ENDOCRINE REGULATION OF PLACENTAL PHENOTYPE

A.L. Fowden[1], A.J. Forhead[1,2], A.N. Sferruzzi-Perri[1], G. J. Burton[1] and O.R. Vaughan[1]

[1]Centre for Trophoblast Research,
Department of Physiology Development and Neuroscience, University of Cambridge,
Cambridge, CB2 3EG, UK
and
[2]Department of Biological and Medical Sciences, Oxford Brookes University,
Oxford, OX3 0BP, UK

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Address for correspondence: Abigail L. Fowden
Department of Physiology Development and Neuroscience
University of Cambridge
Downing Street
Cambridge, CB2 3EG, UK
Telephone: 44 (0)1223 333855
Fax: 44 (0)1223 333840
E-mail: alf1000@cam.ac.uk

ABSTRACT

Hormones have an important role in regulating fetal development. They act as environmental signals and integrate tissue growth and differentiation with relation to nutrient availability. While hormones control the developmental fate of resources available to the fetus, the actual supply of nutrients and oxygen to the fetus depends on the placenta. However, much less is known about the role of hormones in regulating placental development, even though the placenta has a wide range of hormone receptors and produces hormones itself from early in gestation. The placenta is, therefore, exposed to hormones by autocrine, paracrine and endocrine mechanisms throughout its lifespan. It is known to adapt its phenotype in response to environmental cues and fetal demand signals, particularly when there is a disparity between the fetal genetic drive for growth and the nutrient supply. These adaptive responses help to maintain fetal growth during adverse conditions and are likely to depend, at least in part, on the hormonal milieu. This review examines the endocrine regulation of placental phenotype with particular emphasis on the glucocorticoid hormones. It focuses on the availability of placental hormone receptors and on the effects of hormones on the morphology, transport capacity and endocrine function of the placenta.

INTRODUCTION

During development, hormones act as environmental cues in regulating tissue growth and differentiation *in utero*. They signal stress levels, temperature, photoperiod and the availability of nutrients and oxygen (1). Towards term, hormones also act as maturational signals in the final processes of tissue differentiation in preparation for delivery (1, 2). By regulating intrauterine development in relation to these cues, hormones determine the phenotype of the offspring and maximise its chances of survival not only during fetal and neonatal life but also onto reproductive age as an adult (3). While hormones control the developmental fate of the resources available to the fetus, the actual supply of nutrients and oxygen to the fetus depends on the placenta. The placenta is known to adapt its transport phenotype to help maintain fetal growth in response to external environmental conditions, such as malnutrition, dietary composition and maternal psychological stresses of restraint, isolation and inappropriate light exposure (4, 5). It also responds to internal signals of fetal nutrient demands, particularly when there is a mismatch between the placental capacity to supply nutrients and the fetal genetic drive for growth (4, 6). Furthermore, the placenta has endocrine functions itself and can both metabolise and synthesise hormones (1, 2, 7), which influences fetal development directly and indirectly by adapting maternal metabolism in favour of resource allocation to the fetus (8). The placenta is, therefore, exposed to hormones by autocrine, paracrine and endocrine mechanisms from early in development. However, compared to the fetus, less is known about the role of endocrine signals in placental development (2). This review, therefore, examines the endocrine regulation of placental phenotype. It places particular emphasis on the glucocorticoids because these hormones act as both environmental and maturational signals and affect growth and differentiation of many tissues known to be programmed during intrauterine development (1, 4). It does not consider the role of hormones in human trophoblast invasion or in the control of placental blood flow more generally.

PLACENTAL HORMONE RECEPTORS

Hormones can influence placental phenotype either directly via specific receptors on various cell types forming the placenta or indirectly by inducing physiological changes in the fetus

and/or mother, such as alterations in nutrient availability or placental blood flow. The placenta has receptors for a wide range of circulating hormones, including those it produces, from early in development in several species (Table 1). In humans, it also expresses receptors for opioid, neuro-, growth regulatory and vasoactive peptides that are produced endogenously to act locally (7). Receptor expression can be ubiquitous or restricted to specific zones or cell types within the placenta (20, 31, 37, 41, 45, 51, 52, 56, 64). Their abundance may also be sex-linked (9, 14, 26, 69). Multiple isoforms of certain hormone receptors exist in the placenta and can be expressed selectively or differentially in the different placental tissues (9, 31, 42, 46, 55, 69). Some of the variants appear to be unique to the placenta and not every isoform identified in the placenta is expressed in every individual (7, 9, 70). In term human placenta, for instance, there are 5 isoforms of the glucocorticoid receptor (GR) in the endothelium but 12 different variants in the trophoblast, which are differentially expressed in male and female infants (9). Consequently, by late gestation when most fetal endocrine glands are functional (1), the placenta has the necessary receptors to respond to a range of hormones in both the fetal and maternal circulations.

