ENDOCRINE REGULATION OF FETAL METABOLISM TOWARDS TERM

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ABSTRACT

Hormones have an important role in regulating fetal metabolism in relation to the prevailing nutritional conditions both in late gestation and during the prepartum period as the fetus prepares for birth. In particular, the pancreatic, thyroid and adrenal hormones all affect fetal uptake and utilization of nutrients for oxidative metabolism, tissue accretion and fuel storage. These hormones also influence the fetal metabolic preparations for the nutritional transition from intra- to extra-uterine life. This review discusses the role of insulin, glucagon, thyroxine, tri-iodothyronine, cortisol and the catecholamines in these processes during normal intrauterine conditions and in response to maternal undernutrition with particular emphasis on the sheep fetus. It also considers the metabolic interactions between these hormones and their role in the maturation of key tissues, such as the liver, skeletal muscle and adipose tissue, in readiness for their new metabolic functions after birth. Endocrine regulation of fetal metabolism is shown to be multifactorial and dynamic with a central role in optimising metabolic fitness for survival both *in utero* and at birth.

1. INTRODUCTION

During intrauterine development, hormones have an important role in regulating fetal metabolism. They act on feto-placental tissues to match substrate utilisation to the placental supply of nutrients and oxygen (O_2), thereby controlling growth and development in relation to resource availability [1]. In addition, near term, hormones act as signals of impending delivery and adapt key tissues in preparation for their new metabolic functions after birth [2,3]. This review examines the effects of fetal hormones on metabolism *in utero* with emphasis on the pancreatic, thyroid and adrenal hormones, particularly in fetal sheep. It focuses on the metabolic roles of these hormones during late gestation and in response to undernutrition near term. Finally, it considers the endocrine dependence of the prepartum metabolic adaptations that ensure neonatal survival.

2. ENDOCRINE REGULATION OF FETAL METABOLISM DURING LATE GESTATION

By late gestation, most of the endocrine axes involved in regulating adult metabolism are functional and responsive to nutritional and other environmental signals in the fetus [1,2]. However, the set points and the sensitivities of these axes to stimuli often differ *in utero* from extrauterine life [4,5]. The precise timing of their functional development in relation to term also varies between species and with maternal environmental conditions during pregnancy [6,7]. Hormones can have both anabolic and catabolic effects on fetal metabolism but the intrinsic

drive for fetal growth means that their predominant effect is anabolic in enhancing tissue accretion. Even in adverse conditions, fetal hormones often act to sustain intrauterine growth by supporting metabolism of key organs like the placenta, heart and liver that supply substrates to fetal tissues more generally.

2.1 Pancreatic hormones

In fetal sheep, pigs and horses, pancreatic β cells are functional by late gestation and release insulin in response to exogenous administration of glucose and amino acids [4,7,8]. Fetal insulin concentrations correlate positively with the endogenous glucose level during late gestation and fall in hypoglycaemic and hypoxaemic conditions induced by maternal undernutrition or placental insufficiency [7,8,9]. Since amino acids potentiate the response of fetal pancreatic β cells to glucose [8,10], the active transport of amino acids across the placenta ensures a basal insulin concentration is maintained even during hypoglycaemia.

Insulin has an important role in regulating both fetal glucose and amino acid metabolism [2,11]. Exogenous insulin administration to fetal sheep decreases the glucose concentration and increases glucose uptake, utilisation and oxidation by the fetus (Table 1). The fall in fetal glucose concentrations increases the transplacental glucose concentration gradient and, hence, facilitated diffusion of glucose across the placenta from mother to fetus (Table 1). Conversely, when insulin deficiency is induced in fetal sheep by pancreatectomy (PX) or treatment with streptozotocin, fetal glucose concentrations rise and whole-body rates of glucose utilization and oxidation decline in line with the fall in umbilical glucose uptake (Table 1). However, fetal insulin appears to have little direct effect on

125 weight specific rates of uteroplacental glucose utilisation or on placental glucose
126 transport capacity *per se* [27,49,50].
127
128 Insulin administration also increases umbilical uptake of amino nitrogen, and the
129 utilisation and oxidation of specific amino acids, in association with increased
130 protein accretion and reduced protein catabolism in sheep fetuses (Table 1). The
131 insulin-induced increase in amino acid and glucose utilisation is coupled with
132 increased fetal O_2 consumption in the short term [22,25]. The effects of short-term
133 infusion of insulin depend, in part, on the insulin-induced changes in fetal glucose
134 and amino acid concentrations as its anabolic effects are more pronounced when
135 normoglycaemic and euaminoacidaemia are maintained by exogenous infusion of
136 glucose and mixed amino acids alongside insulin administration [17-20, 51, 52].
137 Longer insulin infusions of up to 8 days with euglycamia are not associated with
138 an increase in protein synthesis or oxidative metabolism, although increased
139 glucose utilisation is maintained (Table 1). This suggests chronic fetal
140 hyperinsulinemia may cause adaptations in tissue insulin or energy signalling
141 pathways and/or evoke counter-regulatory endocrine responses that affect
142 insulin sensitivity [26,27].
143
144 Insulin is, therefore, a major anabolic hormone *in utero* that increases cellular
145 availability of both glucose and amino acids for oxidative metabolism and tissue
146 accretion over its endogenous concentration range in fetal sheep [2]. Indeed,
147 insulin deficiency in fetal sheep induced by PX or streptozotocin treatment
148 reduces the fetal growth rate by 50% over the last month of gestation and results
149 in shorter limbs and a 30-40% lower body weight by term [12,14,53]. These

