The maternal, fetal and postnatal somatotrophic axes in intrauterine growth retardation

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Fetal growth regulation is a complex process controlled by the interaction of genetic and environmental factors. Although genetic factors ultimately limit growth potential, the most influential factor during fetal life is substrate supply to the fetus. The inter-relationship of fetal substrate supply with hormones of the somatotrophic axis – growth hormone (GH), insulin-like growth factor (IGF)-I and IGF-II – is central to the regulation of fetal growth. Under conditions of normal fetal growth, fetal and maternal concentrations of somatotrophic hormones and insulin are strongly regulated by substrate supply, particularly in mid to late gestation. These hormones in turn have important effects on the partitioning and metabolic utilization of substrates [1]. However, in conditions of intrauterine growth retardation (IUGR), the regulation of somatotrophic hormones by nutrients may be impaired or altered. In addition, the effect of these hormones on placental function and growth processes is also altered. In adverse conditions there may be adaptive value in fetal growth being modulated in order to maintain viability of pregnancy but perhaps also for pre-adapting the newborn to a restrictive external environment. However, it is probable that any adaptive value of IUGR and the associated re-programming of metabolic and endocrine relationships comes at a cost that becomes more apparent during postnatal life, particularly if the environment is no longer restricting.

The role of the somatotrophic axis in fetal growth

Fetal GH had traditionally been thought to have little or no direct role in fetal growth [2]. However, GH receptors are present in many fetal tissues albeit at low concentrations [3]. Other studies reveal that congenital GH deficiency is associated with reduced body length at birth [4]. The mechanisms behind the function of GH in fetal growth remain to be investigated. IGF-II is important in the promotion of embryonic and early fetal growth while IGF-I is probably more important in the regulation of growth in late gestation [5]. Experiments in mice using homologous recombination of defective IGF-I and/or IGF-I receptor genes to produce mutants homozygous for these defects have demonstrated marked IUGR in affected animals [6].

In all species with a longer intrauterine fetal phase, cord blood IGF-I levels correlate with birthweight [7–9] and are lower in plasma from IUGR fetuses [10,11]. The IGF binding proteins (IGFBPs), which regulate IGF action and bioavailability, are also altered in IUGR levels of...
IGFBP-3 are reduced whereas those of IGFBP-1 and -2 are increased [10].

Insulin has a constitutive role in fetal growth, particularly in late gestation. Elegant pancreatectomy and insulin replacement experiments demonstrate that adequate concentrations of insulin in the fetal circulation are necessary to maintain fetal growth [12]. Other experiments demonstrate that insulin is a primary regulator of fetal IGF-I [13].

Interaction of the somatotrophic axis and nutrient supply

The somatotrophic hormones both in the maternal and fetal circulations have an important role in the regulation of the interplay between placental and fetal nutrient uptake and utilization. Administration of GH to the pregnant ewe increases placental capacity for simple diffusion [14], and in the pregnant rat it increases placental growth and up-regulates gene expression of the placental glucose transporters [15,16]. Infusion of IGF-I to the pregnant ewe increases fetal glucose levels and placental lactate production [17]. Infusion of IGF-I to the fetal sheep reduces protein breakdown, increases fetal glucose uptake and appears to alter nutrient distribution between fetus and placenta. Placental lactate production is reduced by fetal IGF-I infusion, and placental demand for amino acids is also reduced, enhancing fetal nutrient availability [18]. Thus the maternal and fetal somatotrophic axes interact by influencing placental function to favour fetal growth.

Nutritional regulation of the somatotrophic axis

Circulating levels of the somatotrophic hormones in the mother and fetus are under strong nutritional regulation from mid to late gestation. In fetal sheep GH is elevated in response to undernutrition and exhibits a pattern of response very similar to that seen postnatally [19]. In sheep studies we have shown that fetal plasma IGF-I, IGF-II and IGFBP-3 levels, along with glucose and insulin, fall during severe maternal undernutrition or starvation while IGFBP-1 and -2 levels rise [20,21]. During continued maternal starvation, levels of IGF-I in the fetal circulation can be restored within 24 h by replacement of glucose or insulin to the fetus by direct infusion, but restoration of IGF-II levels only occurs with glucose replacement [13,22]. In late gestation IGF-II appears to be more constitutively regulated than IGF-I and requires very severe changes in nutrition or endocrine environment before marked changes in its level occur. The greater sensitivity of fetal IGF-I to nutritional change and to regulation by increasing concentrations of insulin suggests that it may indeed be the dominant IGF involved in the control of growth in late gestation when substrate supply is limiting.

Amniotic growth factors

The fetal fluids represent an additional source of nutrients and hormones for the fetus, including IGF-I and IGFBP-1 [23,24]. The mechanisms of control of utilization of amniotic hormones and nutrients are not understood. There is evidence for a potential role for IGF-I in the enteral utilization of nutrients. The gut wall expresses IGF-I receptors early on in gestation [25] and the presence of luminally administered radiolabelled IGF-I within enterocytes has been demonstrated [26]. Furthermore, if high doses of IGF-I are administered to the fetus enterally, serum levels rise [26].

The late-gestation fetus swallows large amounts of amniotic fluid every day [27]. Human fetuses unable to swallow due to an oesophageal atresia have lower birthweights than controls, especially if born near to term [28,29]. We have shown that ovine fetuses with a ligated oesophagus are smaller than controls and have retarded development of the gut. Infusion of very low doses of IGF-I beyond the ligation prevents the growth restriction and permits normal gastrointestinal development [30].

