Thyroid hormones in fetal growth and *prepartum* maturation

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Abstract

The thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), are essential for normal growth and development of the fetus. Their bioavailability *in utero* depends on development of the fetal hypothalamic–pituitary–thyroid gland axis and the abundance of thyroid hormone transporters and deiodinases that influence tissue levels of bioactive hormone. Fetal T_4 and T_3 concentrations are also affected by gestational age, nutritional and endocrine conditions *in utero*, and placental permeability to maternal thyroid hormones, which varies among species with placental morphology. Thyroid hormones are required for the general accretion of fetal mass and to trigger discrete developmental events in the fetal brain and somatic tissues from early in gestation. They also promote terminal differentiation of fetal tissues closer to term and are important in mediating the *prepartum* maturational effects of the glucocorticoids that ensure neonatal viability. Thyroid hormones act directly through anabolic effects on fetal metabolism and the stimulation of fetal oxygen consumption. They also act indirectly by controlling the bioavailability and effectiveness of other hormones and growth factors that influence fetal development such as the catecholamines and insulin-like growth factors (IGFs). By regulating tissue accretion and differentiation near term, fetal thyroid hormones ensure activation of physiological processes essential for survival at birth such as pulmonary gas exchange, thermogenesis, hepatic glucogenesis, and cardiac adaptations. This review examines the developmental control of fetal T_4 and T_3 bioavailability and discusses the role of these hormones in fetal growth and development with particular emphasis on maturation of somatic tissues critical for survival immediately at birth.

Key Words
- thyroid hormones
- intrauterine growth
- maturation
- neonatal adaptation

Journal of Endocrinology (2014) **221**, R87–R103

Introduction

The thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), are detectable in the fetal circulation from early in gestation and have important developmental, metabolic, and maturational effects in the fetus in all species studied to date including human infants. Their bioavailability in fetal plasma and tissues is regulated developmentally and also varies with species, gestational age, availability of nutrients and oxygen, and the endocrine environment *in utero* (Fowden & Forhead 2009, 2013). Deficiency of thyroid hormones during intrauterine development impairs growth of the fetus and compromises its adaptation to extrauterine life (Fowden *et al.* 1998, Hillman *et al.* 2012, Sferruzzi-Perri *et al.* 2013). Conversely, fetal administration of thyroid hormones can promote tissue differentiation and activation of many of the physiological processes that have little or no function

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DOI: 10.1530/JOE-14-0025

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before birth but which are essential for neonatal survival (Fowden *et al*. 1998). This review examines the developmental control of fetal T_4 and T_3 bioavailability and discusses the role of these hormones in fetal growth and development with particular emphasis on the maturation of somatic tissues essential for survival immediately at birth. The important role of thyroid hormones in brain development is not considered here as this has been reviewed extensively in recent years (Horn & Heuer 2010, Patel *et al*. 2011, Puig-Domingo & Vila 2013, Stenzel & Huttner 2013).

Bioavailability of thyroid hormones before birth

In fetal and adult animals, the bioavailability of thyroid-stimulating hormone (TSH) and the two biologically active thyroid hormones, T_4 and T_3, is determined by several factors: i) the activity of the hypothalamic–pituitary–thyroid axis and production of T_4 and T_3, ii) the peripheral conversion of T_4 to more biologically active T_3 or to inactive metabolites to vary circulating and tissue-specific concentrations, and iii) the uptake of thyroid hormones into target tissues and activation of cellular processes by binding to thyroid hormone receptors (TRs; Fig. 1). Before birth, all of these factors show developmental and tissue-specific regulation. In addition, placental transfer of thyroid hormones from the mother can contribute to the concentration of thyroid hormones in the fetal circulation, depending on the species and placental type (Fig. 1).

Activity of the fetal hypothalamic–pituitary–thyroid axis

The thyroid gland originates as an outgrowth from the developing pharyngeal floor in the early embryo and undergoes three main stages of growth and differentiation: pre-colloid, colloid, and follicular (Brown 2004,