reductions in growth and glucose metabolism can be prevented by insulin administration from the time of PX, which demonstrates that the effects of PX are due mainly to hypoinsulinemia and not to deficiency of other pancreatic hormones [13,14]. Conversely, fetal hyperinsulinemia, particularly associated with the hyperglycaemia induced by maternal gestational diabetes or glucose infusion, increases birthweight and fat deposition in human, other primate and domestic animal species [11]. Thus, the main role of insulin *in utero* is in growth regulation rather than in glycaemic control.

Similarly, the primary role of fetal glucagon does not appear to be in regulating glucose concentration *per se* as occurs in adult animals. In domestic species, fetal concentrations of glucagon are not related to the endogenous glucose level and do not change markedly with hypoglycaemia, unless prolonged [54,55]. However, its concentration *in utero* is increased by hypoxaemia and high fetal catecholamines levels [56,57]. In late gestation, increasing glucagon concentrations in fetal sheep either exogenously or endogenously for short periods activates fetal glucogenesis and increases hepatic glucose output in association with altered hepatic amino acid handling (Table 1). This can lead to fetal hyperglycaemia and a fall in umbilical glucose uptake [29,30]. Longer-term infusion of glucagon into fetal sheep for 8-10 days also decreases umbilical amino acid uptake and reduces protein synthesis and accretion, in association with fetal growth restriction [31]. However, these longer infusions have little effect on fetal glycaemia or umbilical glucose uptake, which suggests fetal glucogenesis cannot be sustained indefinitely [31]. In contrast, they reduce uteroplacental glucose and O_2 utilisation [31]. This may partly explain the decreased umbilical amino acid uptake by limiting

placental ATP availability for active amino acid transport. It also suggests that, unlike insulin, fetal glucagon may have direct actions on placental metabolism and nutrient transport.

Glucagon, therefore, appears to be a catabolic stress hormone *in utero* that ensures a basic glucose supply while minimising protein accretion, thereby reducing the fetal O_2 demand in hypoxaemic and other stressful conditions that raised fetal catecholamine concentrations . However, fetal sheep appear to be less sensitive to the hyperglycaemic effects of glucagon than adults, which may reflect the lower glucagon receptor abundance, glycogen content and gluconeogenic enzyme activities of the fetal liver for much of gestation [29,58,59].

2.2 Thyroid hormones

Thyroid hormones stimulate fetal oxidative metabolism. Infusion of T_3 into fetal sheep in late gestation increases the whole-body rate of O_2 consumption, while, conversely, inducing hypothyroidism by either fetal thyroidectomy (TX) or hypophysectomy (HX) reduces O_2 consumption (Table 1). Normal rates of O_2 consumption are restored in TX and HX fetuses by T_4 replacement [32]. These changes are likely to be mediated, in part, by changes in the tissue content and oxidative phosphorylation (OXPHOS) capacity of the mitochondria. Fetal TX has recently been shown to reduce the respiratory rates and mitochondrial abundance of specific electron transfer system complexes, uncoupling proteins (UCPs) and other proteins involved in OXPHOS in the brain, skeletal muscle and adipose tissue of fetal sheep in late gestation [37,60,61]. Fetal TX may also alter the relative contribution of substrates to the oxidative and non-oxidative

200 metabolic pathways as glucose oxidation is reduced in TX sheep fetuses without
201 any change in glucose utilisation [32,35].
202
203 Changes in fetal thyroid hormone status had no effects on uteroplacental O_2 or
204 glucose consumption, which suggests the ovine placenta may not be as sensitive
205 to thyroid hormones as other fetal tissues [5]. This may reflect differences in
206 tissue activity of the deiodinases that convert T_4 to T_3 and other metabolites as the
207 metabolic effects of the thyroid hormones depend primarily on cellular
208 availability of genomically active T_3. The placenta, for instance, expresses a high
209 level of D3 (*DIO3*), which converts T_4 to its biologically inactive metabolite,
210 reverse T_3 [62].
211
212 The low O_2 consumption of TX fetuses is accompanied by growth restriction by
213 term, which can be prevented by T_4 replacement [32]. Both skeletal and soft tissue
214 growth are adversely affected with decreased protein content and altered lipid
215 composition in individual fetal tissues [36,63]. The thyroid hormones are,
216 therefore, anabolic *in utero* through both metabolic and other more targeted
217 developmental actions analogous to their role in amphibian metamorphosis.
218
219 **2.3 Adrenal hormones**
220 From mid-gestation onwards, fetal adrenal glands secrete both cortisol and
221 catecholamines. However, adrenalectomy (AX) of fetal sheep has little effect on
222 metabolite concentrations or whole-body rates of glucose utilisation during
223 normal conditions in late gestation [39,58]. In contrast, carbohydrate, amino acid
224 and oxidative metabolism are all affected by infusions of cortisol and