With increasing gestational age, there are changes in placental abundance and spatial localisation of several hormone receptors including those for insulin, angiotensin, estrogens, glucocorticoids, adiponectin, leptin and the thyroid hormones (14, 30, 31, 49-51, 58-61, 68). Some of these developmental changes are isoform specific (31, 49, 58, 61, 68, 70). In the human placenta, localisation of the insulin receptor (IR) changes with gestational age from presence primarily in the syncytiotrophoblast facing the maternal circulation in the first trimester to expression predominantly in the placental endothelial cells facing the fetal circulation at term (37). In contrast, the increase in placental GR abundance between mid and late gestation is more widespread, although the magnitude of the increment may vary regionally depending on species (11, 15, 49, 69-73). In rats, for instance, the ontogenic increase in GR is more pronounced in the labyrinthine zone (Lz) responsible for nutrient transfer than in the junctional zone (Jz), the morphologically distinct region with endocrine functions (73). These spatio-temporal changes in placental hormone receptor abundance indicate that hormones are likely to have a significant role in normal placental development

and that the relative importance of fetal versus maternal endocrine signals may change as the metabolic demands of pregnancy increase with fetal growth towards term.

Placental hormone receptor abundance is also responsive to external environmental conditions (4). There are changes in placental abundance of GR, IR, IGFR1 and Ob-R when maternal nutritional state is altered by diabetes or dietary manipulation of calorie, macro- and/or micronutrient intake during pregnancy in experimental animals (11, 12, 38, 40, 74-76). In part, these nutritionally-induced changes in hormone receptor expression may reflect the concomitant alterations in the endocrine environment as direct experimental manipulation of maternal hormone concentrations, particularly of the glucocorticoids, alters placental expression of several hormone receptors including AT2R, Ob-Ra, Ob-Re, FP, EP2, IGF1R and GR itself (17, 33, 49, 57, 69, 77, 78). In addition, clinical complications of human pregnancy that alter placental blood flow or the circulating concentrations of hormones and metabolites, such as gestational diabetes, intrauterine growth restriction (IUGR) and pre-eclampsia, are associated with changes in placental expression of a range of hormone receptors including AT1R, GR, GHR, IGF-1R, OB-R, AR and IR (9, 30, 37, 79-82). Taken together, these observations indicate that hormone receptor abundance in the placenta can vary with gestational age, sex of the offspring and with a range of environmental cues of fetal and maternal origin. In turn, this will influence the effects that hormones can have on the morphological, transport and endocrine phenotype of the placenta.

HORMONES AND PLACENTAL MORPHOLOGY

Changes in trophoblast invasion and in the size and morphology of the definitive placenta have been observed in response to experimental manipulation of both maternal and fetal hormone concentrations (2, 4, 7). These studies have tended to focus on the glucocorticoids and insulin-like growth factors because of their known effects on fetal growth (83, 84). Maternal glucocorticoid administration during the last third of gestation leads to reduced placental weight in a wide range of species including monkeys, sheep, rabbits, rodents and human infants (4, 83, 85, 86). The degree of placental growth restriction depends on the type of glucocorticoid administered, the dose and duration of treatment and the gestational

age at both treatment and assessment (85, 86). The growth inhibitory effects are more pronounced with administration of synthetic than natural glucocorticoids and when glucocorticoid overexposure occurs in mid to late gestation than close to term (87, 88). In rodents, placental growth is also restricted to a greater extent by continuous than intermittent maternal treatment, irrespective of the exact route of glucocorticoid administration (86, 88). Furthermore, growth restriction of the rodent placenta occurs in response to local overexposure to glucocorticoids induced by reducing the activity of placental 11β-hydroxysteroid dehydrogenase-2 (11βHSD2), the enzyme that normally converts active glucocorticoids to their inactive metabolites (89, 90). In contrast, overexposure of the placenta to glucocorticoids via the fetal circulation appears to have less severe effects on placental growth, although this may relate, partially, to treatment later in gestation (91, 92).

These changes in placenta size and/or weight are accompanied by more specific alterations in placental morphology. In sheep, glucocorticoids affect the gross morphology of the placenta whether given maternally or fetally (86). In particular, there is a reduced number of everted placentomes without a change in total number, which leads to an altered frequency distribution of the different placentome types with potential consequences for glucose transport (91). Glucocorticoid treatment of either the mother or fetus in late gestation also reduces the numbers of binucleate cells (BNC) in the ovine placentomes (91, 92). These cells migrate from the fetal trophectoderm across the feto-maternal junction to form a syncytium with the maternal epithelium. They also produce progesterone and placental lactogen that influence maternal metabolism and tissue growth. Changes in BNC frequency and migration induced by glucocorticoid overexposure may, therefore, alter the morphological remodelling of the placenta and the maternal adaptations to pregnancy with consequences for resource allocation to the fetus.

In several species, there are changes in the surface area of the placenta in response to manipulating placental exposure to the glucocorticoids and IGFs (2, 4, 86). In rodents, maternal treatment with natural and synthetic glucocorticoids decreases the volume and surface area of the Lz trophoblast, particularly when treatment coincides with the main period of placental development (14, 49, 57, 69, 87, 88, 90-92). These changes are coupled

with a decrease in placental vascularity and *Vegf* expression, which can persist or reverse after cessation of treatment depending on the gestational age at time of overexposure (14, 69, 87, 88, 93-96). Similarly, there are reductions in the Lz volume and fetal vascularity of the mouse placenta locally overexposed to glucocorticoids by deletion of the *11βHsd2* gene (90). Reduced vascularity of the fetal villi has also been observed in term placenta of asthmatic women treated clinically with high doses of glucocorticoids during pregnancy (97). In mice, high doses of synthetic glucocorticoids have been shown to lead to placental necrosis and increased expression of several apoptotic genes (94). In contrast to the glucocorticoids, IGFs increase placental size, Lz volume and vascularity in mice and guinea pigs (6, 39). The IGFs also decrease the thickness of the interhemel membrane between the maternal and fetal circulations (6). However, the extent to which these hormonally induced changes in placental morphology and vascularity lead to altered placental blood flow still remains unclear as blood pressure is often elevated in response to glucocorticoid administration (85, 86). Nevertheless, changes in placental size and morphology with the endocrine milieu will alter the placental capacity for transfer of oxygen and nutrients to the fetus.