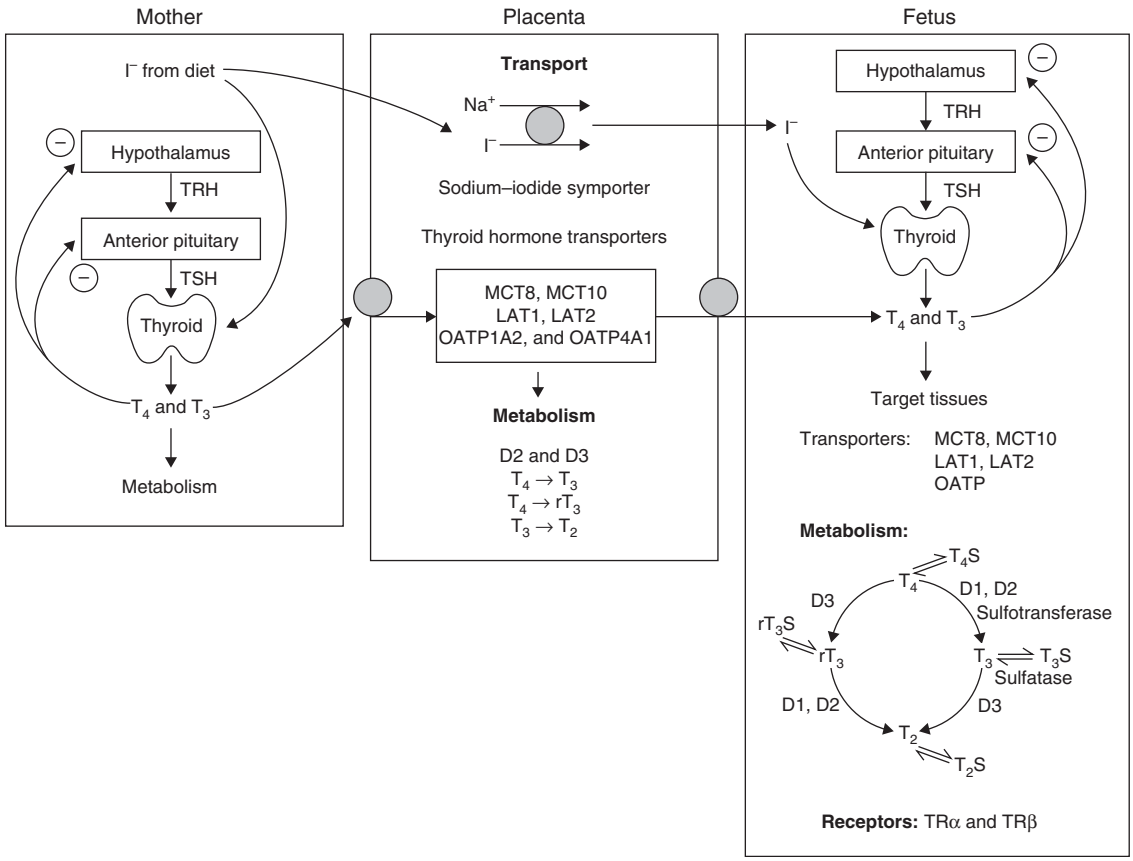

Figure 1
Schematic diagram showing the factors affecting the bioavailability of thyroid hormones in the fetus, placenta, and mother. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T_4, thyroxine; T_3, triiodothyronine; rT_3, reverse T_3; T_2, diiodothyronine; S, sulfated; D1, D2, and D3, deiodinases; OATP, organic anion transporters; LAT1 and LAT2, L-type amino acid transporters 1 and 2; MCT8 and MCT10, monocarboxylate transporters 8 and 10.

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DOI: 10.1530/JOE-14-0025

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Santisteban 2013). The follicular structural development of the thyroid gland coincides with the functional development of the hypothalamic–pituitary–thyroid axis and the secretion of thyroid hormones into the fetal circulation (Table 1). Hypothalamic neurones produce thyrotropin-releasing hormone (TRH), which stimulates the thyrotropes of the anterior pituitary gland to secrete TSH. In turn, TSH acts on the thyroid gland to promote follicular growth and stimulate the synthesis and secretion of the thyroid hormones. In the human fetus sampled by cordocentesis, serum concentrations of TSH and free and total T_4 increase from mid-gestation with an exponential rise in free T_3 closer to term (Thorpe-Beeston *et al.* 1991*a*). In fetal life, as in adult life, the thyroid hormones control their own production by negative feedback effects on the hypothalamus and pituitary, at least by late gestation, although the axis continues to mature in sensitivity postnatally (Hopkins *et al.* 1975, Polk *et al.* 1991, Rakover *et al.* 1999, Hernandez *et al.* 2006). Normal production of thyroid hormones by the fetal thyroid gland depends upon iodide uptake by the follicular cells of the gland and iodide is actively transported from the maternal circulation across the placenta (Fig. 1).