225 catecholamines designed to mimic the concentrations seen close to term (Figure
226 1A) or during adverse intrauterine conditions in the last 80% of gestation (Table
227 1).
228
229 Short term increases in cortisol concentrations decrease amino acid uptake and
230 increase protein catabolism, leading to decreased protein accretion (Table 1).
231 However, there is little effect on fetal glucose and lactate metabolism. In contrast,
232 longer term cortisol infusions decrease umbilical glucose and lactate uptake,
233 activate hepatic glucose production and increase uteroplacental glucose
234 utilisation [43-45]. Collectively, these studies indicate that cortisol is catabolic and
235 growth inhibitory when overexposure is prolonged, which may aid intrauterine
236 survival by decreasing the fetal resource demands and by supporting the
237 metabolic activities of the placenta on which the fetus depends [50,67].
238
239 The catecholamines, noradrenaline and adrenaline, have similar metabolic effects
240 on fetal metabolism in late gestation. They activate hepatic glucogenesis in the
241 short term and reduce glucose utilisation, amino acid uptake and protein accretion
242 with longer exposure (Table 1). Indeed, in late gestation, endogenous glucose
243 production is directly related to total catecholamine concentration in normal and
244 growth restricted fetal sheep [64,68]. Longer term noradrenaline infusion also
245 alters sensitivity of pancreatic β-cells to glucose in fetal sheep [69].
246
247 **2.4 Hormone interactions**
248 Clearly, there is extensive interactions between these hormone groups and with
249 other endocrine systems that have metabolic functions *in utero* like the adipokines

and insulin-like growth factors (IGFs) [70-72]. Cortisol increases fetal T_3 bioavailability via actions on specific tissue deiodinases that lead to cortisol acting indirectly via changes in T_3 bioavailability [62]. The catecholamines inhibit insulin secretion and stimulate glucagon release with longer term effects on pancreatic β-cell sensitivity to glucose and on tissue insulin sensitivity [29,31,48,55]. Similarly, fetal hypothyroidism stimulates pancreatic β-cell proliferation but impairs pituitary-adrenal axis development in fetal sheep during late gestation [37,73]. Deficiency of pancreatic hormones appears to alter sympatho-adrenomedullary development and increases the adrenaline component of the catecholaminergic response to stimuli [49]. Cortisol, T_3 and insulin all affect either tissue expression or circulating concentrations of IGF-I [71,74]. In turn, IGF-I suppresses insulin secretion in fetal sheep [71,72]. Collectively, these endocrine interactions fine tune fetal metabolic responses to environmental cues during late gestation.

3. ENDOCRINE REGULATION OF FETAL METABOLISM DURING UNDERNUTRITION

By late gestation, many of fetal endocrine systems respond readily to common intrauterine challenges like hypoglycaemia and hypoxaemia caused by conditions such as maternal undernutrition and cord compression. Fasting pregnant ewes for 48h in late gestation reduces the umbilical glucose supply by approximately 50% and leads to fetal hypoglycaemia, hypoinsulinaemia and increased cortisol and catecholamine concentrations (Table 2). These endocrine changes activate endogenous glucose production by the sheep fetus near term, although not earlier

in gestation [64]. A significant fall in fetal glucose utilisation is, therefore, prevented near term, despite the reduced umbilical glucose supply (Table 2). Glucose production is accompanied by reduced glycogen content and increased activities of key gluconeogenic enzymes in the fetal liver, which suggest that glucogenesis is dependent on both glycogenolysis and gluconeogenesis [64].

In normal sheep fetuses, glucose oxidation declines during short-term maternal fasting but without a change in total O_2 consumption (Table2), so fetal oxidative metabolism must be maintained by increasing oxidative use of other substrates such as lactate and amino acids. Together with the hypoinsulinaemia and increased gluconeogenesis (Table 2), this reduces the cellular availability of amino acids and other substrates for tissue accretion. Consequently, the fetal nutrient demand decreases in line with the restricted maternal nutrient availability. Together, the fetal endocrine changes during short-term fasting tailor fetal metabolism and growth to the nutrient supply while maintaining a glucose supply for essential tissues like the heart and brain (Table 2).

The role of specific hormones in these fasting-induced metabolic adaptations has been investigated by surgical ablation of individual endocrine glands in fetal sheep. In PX, TX and AX fetuses, maternal fasting for 48h near term reduces umbilical glucose uptake by 40-60% and leads to a similar degree of fetal hypoglycaemia as seen in the intact fetuses (Table 2). Glucogenesis occurred in these fasted PX fetuses which prevented a significant fall in fetal glucose utilisation, in common with the findings in intact fetuses (Table 2). Glucogenesis was activated without an increment in cortisol or depletion of hepatic glycogen in

PX fetuses but was accompanied by higher gluconeogenic enzyme activities at the onset of fasting than seen in intact fetuses [49]. This suggests that PX fetuses may be more dependent on gluconeogenesis than glycogenolysis for hepatic glucose production, consistent with their higher amino nitrogen concentrations. Thus, changes in fetal pancreatic hormones and cortisol do not appear to be essential for activating fetal glucogenesis during hypoglycaemia but may be involved in mobilisation of hepatic glycogen in late gestation (Table 2). Indeed, insulin is unable to inhibit fetal glucogenesis, once initiated by hypoglycaemia in normal and growth restricted fetal sheep [16,68].