HORMONES AND PLACENTAL NUTRIENT TRANSPORT

Using both *in vivo* and *in vitro* experimental methods, a wide range of different hormones have been shown to alter placental uptake and/or transplacental transfer of glucose and amino acids (Table 2). In some instances, these changes are associated with altered placental abundance of the transporters required for active transport of amino acids or facilitated diffusion of glucose from mother to fetus (Table 2). Much less is known about the endocrine regulation of placental lipid transport, although environmental factors such as maternal obesity and gestational diabetes can influence placental abundance and activity of the fatty acid transfer proteins involved in fetal uptake of fatty acids (131, 132). The hormonally induced changes in trophoblast surface area, thickness and vascularity will also influence the passive diffusion properties of the placenta and, hence, transport by simple diffusion of oxygen and waste products like urea and carbon dioxide (2, 5). In addition, both the glucocorticoids and the IGFs are known to alter placental production of the fetal

metabolic substrate, lactate, and its distribution between the uterine and umbilical circulations (91, 117, 118). Furthermore, fetal cortisol infusion has been shown to increase glucose consumption by the ovine placentomes, thereby limiting the proportion of uterine glucose uptake that is passed onto the fetus (91). Thus, hormones affect placental delivery of nutrients to the fetus not only by altering the morphological and functional characteristics of the actual transport processes but also by actions on the production and consumption of nutrients by the placenta *per se*.

Not all hormonal actions on placental nutrient delivery are direct. Some are mediated indirectly by physiological actions in the mother and fetus or by effects on energy availability for active transport or on the sodium concentration gradient used to drive secondary active, sodium-coupled amino acid transport (133). For example, the inhibitory effect of angiotensin II on sodium dependent MeAIB transport in human placental villous fragments appears to be mediated by AT-1R induced down-regulation of Na^+-K^+ ATPase activity that maintains the transcellular sodium concentration gradient (130). With simple or facilitated diffusion, the hormonal effects on transport may be the result of alterations in placental blood flow or the transplacental concentration gradients driving net transfer. For instance, insulin administration to pregnant ewes lowers maternal glucose levels and reduces facilitated diffusion of maternal glucose to the fetus in proportion to the decrease in the transplacental concentration gradient (111). Thus, insulin appears to have little direct effect on the placental capacity for glucose transport *per se* in sheep in late gestation with no changes in placental glucose transporter (GLUT) abundance or glucose partitioning in the short term (111, 112, 132). Similarly, insulin has no effect on glucose uptake by villous fragments of term human placenta *in vitro* (122). When insulin infusion is more prolonged in pregnant ewes *in vivo*, there are changes in placental GLUT expression in line with the reduced glucose transport, although whether these changes are the consequence of the sustained hyperinsulinaemia or of the concomitant hypoglycaemia still remains unclear (111, 112, 134). However, in rats, short term insulin infusion in euglycaemic conditions has been shown to increase placental glucose uptake at day 19 of pregnancy but not closer to term (114). In *in vitro* studies, insulin has been shown to increase amino acid uptake by villous fragments of term human placenta after periods of between 2-24h in culture (110, 122, 130). These actions of insulin and IR localisation suggest that insulin may be involved in

the growth and remodelling of the placenta from early in gestation and, particularly, the placental vasculature nearer to term (37). However, like the brain, uptake and utilisation of glucose by the placenta appears to be insulin insensitive, despite the presence of insulin receptors (Table 1), which probably relates to the lack of insulin-sensitive glucose transporters, GLUT4, in the placenta (135).

In part, the effects of hormones on nutrient transfer depend on their route of administration and on whether measurements are made during or after ending treatment. Short term infusion of IGF-I increased placental lactate production when given maternally but not fetally while, conversely, umbilical uptake of glucose is increased with fetal but not maternal administration in the sheep (117, 118). In both sheep and mice, glucocorticoid overexposure during late gestation reduces placental transport of glucose and amino acids during the period of overexposure, irrespective of its duration, method of induction, or the type of glucocorticoid involved (Figure 1). In contrast, after glucocorticoid treatment, transport of glucose and amino acids by the growth restricted mouse placenta tends to increase compared to age matched controls, although the precise response appears to depend on the interval between ending treatment and measuring transport (Figure 1). In part, the up-regulated nutrient transport seen after treatment may reflect an increased demand for nutrients from the growth restricted fetus once the glucocorticoid has cleared from the tissues. Indeed, increased placental nutrient transport, particularly of the amino acids, is also seen when there is a disparity between the placental capacity to supply nutrients and the fetal nutrient demands for growth, irrespective of whether this mismatch is induced nutritionally or genetically (4, 6).

