia responds with an intense peripheral vasoconstriction which is 4-5 times greater than that found in fetal sheep. This intense peripheral vasoconstriction is not changed by section of the fetal carotid sinus nerves (Llanos et al. 2003). Therefore, the response is not mediated by a chemoreflex; instead endocrine and local vascular factors play a major role. We have reported that in the fetal llama, vasopressin, nitric oxide (NO) provides an important vasodilator tone to brain, adrenal, kidney, gut and carcass vascular beds during normoxaemia and hypoxaemia. Interestingly, adrenal blood flow does not increase during hypoxaemia in fetal llamas treated with L-NAME, an inhibitor of endothelin-A receptor, does abolish the marked increase in femoral vascular resistance observed during hypoxaemia in the llama fetus (Llanos et al. 2003). Local endothelial factors, such as nitric oxide (NO) provides an important vasodilator tone to brain, adrenal, kidney, gut and carcass vascular beds during normoxaemia and hypoxaemia. Interestingly, adrenal blood flow does not increase during hypoxaemia in fetal llamas treated with L-NAME, an inhibitor of nitric oxide synthase (Llanos et al. 2003). Treatment with BQ-123, an inhibitor of endothelin-A receptor, does abolish the marked increase in femoral vascular resistance observed during hypoxaemia in the llama fetus (Llanos et al. 2003). In the brain, there is little or no increase in cerebral blood flow during acute hypoxaemia in the llama fetus, decreasing brain oxygen delivery pari passu with the decrease in carotid artery O2 content. In spite of this lack of increase in brain blood flow, there is no increase in O2 extraction across the brain, therefore a decrease in cerebral oxygen uptake occurs during different degrees of hypoxaemia in the llama fetus (Llanos et al. 2003). The fetal electrocorticogram (ECOG) mirrors this substantial reduction in cerebral oxygen consumption, since it remains flat during a 40 min hypoxic insult, returning to normal during the immediate (60min) and late (48h) post-hypoxic periods (Llanos et al. 2003). With a more prolonged hypoxaemia (24h), there is a decrease in the fetal brain temperature with a reduction in activity of the Na+/K+ATPase in the cerebral cortex. Therefore, we propose that the fetal llama brain responds to hypoxia with a marked hypometabolism. The neonatal llama also responds to acute hypoxaemia with an intense femoral vasoconstriction, as intense as in the fetal life. The sensitivity to noradrenaline of the small femoral arteries is greater in the neonatal llama compared to the newborn sheep, explaining partially the intense femoral vasoconstriction observed in the former. In the pulmonary circulation, the neonatal llama has the same basal pulmonary arterial pressure in high altitude (HA) (3,580m) and in low altitude (LA) (Herrera et al. 2004). In contrast, the newborn lamb in HA has pulmonary hypertension, with the pulmonary arterial pressure 80% higher than at sea level. Clearly there is in the llama an important adaptation of the pulmonary circulation to the chronic hypoxia found in the Andean altiplano.

We observed no increase in brain blood flow, but a reduction in brain oxygen uptake, decrease in Na+/K+ATPase activity cerebral cortical cells in the llama fetus. Furthermore, the fetal and neonatal llama respond to hypoxemia with an intense peripheral vasoconstriction. These responses are different from those present in lowland species and could be explained by a profound hypometabolism, both in the brain as well as in the whole body. How this hypometabolism is produced and how the cells are preserved during this condition remains to be elucidated.


Herrera et al. (2004) Fetal and Neonatal Physiological Society, Castelvecchio Meeting, Italy.

Funded by Fondecyt 1010636, 1020599, and The Wellcome Trust, CRIG 072256.

Genetic factors influence susceptibility to hypoxia-associated reductions in birth weight.