In contrast, there is no fasting-induced glucogenesis after TX or AX (Table 2), so fetal glucose utilisation decreased significantly in line with the fall in umbilical glucose uptake in these fetuses [35,39]. Hepatic glycogen levels and key gluconeogenic enzyme activities were lower in AX and TX than intact fetuses at the end of the 48h fast with smaller or no increments in enzyme activities during this short period of fasting [35,39]. Since AX fetuses lack a cortisol increment and TX fetuses cannot increase T_3 in response to their fasting-induced cortisol increment, these findings suggest that hepatic glucogenic capacity is dependent, in part, on cortisol-stimulated T_3 production [35,39]. In addition, the fetal catecholaminergic response to fasting was smaller in TX and AX than intact fetuses, whereas it was unaffected in PX fetuses (Table 2). Overall, these findings suggest that, while the capacity for glucogenesis depends on cortisol and T_3, its activation during short-term hypoglycaemia is determined by the catecholamine increment.

During short-term fasting, glucose oxidation fell in AX and intact fetuses but not in TX or PX fetuses that already had low glucose oxidation rates in the fed state [35,39,49,64]. Since oxidative use of glucose depends on both the insulin and glucose concentration [21], these differences may reflect, in part, the differing insulin responses to fetal hypoglycaemia induced by short-term maternal fasting with falls in insulin in AX and intact fetuses but not after fetal PX [39,49,64]. This suggest that glucose oxidation may be more dependent on insulin than glucose at physiological concentrations. However, insulin levels did decrease in TX fetuses during short-term fasting [35], which suggests glucose oxidation may already be at the minimum before fasting in these fetuses, in line with their low O_2 consumption and tissue mitochondrial content [32,60,61,75]. Indeed, glucose oxidation rates of TX fetuses in the fed state were already at the values seen in intact, AX and PX fetuses during short-term fasting.

In AX and PX fetuses, the changes in glucose metabolism during short-term fasting were accompanied by a 15-20% decrease in fetal O_2 consumption (Table 2), which suggests that these fetuses are unable to mobilize reserves to maintain a supply of oxidative substrates during hypoglycaemia. Cortisol concentrations did not change during fasting in AX and PX fetuses, which indicates that a cortisol increment is required for recruitment of alternative oxidative substrates, in keeping with the known actions of cortisol in stimulating protein catabolism and amino acid oxidation in intact fetal sheep (Table 1). The PX fetuses were also growth retarded and already using substrates other than glucose to maintain OXPHOS in the fed state so may have had little further reserves to maintain oxidative metabolism during fasting [49,53].

The findings in the hormone deficient sheep fetuses in response to short-term fasting are consistent with the metabolic effects observed with infusing the hormones exogenously in intact fetuses (Table 1). Together, the studies show that, at endogenous concentrations, insulin is required for tissue uptake of glucose and amino acids, cellular glucose oxidation and tissue accretion. Cortisol regulates fetal protein turnover and hepatic glucogenic capacity. Its concentration is also positively correlated with both hepatic glucose output and total fetal rates of glucose production during hypoglycaemia [55,64]. Catecholamines and glucagon can activate glucogenesis, once fetal cortisol and T_3 levels have increased hepatic glucogenic capacity sufficiently [58,76-78], while thyroid hormones also regulate oxidative metabolism, probably through mitochondrial effects [32,60,61]. However, the endocrine changes and their effects on the fetal metabolism appear to differ between short-term and more chronic undernutrition due to changes in the responsiveness of both the endocrine glands themselves and their target tissues with the duration of nutrient restriction [26, 27, 79]. Endocrine regulation of fetal metabolism, therefore, appears to adapt to the specific intrauterine conditions in matching fetal development to resource availability during environmental challenges.

4. ENDOCRINE REGULATION OF METABOLIC PREPARATIONS FOR BIRTH

Birth is a major metabolic challenge to the neonate [80]. It must switch from a continuous parenteral supply of nutrients via the placenta to intermittent enteral nutrition while maintaining its internal environment [81]. This requires onset of

several vital, energy-demanding processes including thermoregulation, gluconeogenesis, lipolysis, pulmonary respiration and other locomotive muscular activities (Figure 2). Fetal hormones have a major role in preparing the fetus for these metabolic changes and in activating them at birth.

Before delivery, fetal concentrations of several metabolic hormones increase in the absence of any maternal nutritional or other environmental stimuli (Figure 1A). These endocrine changes are primarily driven by activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis and increased adrenal cortisol secretion [3,66]. In turn, the prepartum cortisol surge increases circulating concentrations of T_3, leptin and adrenaline through actions on their biosynthetic pathways [2,3,62]. Endocrine systems *per se* must also adapt to new functions after birth [80]. For example, thyroid hormones become thermoregulatory while insulin assumes a major glucoregulatory role postpartum.