When all the mouse transport data at day 19 of pregnancy are combined, irrespective of the period of corticosterone treatment, there is a significant inverse correlation between maternal corticosterone concentrations and placental MeAIB transport (87). This is consistent with the concept that there is a dynamic balance in resource allocation between the mother and fetus that is responsive to environmental conditions (4, 8). By reducing placental size and nutrient transport, increased maternal glucocorticoids levels spare nutrients for maternal use during stressful periods and, by limiting fetal growth, further reduce the nutritional demands on the mother if the stress is prolonged. Conversely, when

maternal stress and glucocorticoid levels are low, more maternal nutrients can be diverted to the gravid uterus, particularly when there is an increased demand signal from fetuses growth restricted below their genetic potential by earlier periods of adverse environmental conditions.

HORMONES AND PLACENTAL ENDOCRINE FUNCTION

The placenta produces a wide range of hormones including sex steroids, eicosanoids, glycoprotein and peptide hormones, some of which are unique variants of pituitary hormones (1, 7). Secretion of several of these is sensitive to the endocrine milieu and, particularly, to the glucocorticoids (Table 3). Increasing placental exposure to glucocorticoids *in vivo* in late gestation has been shown to increase placental production of PGE_2 and estrogen, and reduce secretion of placental lactogen, leptin, IGF-I and the family of prolactin hormones depending on the specific species (Table 3). In rodents, these changes are often Jz specific (93, 147). Similarly, glucocorticoids have been shown to alter secretion of leptin, placental GH, hCG and PGE_2 by human villous fragments and trophoblast cell lines *in vitro* (Table 3). In most species studied to date, glucocorticoid-induced changes in placental hormone production form part of the normal sequence of prepartum maturational events that ensure fetal maturation is co-ordinated with the onset of labour and lactation (1, 151). However, changes in placental hormone production induced by glucocorticoids earlier in gestation as a result of stressful conditions can have adverse consequences for fetal development, maternal recognition of and metabolic adaptation to pregnancy as well as for lactation. Indeed, in mares, preterm changes in placental progestagen production induced by stress or more direct glucocorticoid administration are associated with prepartum running of milk, poor colostrum production at birth and failure of foals to thrive postnatally if they are not given supplementary immunoglobulins (152).

The placental endocrine phenotype depends not only on the production of hormones but also on their metabolism. In several species including rodents, sheep and humans, the placenta inactivates glucocorticoids and prostaglandins, thereby reducing their circulating and placental bioavailability. In turn, the inactivating enzymes are responsive to hormones (1, 2, 83). Both progesterone and cortisol have been shown to regulate placental activity of

11βHSD2 and prostaglandin dehydrogenase (PGDH), the enzymes responsible for inactivating glucocorticoids and prostaglandins, respectively (83, 85). However, the specific response of these placental enzymes to hormonal signals depends on species, gestational age, duration of treatment and maternal nutritional state (2, 83, 149).

CONCLUSIONS

Hormones in the fetal and maternal circulations have an important role in determining placental phenotype (Figure 2). They signal fetal wellbeing and maternal environmental conditions to the placenta, respectively. In turn, placental hormones signal resource availability to the fetus and fetal nutrient demands to the mother based on the genetic drive and current mass of the fetus (Figure 2). The placenta integrates all these hormonal signals and adapts its phenotype to optimise resource allocation between the mother and growing fetus with respect to both fetal and maternal fitness. The hormonally-induced adaptations can be either short lived to allow a rapid response to environmental change or persist to transmit memories of earlier events to the fetus later in development. Endocrine regulation of placental phenotype, therefore, provides a unifying mechanism for determining the phenotype of the offspring that develops from the genotype inherited at conception. However, little is yet known about the specific cellular and molecular pathways in the placenta that sense the hormonal signals and then mediate the adaptive responses. Nor is it clear whether hormones alter the placental epigenome, although epigenetic modifications in the placenta occur during normal development and growth restriction as well as in several other clinical complications of human pregnancy (6, 153, 154).

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FIGURE LEGEND

Figure 1: Effects of glucocorticoids during and after treatment on placental transport of glucose and amino acids in sheep and mice during late gestation. In sheep, placental glucocorticoid overexposure was increased by fetal intravenous treatment with either for cortisol for 5 days (Cort, hatched columns) or dexamethasone for 24h (Dex, grey columns) and measurements of transport made during the final hours of treatment. In mice, placental overexposure was induced either to the synthetic glucocorticoid, dexamethasone (Dex, grey columns) by maternal administration for 5 days or to the natural glucocorticoid, corticosterone (Cort, hatched columns), by deletion of the *11ϐhsd2* gene or maternal corticosterone administration for 5 days. In the mice, transport measurements were made either during overexposure (during treatment) alone and/or after cessation of treatment (after treatment with the timing indicated as + days from ending treatment). All values are expressed as % of that in the control animals (open columns).
* significantly different from control by the statistical analyses used in the relevant study.
Data from references 87, 88, 90, 91, 101-103, 106 and 107.

Figure 2: A schematic diagram showing the role of hormones in regulating placental phenotype with respect to balancing maternal resource availability with fetal resource demands for optimal intrauterine growth.