Intrauterine growth retardation

The causes of pathological IUGR are genetic/chromosomal abnormalities, the toxic embryopathies (such as congenital rubella syndrome) and substrate limitation. In addition to the more common genetic abnormalities, a case of IGF-I gene deletion causing IUGR and severe short stature has recently been described [31]. Substrate limitation resulting in fetal undernutrition accounts for the largest number of IUGR babies. Most causes of substrate limitation in the Western world are due to deficiencies in the supply of nutrients to the fetus, commonly at the uteroplacental level, rather than to inadequate levels of maternal intake. While IUGR may be an adaptation to environmental stress it remains the major cause of perinatal mortality [32–34].
There are various models of IUGR in the sheep, including maternal undernutrition, heat stress, limitation of placental size by carunclectomy, and placental damage by embolization of either the uterine or umbilical placental supply with microspheres. The acute metabolic response by the fetus to a reduction in nutrient supply involves the breakdown and oxidation of endogenous substrates. Protein oxidation may account for up to 80% of oxygen consumption and protein synthesis is inhibited [35]. In the face of longer term reductions in nutrient supply the fetus decreases glucose uptake and utilization [36–38]. Urea production increases by 50% suggesting that amino acids (both endogenous and transplacental) are substituted for glucose as an oxidative fuel [39]. The placenta also has significant oxidative demands and may compete directly with the fetus. Glucose may be taken up from the fetal circulation by the placenta [40,41], and under severe conditions the placenta may also take up amino acids from the fetus [42].

Placental glucose transporters themselves are altered in models of IUGR. Placental GLUT1 but not GLUT3 gene expression is enhanced in IUGR secondary to maternal dietary restriction [43]. However, GLUT1 protein translocation to the cell membrane for activation is actually reduced in this model of IUGR and also in placenta of spontaneously hypertensive rats [43].

The metabolic changes observed in situations of longer term restriction of nutrient supply are accompanied, and may be driven by, changes in the levels of the somatotrophic hormones and their binding proteins. Fetal IGF-I and IGFBP-3 levels fall [10], IGFBP-1 levels increase [44,45] while GH and its binding protein are reduced [46]. In humans, concentrations of placental GH (GH-v) and IGF-I are reduced in the maternal circulation [47]. The balance of fetal and maternal hormones and the modulating influence of their binding proteins may regulate the distribution and utilization of nutrients by the placenta in IUGR fetuses.

We have recent data suggesting in vivo IGF-I resistance in IUGR sheep fetuses, which have blunted metabolic responses to an acute IGF-I infusion (E. Jensen, J. E. Harding and P. D. Gluckman, unpublished work). Furthermore, in normal fetal growth the placenta may directly participate in the regulation of circulating fetal IGF-I, and therefore its activity, by taking up IGF-I when fetal levels are high and releasing IGF-I when fetal levels are low [48]. Our data suggest that nutritional restriction in late gestation disturbs IGF regulation by the placenta (J. E. Harding, unpublished work).

**Long-term consequences of IUGR**

Infants born with IUGR have longer term sequelae in addition to the short-term problems. They are at risk of long-term growth failure [49] with most catch-up growth occurring in the first year of life. Those who are still small at 1 year of age have lower IGF-I levels and a lower serum growth-promoting activity than those who have caught up [50]. The growth-promoting activity correlates better with catch-up than the actual IGF-I levels as other factors such as serum IGF binding proteins may act to modulate IGF activity when measured by this type of assay system. In fact, although the IGF-I levels are lower than in normal children, if the children are matched against those of similar body proportions, IGF-I levels are relatively high, suggesting a degree of hormone resistance [51].

IUGR babies are reported to have reduced cord levels of GH binding proteins [46] and children from IUGR pregnancies have been shown to have enhanced GH secretion and responsiveness to GH releasing factor [52,53]. We have observed that young rats with IUGR exhibit reduced GH binding to liver and reduced plasma IGF-I levels [54]. These observations may indicate the possibility of a GH receptor defect.

Accumulating epidemiological evidence over the course of this decade has suggested that infants born with IUGR have increased risks of developing adult diseases later in life such as hypertension, cardiovascular disease and metabolic diseases such as non-insulin-dependent diabetes mellitus (Type 2) and syndrome X (hypertension, Type 2 diabetes mellitus and hyperlipidaemia) [55,56]. The mechanism by which events in fetal life manifest as pathological processes in later life has been termed ‘programming’ [57]. It has been proposed that the risk of adult hypertension is mediated by insulin resistance [58]; insulin resistance has been shown postnatally in small-for-gestational-age short children [51]. There are increasing experimental data to support the epidemiological data. We and others have shown that the offspring of rats fed 30% of an ad libitum diet have higher blood pressures [59] and insulin levels [54]. Furthermore, these effects are amplified if the offspring are fed a high fat diet. Growth-restricted guinea pigs.
pigs also have elevated blood pressure at 3–4 months of age [60], and fetal sheep exposed to acute maternal undernutrition in late gestation develop elevated blood pressure upon refeeding [39]. When sheep manipulated in this manner reach 30 months of postnatal age they exhibit evidence of impaired glucose regulation (M. H. Oliver and J. E. Harding, unpublished work). The influence of the timing of a nutritional insult on programming is a complex issue. We have previously reported that periconceptual undernutrition can markedly influence fetal plasma IGFBP-1 and -3 responses to undernutrition in late gestation [61]. This same periconceptual undernutrition leads to a slower fetal growth rate that is associated with evidence of insulin resistance [62].

Summary

Both the maternal and fetal somatotrophic axes are closely linked to fetal substrate supply. Nutritional insults at critical stages of fetal development may lead to permanent reprogramming of the relationships between these factors. The consequences of reprogramming during fetal life may be harmful to metabolic, endocrine and cardiovascular homoeostatic mechanisms in postnatal life. The exact mechanisms that lead to reprogramming during fetal life need thorough investigation before effective strategies to deal with this problem can be devised.

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