As cortisol concentrations rise towards term, umbilical glucose uptake decreases and fetal glucose production increases (Figure 1B & C), consistent with the effects of cortisol administration earlier in gestation (Table 1). Fetal growth rate declines and tissues differentiate structurally and biochemically in response to the prepartum endocrine changes in readiness for their new postnatal metabolic functions [66, 67]. The placenta increases synthesis of steroids and prostaglandins that trigger parturition, aided by the cortisol-induced diversion of uterine glucose uptake away from the fetus to placental use [43,50].

4.1 Liver

400 At birth, the liver takes on a more prominent metabolic role. It must be able to
401 store and mobilise glycogen and activate gluconeogenesis from amino acids and
402 other substrates. In most domestic species, hepatic glycogen content rises
403 towards term, along with increased activities of several transaminases and the
404 rate-limiting gluconeogenic enzymes, glucose-6-phosphatase and
405 phosphoenolpyruvate kinase [66,77,78,82]. These changes occur in parallel with
406 the prepartum cortisol surge and, in sheep, can be stimulated prematurely by
407 cortisol infusion and prevented by fetal AX [58,78]. The prepartum increases in
408 glycogen content and gluconeogenic enzyme activities depend, in part, on the rise
409 in T_3 and can be induced by T_3 infusion earlier in gestation, although T_3 is less
410 effective than cortisol at stimulating hepatic glycogen accumulation [76-78].
411
412 Hepatic glucogenesis at birth is triggered by postnatal increases in catecholamine
413 and glucagon concentrations and by a fall in insulin levels, which occur in response
414 to transient hypoxaemia during labour and the immediate fall in glucose levels
415 after loss of the placenta [83]. The hepatic β-adenoreceptors required for
416 catecholaminergic activation of glucogenesis are also upregulated in parallel with
417 the prepartum rise in cortisol in fetal sheep and pigs [84,85]. Hepatic glycogen
418 levels are therefore depleted rapidly after birth in ensuring an immediate glucose
419 supply [82]. Indeed, when prepartum accumulation of hepatic glycogen and the
420 postnatal catecholamine surge are impaired by fetal AX, the neonate becomes
421 profoundly hypoglycaemic [86].
422
423 **4.2 Skeletal Muscle**

After birth, energy demands for locomotion and shivering increase. These are met by perinatal upregulation of mitochondrial number and OXPHOS capacity in skeletal muscle [60]. Muscle fibres also differentiate into slow twitch, oxidative fibres and fast twitch, more glycolytic fibres during late gestation in a muscle specific manner [87]. This leads to specific muscle fibre compositions suited to the postural and locomotive activities of neonates that must be mobile at birth. These maturational changes depend largely on thyroid hormones and are prevented by TX in fetal sheep [60,87]. Muscle respiratory rates using fats and carbohydrates and the activity of β-hydoxyacyl-CoA dehydrogenase, an enzyme involved in β-oxidation of fats, increase towards term in intact but not TX fetuses [60].

In fetal pigs and sheep, glycogen content of skeletal muscle increases towards term [82], which appears to be a cortisol dependent process in pigs [88]. By birth, glycogen content of porcine muscle is double that in other species, consistent with the greater dependence of newborn piglets on shivering thermogenesis. Increased fetal cortisol exposure also upregulates proteins in the insulin signalling pathways of ovine skeletal muscle, which may alter its insulin sensitivity postnatally [26, 89].

4.3 Adipose tissue

Most large domestic animals are born with 2-3% of birthweight as body fat which has number of important metabolic and endocrine functions [90]. White adipocytes primarily store lipid as an insulator and energy source, and produce adipokine hormones, such as leptin. Brown adipocytes are rich in mitochondria

449 that have the capacity for non-shivering thermogenesis, due to the expression of
450 UCP-1 which uncouples the electron transport chain to generate heat. The relative
451 proportions of white and brown adipocytes in the fetus and newborn vary widely
452 between species and, in sheep, correlate with the cortisol and thyroid hormones
453 concentrations [11, 37, 91-93].
454
455 In late gestation, adipogenesis and triglyceride synthesis is promoted by insulin,
456 using glucose and fatty acids derived from fetal tissues and placental transfer from
457 the mother [91]. Excess fat deposition is commonly observed in offspring of
458 mothers with gestational diabetes due to combined fetal hyperglycaemia and
459 hyperinsulinaemia [11, 93,94]. Similarly, in fetal sheep, hyperinsulinemia induced
460 by fetal glucose infusion increases white adipose mass [95]. Lipolysis and fatty
461 acid oxidation are normally low in the fetus but can be activated to provide energy
462 substrates, especially ketones for use by the brain, in conditions of hypoglycemia
463 [96]. Indeed, at birth, lipolysis is induced by the high circulating concentrations
464 of catecholamines, cortisol and T_3, and reductions in the insulin:glucagon ratio
465 [80,81]. Adrenalectomy, therefore, abolishes the increment in free fatty acid
466 concentrations in ovine neonates [86].
467
468 Most newborn species, except the pig, cannot shiver and therefore, maintenance
469 of body temperature is dependent upon non-shivering thermogenesis in brown
470 adipose tissue. Expression of UCP-1 increases in ovine fetal adipose tissue
471 towards term, due to the prepartum rises in cortisol and T_3 [92,95]. Further
472 increases in UCP1 and activation of thermogenesis are induced by thyroid
473 hormones and catecholamines upon delivery into a cold environment [97,98].