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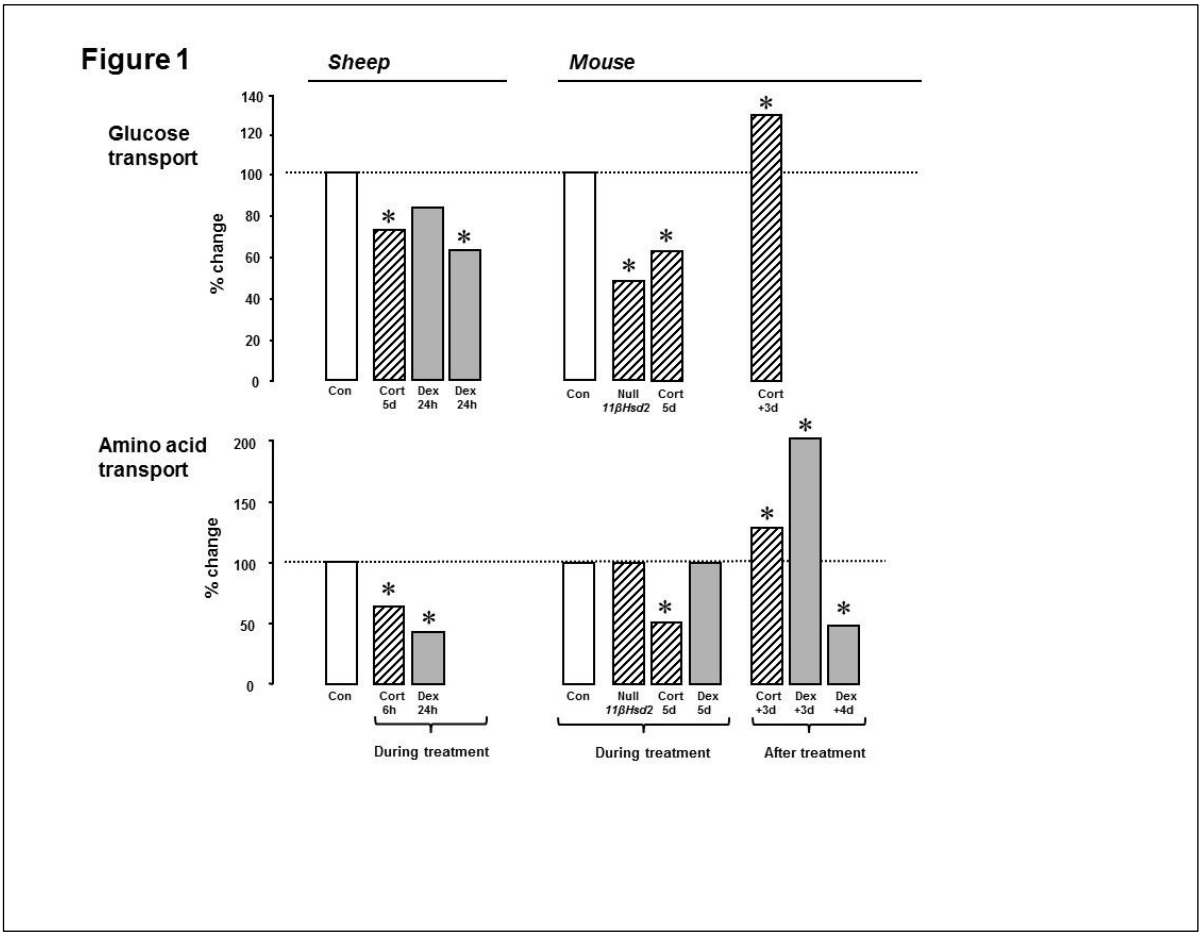
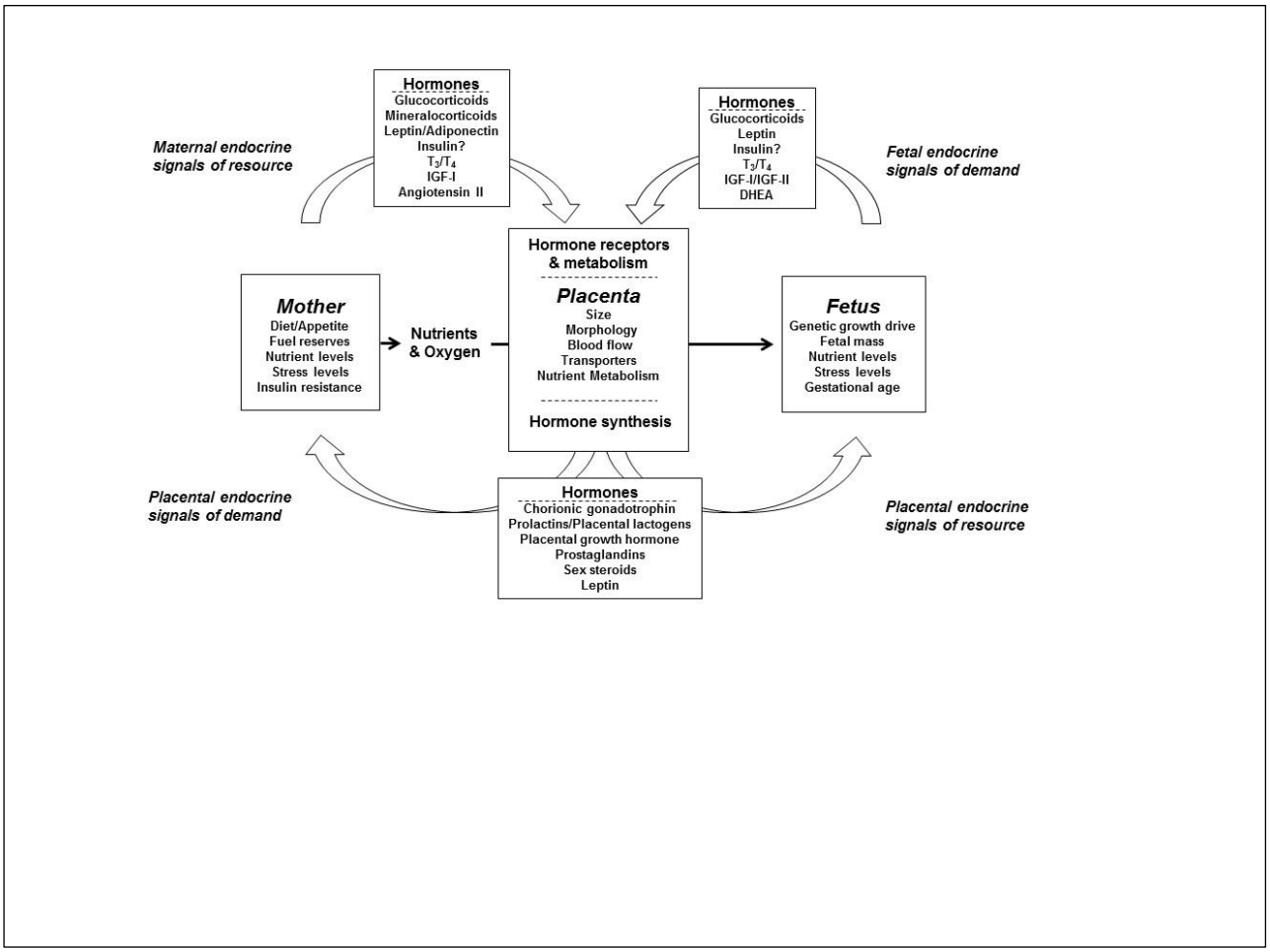