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Coordinated maternal, fetal and placental responses to pregnancy are required to ensure a continuous delivery of nutrients to the developing organism. Oxygen can be viewed as one such nutrient since fetal growth is impaired under the conditions of chronic hypoxia present at high altitude (>2500 m), during severe maternal anemia or uteroplacental ischemia. Some 140 million persons live at high altitude worldwide and thus comprise the largest single group at risk for fetal growth restriction. Of interest is that not all human populations are equally susceptible to altitude- associated fetal growth restriction. Comparing literature observations for some 4 million births at 0 – 5000 m, multi- generational Tibetan and Andean populations demonstrate less altitude- associated reduction in birth weight than Europeans or Han (Chinese) who have resided there for <1 or only a few generations. Our current studies in Bolivia use this experiment of nature to test the hypothesis that genetic factors (a) influence susceptibility to altitude- associated fetal growth restriction, (b) act on maternal uteroplacental and systemic vascular adaptations to pregnancy which determine uteroplacental blood flow, and (c) involve genes which regulate and/or are regulated by hypoxia-inducible factors (HIFs). In 3538 prenatal, labor and delivery, and newborn records at 300–4100 m from both public and private facilities in Bolivia, there is less altitude- associated fetal growth restriction in babies born to Andean vs. European–surnamed parents. Birthweight reductions are intermediate in mestizo (“mixed”)–surnamed infants. A more refined classification using 5 ancestry groups for the high–altitude deliveries suggest that the protective effect of Andean ancestry is “dose–dependent”. To determine whether maternal oxygen delivery to the uteroplacental circulation differs in women of
Andean vs. European ancestry, we conducted physiological studies at 20, 30 and 36 weeks of pregnancy as well as when non-pregnant (3 mo postpartum) in 50 Andean and 25 European women residing at 3200–4100 m. Both groups show similar increases in ventilation and blood volume with pregnancy, but O2 content falls slightly as the result of greater plasma volume than red cell mass expansion. There is less pregnancy–associated increase in uterine artery diameter in the European than Andean women with the result that calculated uterine artery blood flow and O2 delivery is lower in the European women from pregnancy wk 20 until term. Preliminary measurements of the products of HIF–targeted genes indicate that Andean women have lower levels of the circulating vasoconstrictor endothelin–1 (EDN) during pregnancy than European women. Initial genomic studies using single nucleotide polymorphisms (SNPs) suggest that a considerable proportion (44%) of the differences between Andean populations and low–altitude controls resides near HIF–targeted genes. Future studies are planned for deciding whether genetic factors influence susceptibility to hypoxia–induced fetal growth restriction and the particular genes or genomic regions involved. In relation to developmental programming, studies at high altitudes raise questions as to whether hypoxia “programs” developmentally and if so, what are the relative contributions of genetic vs. developmentally–acquired influences on the programmed phenotype.

Small birthweight and developmental programming of adult disease: what is it telling us?

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There is an epidemic of obesity, with associated type 2 diabetes and metabolic syndrome in developed societies, and in some developing societies such as parts of the Indian sub-continent and China. The epidemic brings an enormous burden of chronic illness including cardiovascular disease and bone and joint disorders, which will have tremendous economic and humanitarian cost. Prevention of disease is difficult if its causes are not known. The speed of development of this problem rules out a genetic origin, although the action of early environmental factors on gene expression must be involved. It clearly results from some environmental change, and this underlines its prominence in populations in transition. In part the changing environment relates to nutrition, or probably more likely the balance between energy expenditure and calorific intake. The focus on the early origins of such disease has drawn attention to the ways in which predictive adaptive responses may play a part. These are induced by cues from the mother about the external environment including her dietary balance, body composition and metabolism. The effects can be mediated even on the pre–implantation embryo and determine the ways in which the late gestation fetus and the placenta interact. Maternal adaptations to pregnancy also play a role. During evolution these predictive responses conferred survival advantage in a poor or uncertain nutritional environment. But when the prediction is inappropriate, e.g. in a modern energy-rich environment, they are associated with greater risk of later disease. The mechanisms involved include epigenetic gene-environment interactions, e.g. changes in DNA methylation. In addition the effects of gene polymorphisms which confer susceptibility to disease in affected individuals become manifest when coupled with prenatal restriction of growth. Animal and human physiological studies are giving insights into these processes – one particular focus being on endothelial function. They also show that both the metabolic and the cardiovascular effects of an impaired intrauterine environment can be passed across two or more generations, questioning the ways in which we have traditionally thought about ‘inherited’ components of disease risk.

SA15

Can birthweight and pregnancy outcome be improved by nutritional supplementation? A study in Chilean women.

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Background: The Chilean Ministry of Health initiated powdered milk delivery to pregnant women in 1954. As a result of this and other health interventions, 99.9% of all pregnant women have regular ante natal checks and have their deliveries in maternity hospitals in Chile. The present powdered milk product delivered by the Ministry of Health to underweight pregnant women is called “Purita Fortificada” (PF). Women are classified as underweight using their weight/height ratio at the beginning of pregnancy. The Research Division of Parmalat spa and the Catholic University of Chile designed a new powdered milk–based product fortified with multi-micronutrients called Mamán (M). Amino–chelated iron is one of the novel components of this product. Omega–3 is also included.

Aim: We report the results of an experimental trial of food supplementation in underweight Chilean women performed in 2002-2003. Fetal growth was compared in women receiving two different food supplements during pregnancy.

Methods: Women were randomly assigned to either a control group receiving the regular 2 kg per month of powdered milk (PF) or an experimental group receiving 2 kg of M. The two groups were informed about the nutritional value and preparation of either supplement. Both are diluted at 10% and a daily consumption of 660 ml was recommended. During the monthly check–ups maternal weight changes and conditions or complications of pregnancy were registered. Women were also visited at home twice (20 and 35 w pregnancy) to study the home diet (24-h recall method) and socio-economic status.