Fetal TX influences one-third of the genes in the ovine adipose transcriptome, reduces adipose mitochondrial density, and UCP1 mRNA and protein expression, and leads to hypothermia at birth [37,98]. It also prevents the increase in neonatal O_2 consumption [75].

In fetuses and neonates, adipose-derived adipokines are responsive to the endocrine environment and are maturational hormones themselves. Circulating and adipose mRNA levels of leptin in the sheep fetus are increased by insulin and glucocorticoids, especially near term [65,98,99]. In turn, leptin appears to be affect maturation of several fetal organs involved in the metabolic preparation for birth including the HPA axis [70,100-102]. Indeed, the rise in circulating leptin over the perinatal period influences development of the hypothalamic networks that govern appetite postnatally [103]. Leptin also appears to limit the stimulatory actions of cortisol and T_3 on hepatic glycogen accumulation in late gestation [70]. Adipose-derived leptin, therefore, appears to be an important signal of energy reserves in the fetus which interacts with other maturational hormones to ensure an appropriate balance of fuel reserves for the nutritional transition at birth.

5. CONCLUSIONS

Hormones have an important role in regulating fetal metabolism by matching fetal metabolism to the prevailing nutritional conditions *in utero*. They are also responsible for prepartum maturation of several metabolic processes that have little or no function prenatally but must be activated immediately after birth for neonatal survival (Figure 2). While the hormonal effects on fetal metabolism are

well established at the systems level, further studies are needed to identify their full range of molecular and genomic actions *in utero*. Whatever the sub-cellular mechanisms involved, endocrine regulation of fetal metabolism is a dynamic, multifactorial process that is vital to optimising metabolic fitness for the nutritional transition at birth.

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FIGURE LEGENDS

Figure 1: Relationships in (A) between proximity to delivery and the plasma concentrations of cortisol (filled circles), leptin, (open circles and solid lines), T_3 (triangles) and adrenaline (open circles & dashed lines), (B) the plasma concentration of cortisol and the rate of umbilical uptake of glucose and (C) the plasma concentration of cortisol and the rate of endogenous glucose production by fetal sheep during late gestation. Data from references [43,44,45,58,64-66].

Figure 2: Summary diagram of the effects of the pancreatic, thyroid and adrenal hormones on prepartum metabolic maturation of the liver, skeletal muscle and adipose tissues together with the effects that these changes on the neonatal metabolic adaptations and establishment of the new postnatal metabolic functions in fetal sheep. PNMT=Phenyl-N-methyl-transferase which metabolises noradrenaline to adrenaline. Arrows indicate effects of hormones on other hormone concentrations (plus symbol, + = stimulatory effect of cortisol on adrenal PNMT and on tissue deiodinases converting T_4 to T_3; minus symbol, - = inhibitory effect of thyroid hormones on pancreatic β-cell proliferation and insulin concentrations. Data from references 2, 37, 62).

Table 1: Effects of hormones on weight specific rates of metabolism of oxygen, carbohydrates, amino acids and lipids in sheep fetuses in the fed state in late gestation (≥80% of term). ↑ increase rate in endocrine manipulated fetuses compared to control fetuses. ↓ decreased rate in endocrine manipulated fetuses compared to control fetuses. No Δ = no change in rate in in endocrine manipulated fetuses compared to control fetuses. ? = No data given in the paper.

Hormone	**Manipulation**	**Fetal metabolic rates**			**Reference**
		Oxygen	***Carbohydrate***	***Amino acids/ Lipids***	
Insulin	***Deficiency***				
	Pancreatectomy	No Δ	↓ glucose uptake ↓ glucose utilisation ↓ glucose oxidation No Δ lactate uptake No glucose production	↑ urea production	[12] [13]
	Streptozotocin treatment	No Δ No Δ	↓ glucose uptake ↓ glucose utilisation ↓ glucose oxidation ↑ glucose production		[14] [15] [16]
	Somatostatin infusion			↓ leucine clearance No Δ protein synthesis No Δ protein catabolism	[17]
	Excess				
	Tolbutamide infusion <2h Short insulin infusion 2-6h	No Δ No Δ ↑ consumption	↑ glucose uptake ↑ glucose uptake ↑ glucose uptake ↑ glucose utilisation ↑ glucose oxidation	↑ amino nitrogen uptake ↑ amino acid utilisation ↑ protein accretion ↓ protein catabolism ↑ amino acid oxidation	[18] [19] [20-24]