Figure 1
Sheep
Mouse
Glucose transport
% change
140
120
100
80
60
40
20
0
Con
Cort 5d
Dex 24h
Dex 24h
Con
Null 11βHsd2
Cort 5d
Cort +3d
Amino acid transport
% change
200
150
100
50
0
Con
Cort 6h
Dex 24h
Con
Null 11βHsd2
Cort 5d
Dex 5d
Cort +3d
Dex +3d
Dex +4d
During treatment
During treatment
After treatment


Hormones
Glucocorticoids
Mineralocorticoids
Leptin/Adiponectin
Insulin?
T_3/T_4
IGF-I
Angiotensin II
Maternal endocrine signals of resource
Hormones
Glucocorticoids
Leptin
Insulin?
T_3/T_4
IGF-I/IGF-II
DHEA
Fetal endocrine signals of demand
Hormone receptors & metabolism
Placenta
Size
Morphology
Blood flow
Transporters
Nutrient Metabolism
Hormone synthesis
Mother
Diet/Appetite
Fuel reserves
Nutrient levels
Stress levels
Insulin resistance
Nutrients & Oxygen
Fetus
Genetic growth drive
Fetal mass
Nutrient levels
Stress levels
Gestational age
Placental endocrine signals of demand
Hormones
Chorionic gonadotrophin
Prolactins/Placental lactogens
Placental growth hormone
Prostaglandins
Sex steroids
Leptin
Placental endocrine signals of resource

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953
954

Table 1: Presence of hormone receptors in the placenta with respect to gestational age in different species.
(d = days, w = weeks. Term : human 40 weeks, horse 335 days, cow 280 days, baboon 168 days, sheep 145 days, pig 115 days, guinea pig 70 days, cat 65 days, rabbit 30 days, rat 22 days, spiny mouse 39 days, mouse 20 days)

Hormone group	**Specific Receptor (Abbreviation)**	**Isoforms**	**Species**	**Gestational age (days,d/weeks, w)**	**Reference**
Steroids	Glucocorticoids (GR)	GRα, GRβ	Human	Term	9
			Sheep	51-140d	10, 11
			Pig	94d	12
			Rat	16-22d	13
			Spiny Mouse	23-37d	14
			Mouse	9.5d - term	15
	Mineralocorticoids (MR)	MR	Human	5-40 w	16
			Pig	94d	12
			Sheep	138d	17
	Estrogens (ER)	ERα, ERβ	Human	Term	18, 19
			Horse	110-309d	20
			Sheep	13-30d	21
			Rabbit	10-14d	22
	Progesterone (PR)	PR-A, PR-B	Human	Term	19, 23
			Horse	110-199d	20
			Sheep	30d & 84-112d	21, 24
			Rabbit	10-16d	22
			Rat	12d	25
	Androgens (AR)	AR-A, AR-B	Human	16w - term	26
			Cow	50d – term	27
			Rat	21d	28
Iodothyronines	Thyroid hormones (TR)	TRα, TRβ	Human	13w - term	29, 30
			Rat	16-21d	31
Eicosanoids	Prostaglandins (PG) PGE_2	EP1,2,3 & 4	Human	38-41w	32
			Sheep	Term	33
	$PGF_{2\alpha}$	FP	Human	38-41w	32
			Sheep	Term	33