Results: Each group consisted of 332 (PF) and 347 (M) women. Maternal anthropometric variables at recruitment were similar between the two study groups (e.g. a BMI mean value of 20 in the two groups at week 11 of gestation). Other control variables such as the characteristics of the home diet and the family socio-economic status were also similar. Mean daily consumption of the two supplements was slightly higher in the control group (over 30 g/d in the two groups), i.e. somehow lower than two cups; the lower amount consumed in the experimental group is related to the presence of a higher proportion of non-consumers.
in this M group. Newborn characteristics in each study group were analysed according to the presence or absence of medical and obstetrical complications, including smoking. Smokers of at least one cigarette per day were 27 in the PF group meanwhile in the M group they were 33. The pregnancies of women in the experimental group lasted on average 273.3 ± 10.3 d, three days longer than the control group (p < 0.01). Mean birth weight was 124 g higher in the M group (p < 0.001) Proportions of low birth weight (< 2,501 g) and birth weight < 3,001 g were significantly lower in the experimental group. Significant differences in mean birth length and mean head circumference were also found. Maternal weight gain was somewhat higher in the experimental group but the difference was not statistically significant. Conclusion: Fetal growth in mildly malnourished women may be greatly enhanced with multi-micronutrients supplementation. These results are notably better than those previously published by us in the Santiago study (Mardones-Santander et al., 1988). The Santiago study has been selected as one the four best trials done elsewhere (Pojda & Kelly, 2000).

Mean birth weight in the M group almost doubled (124 g) the figure observed in the experimental group of the Santiago study (73 g) which also received a milk-based product fortified with multi-micronutrients. The present study also reached a favourable significant difference on birth length for the experimental group but the difference was not statistically significant.

These results are also consistent with previous data about the possible beneficial effects of omega-3 supplementation on pregnancy duration.


Animal models of developmental programming: what have we learnt from them?

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Developmental programming in the animal kingdom has been recognised for decades amongst animal breeders and from studies of natural disturbance of the maternal/fetal environment. However, associations between birth weight and susceptibility to adulthood disease described by Barker and colleagues led to a plethora of studies in experimental animals designed to determine whether modulation of the in utero and/or neonatal environment has lasting consequence for offspring cardiovascular and metabolic function in adulthood. The earliest models described how diabetes in rodent pregnancy or a maternal diet deficient in protein led to disorders of glucose homeostasis in the offspring. Those currently employed include studies in which the maternal diet has been manipulated, determination of the consequences of reduced blood flow to the uterus and investigations into the effects of maternal stress or behavioural disturbance. Rats, rabbits, mice, guinea pigs and sheep have been utilised.

Review of the literature reveals remarkable diversity of protocols eg in the timing of the nutritional intervention and in the parameters of cardiovascular and metabolic function evaluated in the offspring. Even amongst studies of the same intervention and the same animal, protocols between laboratories vary. Whilst this has not facilitated assimilation of information or the drawing of definite conclusions, similarities are apparent which may indicate commonality of mechanism. Offspring of rodents subjected to maternal hyperglycaemia, maternal protein restriction, global reduction of maternal diet or maternal dietary fat supplementation share common disorders of glucose homeostasis. Offspring are frequently insulin resistant and show early anomalies of pancreatic function and structure. Adulthood insulin resistance has also been associated with exposure in pregnancy to raised concentrations of maternal glucocorticoids and permanent alteration in the offspring HPA axis is a likely mechanism underlying developmental programming in at least some of the animal models. The supposition that several of the models share characteristics of human metabolic syndrome is not entirely justifiable from the available data, as few laboratories study all of the constellation of disorders that contribute to this syndrome (insulin resistance, dyslipidaemia, hypertension, obesity). Amongst the nutritional models the development of hypertension is variable and dyslipidaemia is infrequently reported. It must also be considered that there are important differences in lipid metabolism between rodents and man.

The recent observation that programmed disturbances of offspring's stress responses are associated with hypomethylation status of the glucocorticoid receptor gene has fuelled speculation that altered methylation status may contribute to permanent programming of offspring gene expression and thence to phenotype. In addition, the transmission of certain phenotypic characteristics through the maternal line support a proposed role for permanent alteration in the mitochondrial genome. Imbalance of maternal nutrition may produce limits of tolerance in the offspring to nutritional challenge in later life (predictive adaptive responses). This intriguing hypothesis is one which can be put to the test in the different animal models.


Weaver IC et al. (2004). Nat Neurosci 7, 847-54.


LP is funded by Tommy’s the Baby Charity. We thank the British Heart Foundation for support.