	Chronic insulin infusion -24h -2-8days	↑ consumption ↑ consumption No Δ	↑ glucose uptake ↑ glucose/O_2 quotient ↑ glucose utilisation	↑ amino nitrogen uptake No Δ protein synthesis No Δ protein accretion	[22] [25] [26,27]
Glucagon	***Excess***				
	Glucagon Infusion - 10min - 3h - 20h - 8-10 days	No Δ ? No Δ No Δ	↑ hepatic glucogenesis ↑ glucose production ↑ hepatic glucogenesis ↓ glucose uptake No Δ glucose uptake No Δ lactate uptake	 ↓ amino acid uptake ↓ hepatic pyruvate output ↓ amino acid uptake ↓ protein synthesis ↓ protein accretion	[28] [29] [30] [31]
	Streptozotocin treatment (↑ glucagon ↓ insulin)	No Δ	↑ glucose production		[15]
Pituitary Hormones	***Deficiency***				
	Hypophysectomy	↓ consumption	No Δ glucose uptake No Δ glucose utilisation No Δ glucose oxidation	 ↑ Body lipid content	[32] [33] [34]
Thyroid hormones	***Deficiency***				
	Thyroidectomy	↓ consumption	No Δ glucose uptake No Δ glucose utilisation ↓ glucose oxidation	 ↓ tissue protein content ↓ brain lipid content	[32,35] [36]

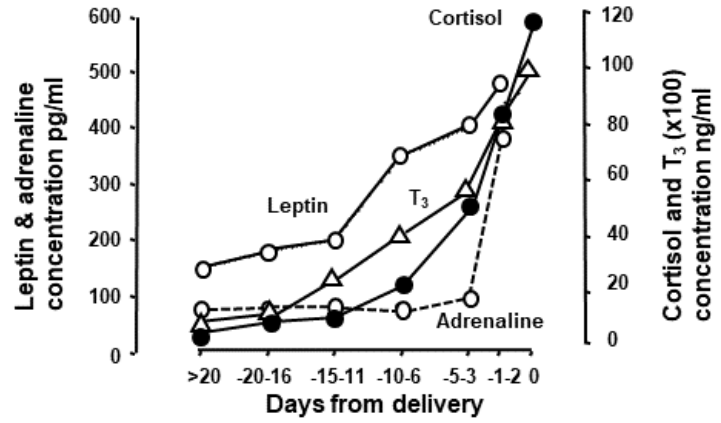
				↑ white fat deposition	[37]
	Excess				
	T_3 Infusion – 5days	↑ consumption			[38]
Adrenal Hormones	***Deficiency***				
	Adrenalectomy	No Δ	No Δ glucose uptake No Δ glucose utilisation		[39]
	Excess				
	Cortisol infusion - <6h	No Δ	No Δ glucose uptake No Δ lactate uptake	↓ amino nitrogen uptake ↓ protein accretion ↑ protein catabolism	[40,41]
	- 2days		↑ hepatic glucogenesis		[42]
	- 5days	No Δ	↓ glucose uptake ↓ lactate uptake	No Δ amino-nitrogen uptake	[43-45]
	Noradrenaline infusion - 10min	No Δ	↑ hepatic glucogenesis		[28]
	- <1h	↑ consumption			[46]
	- <6h	↑ consumption	No Δ glucose uptake ↓ lactate uptake	↓ amino nitrogen uptake ↓ protein synthesis ↓ protein accretion	[47]
	- 5days	No Δ	↓ glucose utilisation No Δ glucose oxidation No Δ lactate uptake		[48]
	Adrenaline infusion - 10min	↓ consumption	No Δ glucose uptake ↑ hepatic lactate output ↑ hepatic glucogenesis		[28]

Table 2: Effect of short-term maternal fasting for 48h in late pregnancy (>137days, term approx. 145 days) on the changes in hormone concentrations and in oxygen consumption and glucose metabolic rates expressed per kg fetal body weight in intact (sham-operated) and endocrine deficient sheep fetuses.

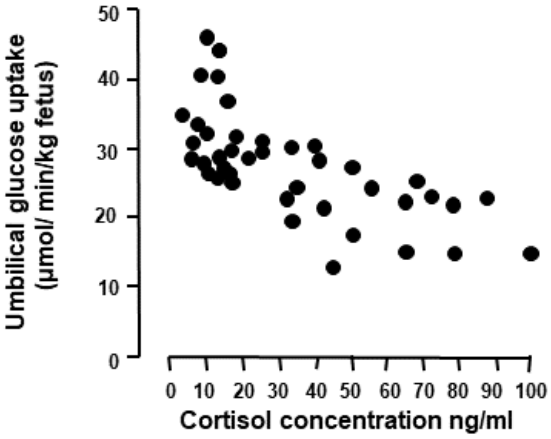
	Hormones concentrations			**Metabolic rates**				
Treatment	Insulin	Cortisol	Total Catecholamines	Oxygen consumption	Glucose uptake	Glucose utilisation	Glucose production	Glucose oxidation
Intact	↓	↑	↑	No Δ	↓	No Δ	↑	↓
Pancreatectomised	No Δ*	No Δ*	↑	↓*	↓	No Δ	↑	No Δ
Thyroidectomised	↓	↑	↑*	No Δ*	↓	↓	None	No Δ
Adrenalectomised	↓*	No Δ*	↑*	↓	↓	↓	None	↓