Glycoproteins	Chorionic gonadotrophin	LH receptor TGFβ receptor2	Human Horse	Term 27-34d	34 35
Proteins	Insulin (IR)	IR-A, IR-B	Human Monkey Rat Mouse	1st trimester & term Near term Term 16-19d	36, 37 36 36 38
	Insulin-like growth factors (IGFR)	IGFR1, IGFR2	Human Sheep Guinea pig Rat Mouse	1st trimester & term 138d 35d 21d 16-19d	37 11, 17 39 40 38
	Prolactin (PRLR)	PRL-R	Human Baboon Rat	Term 39d & Term 15-17d & 19d	41, 42 43 41, 44
	Leptin (OBR)	Ob-Ra, Ob-Rb	Human Baboon Sheep Pig Cat Rat Mouse	Term 60-164d 128d 30d & 100d Term 16-22d 11.5-18.5d	45 46 47 47 48 49 50
	Adiponectin	Adipo-R2	Human Rat	1st trimester & term 12-21d	51 51
	Growth hormone (GHR)	GHR	Human Sheep	8w & Term 20-120d	7 52, 53
	Corticotrophin Releasing Hormone (CRH)	CRH-R1, CRH-R2	Human	Term	54, 55
	Kisspeptin	Kiss1R	Human Rat	Term 16d & 22d	56 57
Peptides	Gonadotrophin releasing hormone (GnRHR)	GnRHR-I & -II	Human	6-20w	58
	Angiotensin (ATR)	AT_1R, AT_2R	Human Sheep	10w-term 27-140d	59 60, 61

			Pig Rabbit Mouse	30d-term 14-28d 16.5d & 18.5d	62 63 64
	ANP		Human	Term	65
	Adrenomedullin		Human Cow Rat	Term 200d 12d & 17d	66 67 68

Table 2: Effect of hormone administration on the transport phenotype of the placenta in different species with respect to gestational age at treatment and assessment.

Hormone	Species	Type and route of treatment	Gestational age (days)		Placental transport phenotype	Reference
			At treatment	At study		
Glucocorticoids	Human *-in vitro*	Cortisol In culture	Cell line	Cell line +24h	↑ MeAIB uptake ↑SNAT2	98
			Term	Term	↑ Na^+/H^+ exchanger activity	99
		Dex In culture	Term	Term	↑ MeAIB uptake	100
	Sheep *-in vivo*	Fetal cortisol iv infusion	120-122	120-122 +6h	↓ Amino-nitrogen delivery	101
			125-130d	130d	↓ Glucose delivery	91
					↑ Glucose consumption	91
		Fetal dex iv infusion	Near term	Near term	↓ Alanine delivery	102
				+24h	↓ Glutamate uptake	102
					↑ Placental lactate delivery	102
					↓ Glucose delivery	103
	Rat *-in vivo*	Maternal dex sc infusion	15-21d	21d	↑ GLUT 1 & 3	104
		Maternal dex sc injection	15-19d	20d	↑ Folate transport ↓ Choline transport	105
	Spiny mouse *-in vivo*	Maternal dex sc infusion	20-22.5d	23d	↓ SLC2A1	14
				37d	↓ SLC2A1 – males only	14
	Mouse *-in vivo*	Maternal corticosterone po	11-16d	16d	↑*Slc38a1*&*2* ↓*Slc2a1 & 3*	87, 106
		In drinking water	11-16d	19d	↑ MeAIB transport ↑*Slc38a1*	87
					↑ Glucose transport	106
			14-19d	19d	↓ MeAIB transport	87
		Maternal dex po	11-16d	19d	↑ MeAIB transport	88
		Maternal dex sc injection	13.5 & 14.5d	18.5d	↓ MeAIB transport	107
		11ϐHsd2 null	Conception	15d	↑ MeAIB transport ↑*Slc38a2*	90
			Conception	18d	↓ Glucose transport ↓*Slc2a3*	90
Aldosterone	Human *-in vitro*	In culture	Term	Term	↑ Na^+/H^+ exchanger activity	99
Testosterone	Rat *-in vivo*	Maternal sc injection	15-19d	21d	↓ MeAIB uptake & transport ↓SNAT2	108
Estrogen	Rat *-in vivo*	Maternal po daily	4-8d	13d	↓ GLUT1	109

Insulin	Human *-in vitro*	In culture	Term	Term +24h	↑ MeAIB uptake	110
	Sheep *-in vivo*	Maternal iv infusion Fetal iv infusion	105d 135d	130-141d 135d +4h	↓ Glucose utilisation & delivery ↓ GLUT1 ↑ Glucose delivery	111 112 113
	Rat *-in vivo*	Maternal iv infusion	19d	19d +4h	↑ Glucose uptake & utilisation	114
Insulin-like growth factors (IGFs)	Human *-in vitro*	In culture	1st Trimester Term	1st Trimester Term	↑ Glucose and amino acid uptake ↑ MeAIB uptake	115 116
	Sheep *-in vivo*	Maternal iv infusion Fetal iv infusion	132d 130d 120-130d	132d +4h 130d +4h 130d	↑ Placental lactate production & delivery ↓ Placental lactate production & delivery ↑ Glucose delivery ↓ Glucose and MeAIB clearance	117 118 118 119
	Guinea pig *-in vivo*	Maternal sc infusion	20-35d 20-38d	35d 60d	↑MeAIB uptake & transport ↑ Glucose uptake & transport	120 121
Growth hormone	Human *-in vitro*	In culture	1st Trimester Term	1st Trimester Term	↓ MeAIB uptake ↑ Glucose uptake	122 122
	Pig *-in vivo*	Maternal iv injection daily	25-50d	50d	↑ GLUT1, ↑ SNAT2	123
	Sheep *-in vivo*	Maternal sc daily injections	125-135d	135d	↑ Placental glucose clearance ↑ Placental capacity for simple diffusion	124 124
Leptin	Human *-in vitro*	In culture	Term	Term +1h	↑ MeAIB uptake	125
Parathyroid related protein (PTHrP)	Mouse *-in vivo*	*PTHrP* null	Conception	18d	↑Materno-fetal calcium flux	126
Adiponectin	Human *-in vitro*	In culture	Term	Term +24h	↑ MeAIB uptake	127
	Mouse *-in vivo*	Maternal sc infusion	14.5-18.5d	18.5d	↓ System A and L amino acid transport ↓ SNAT1, 2 & 4, ↓ LAT1 &2	128
Corticotrophin releasing Hormone (CRH)	Human *-in vitro*	In culture	Term	Term +24h	↓ MeAIB uptake	129
Angiotensin II	Human *-in vitro*	In culture	Term	Term +4h	↓ MeAIB uptake ↓ Na^+-K^+ATPase activity	130 130

po = per os, iv = intravenous, sc = subcutaneous, *Slc38a 1&2* and SNAT 2 & 4 = Sodium coupled neutral amino acid transporter genes and proteins, Lat 1 & 2 = L-type amino acids transporters, GLUT 1 & 3 = glucose transporters, Dex = Dexamethasone

Table 3: Effect of hormone administration on the endocrine phenotype of the placenta in different species with respect to gestational age at treatment and assessment.

Hormone	Species	Type and route of treatment	Gestational age (hours/days) At treatment	Gestational age (hours/days) At study	Placental endocrine phenotype	Reference
Glucocorticoids	Human *-in vitro*	Dex in culture	Cell line	Cell line +72h	↑ hCG	136
			Term	Term +72h	↑ Leptin	137
			Term	Term +96h	↓ PGE_2	138
		Cortisol in culture	Cell line	Cell line + 72h	↓ Placental GH	139
			Term	Term +144h	↑ hCG	140
	-in vivo	Dex im	3rd trimester	3rd trimester +5h	↓ Estradiol and estrone	141
		Beta im x3 daily	3rd trimester	3rd trimester +48h	↑ CRH	142
		Dex im x3 daily	3rd trimester	3rd trimester +7d	↓ Placental lactogen	143
	Cow *-in vitro*	Dex in culture	Term	Term + 18h	↓ $PGF_{2\alpha}$	144
	Sheep	Maternal beta im 3x	103-118d	109-121d	↓ Placental lactogen	92
	-in vivo	Fetal dex iv infusion	Term	Term	↓ Progesterone, ↑ Estrogens	145
		Fetal beta im injection	131d	134d	↑ PGE_2, ↑ $PGF_{2\alpha}$	146
		Fetal cortisol iv infusion	125-128d	128-131d	↑PGE_2 ↑Estrogens	147
	Rat	Maternal dex sc infusion	13-20d	20d	↓ IGF-II, ↓ Prolactin gene family	93
	-in vivo		15-21d	21d	↓ Leptin	148
	Spiny mouse *-in vivo*	Maternal dex sc infusion	20-22.5d	23d & 37d	↓ *IGF-I*	14
	Mouse *-in vivo*	Maternal dex ip injection daily	7.5-9.5d	18.5d	↓ *PLII*, ↓ *Prp*	149
Testosterone	Rat *-in vivo*	Maternal sc injection	16-19d	21d	↑Estrogen	28
Progesterone	Human *-in vitro*	In culture	Term	Term +144h	↓hCG	140
Insulin	Human	In culture	Term	Term +72h	↑ Leptin	137
	-in vitro		Cell line	Cell line + 72h	↓ Placental GH	143
Insulin-like growth factors (IGF)	Human *-in vitro*	In culture – IGF-I	Cell line	Cell line +24h	↑ hCG, ↑ Progesterone	150

Leptin	Human *-in vitro*	In culture	Cell line	Cell line +72h	↓ Placental GH	139

im = intramuscular, iv = intravenous, sc = subcutaneous, ip = intraperitoneal, hCG = human chorionic gonadotrophin, GH = growth hormone, PGE_2 = Prostaglandin E_2, $PGF_{2\alpha}$ = Prostaglandin $F_{2\alpha}$, CRH = Corticotrophin releasing hormone, IGF = Insulin-like growth factor – I and –II, *PLII* = Placental lactogen II gene, Prp = Prolactin related protein gene, Dex = dexamethasone, Beta = Betamethasone.