No Δ = No change during fasting None= No glucose production before or during maternal fasting.
Arrows up and down indicate significant increases or decreases in value during fasting.
* Significantly lower value than in intact fetuses at the end of the fast.
Data from references [35,39,49,64]

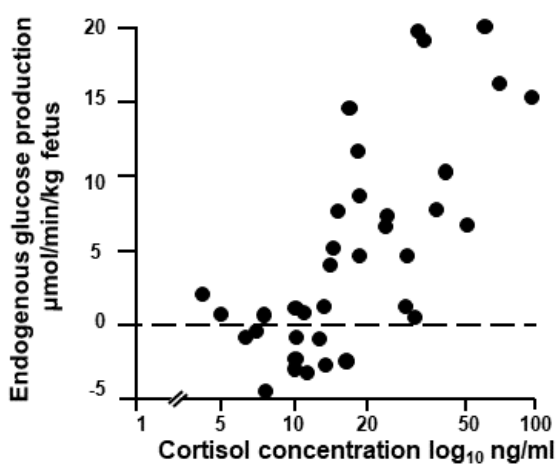
A.

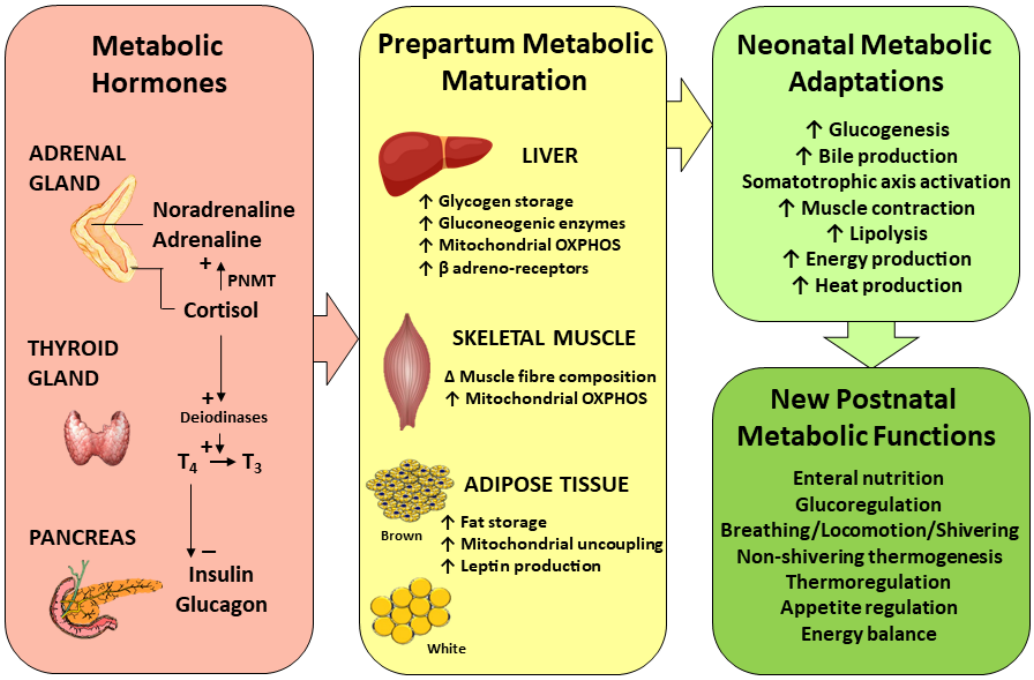

Leptin & adrenaline concentration pg/ml
600
500
400
300
200
100
0
Cortisol
Leptin
T3
Adrenaline
120
100
80
60
40
20
0
Cortisol and T3 (x100) concentration ng/ml
>20 -20-16 -15-11 -10-6 -5-3 -1-2 0
Days from delivery

B.


Umbilical glucose uptake (µmol/ min/kg fetus)
50
40
30
20
10
0
0 10 20 30 40 50 60 70 80 90 100
Cortisol concentration ng/ml

C.


Endogenous glucose production µmol/min/kg fetus
20
15
10
5
0
-5
1 5 10 20 50 100
Cortisol concentration log10 ng/ml


Metabolic Hormones
ADRENAL GLAND
Noradrenaline
Adrenaline
+
PNMT
Cortisol
THYROID GLAND
+
Deiodinases
+
T_4 → T_3
PANCREAS
–
Insulin
Glucagon
Prepartum Metabolic Maturation
LIVER
↑ Glycogen storage
↑ Gluconeogenic enzymes
↑ Mitochondrial OXPHOS
↑ β adreno-receptors
SKELETAL MUSCLE
Δ Muscle fibre composition
↑ Mitochondrial OXPHOS
ADIPOSE TISSUE
Brown
↑ Fat storage
↑ Mitochondrial uncoupling
↑ Leptin production
White
Neonatal Metabolic Adaptations
↑ Glucogenesis
↑ Bile production
Somatotrophic axis activation
↑ Muscle contraction
↑ Lipolysis
↑ Energy production
↑ Heat production
New Postnatal Metabolic Functions
Enteral nutrition
Glucoregulation
Breathing/Locomotion/Shivering
Non-shivering thermogenesis
Thermoregulation
Appetite regulation
Energy balance