The pattern of thyroid gland development and thyroid hormone activity is comparable in all mammals studied, but the timing of the developmental stages can vary between species. Table 1 compares the ontogeny of aspects of thyroid hormone activity in human, sheep, and rats. These include development of the hypothalamic–pituitary–thyroid axis, onset of thyroid hormone production, and expression of TRs. Overall, human and ovine fetuses are similar in the timing, relative to gestational age, of the structural development of the thyroid gland and the onset of thyroid hormone activity, while rodent species show relatively delayed maturation of thyroid hormone bioavailability (Table 1; Fisher & Polk 1989, Polk 1995). From mid-gestation in human and ovine fetuses, the thyroid gland secretes T_4 and T_3 under the control of the hypothalamic–pituitary axis and the thyroid hormone axis is fully functional around the time of birth (Table 1). In rats, however, maturation of thyroid hormone activity continues up to 4 weeks of postnatal life (Table 1).

Metabolism of thyroid hormones *in utero*

The circulating concentrations of the thyroid hormones are controlled, not only by the output of the thyroid gland, but also by metabolism in peripheral tissues (Fig. 1). In the fetus, thyroid hormones can undergo deiodination and sulfation to more or less active metabolites. The metabolism of T_4 into more genomically potent T_3 or relatively bio-inactive reverse T_3 (rT_3) depends on the activity of deiodinase enzymes, which are developmentally regulated in specific tissues (Brent 2012,

Table 1 Comparison of the timing of developmental stages of thyroid hormone bioavailability among human, sheep, and rat fetuses. Data adapted from Thorburn & Hopkins (1973), Bernal & Pekonen (1984), Perez-Castillo *et al.* (1985), Ferreiro *et al.* (1987), Polk *et al.* (1989, 1991), Thorpe-Beeston *et al.* (1991*b*), Polk (1995), Brown (2004), and Chan *et al.* (2011)

Developmental stage	**Human** (weeks)	**Sheep** (days)	**Rat** (days)
Gestational age at term	40	145	21
Thyroid gland organogenesis			
Pre-colloid	7–13 (0.18–0.33G)		
Colloid	13–14 (0.33–0.35G)	50–55 (0.34–0.38G)	17 (0.81G)
Follicular	>14 (>0.35G)	>55 (>0.38G)	18 days–3 weeks postnatally
TRH in hypothalamus	10–12 (0.25–0.30G)	<60 (0.40G)	16 (0.76G)
TSH in anterior pituitary gland and circulation	10–12	<60	17 (0.81G)
TSH receptor in thyroid gland	10–12		15 (0.71G)
Iodide uptake in thyroid gland	10–12	50 (0.34G)	
Thyroglobulin synthesis	10–12		15
Iodinated amino acids	14 (0.35G)	70 (0.48G)	17 (0.81G)
Synthesis and secretion of thyroid hormones	16–18 (0.40–0.45G)	60–70 (0.40–0.48G)	17.5 (0.83G)
Rise in plasma T_3	30 weeks to birth	135 days to birth	Birth to 3 weeks postnatally
Gene and protein expression of thyroid hormone transporters	7–9 (0.18–0.23G) cerebral cortex		
Thyroid hormone receptor binding	10–16 (0.25–0.40G) brain, heart, liver, and lung	<50 (0.34G) brain, liver, and lung	14–16 (0.67–0.76G) brain, heart, liver, and lung

Percentage of total gestation (G) are given in brackets.

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DOI: 10.1530/JOE-14-0025

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Chi *et al*. 2013). Three key deiodinase enzymes are found in both fetal and adult tissues: D1, D2, and D3 (Bianco *et al*. 2002). D1 is primarily a 5′-monodeiodinase enzyme that catalyzes outer-ring deiodination of T_4 to T_3 and of rT_3 to T_2. This enzyme is present in the fetal liver, kidney, and thyroid and pituitary gland, and the production of T_3 by hepatic D1 is considered to be the major endocrine source of circulating T_3 concentrations (Polk 1995). D2 is also a 5′-deiodinase enzyme with kinetic characteristics different from D1 that is found primarily in the brain, pituitary gland, placenta, and brown adipose tissue. In these tissues, D2 generates local concentrations of T_3 that are essential for normal tissue development and function, rather than contributing significantly to the circulating pool of T_3. D3 is a 5′-monodeiodinase enzyme that catalyzes inner-ring deiodination of T_4 to transcriptionally inactive rT_3, and of T_3 to inactive T_2. This enzyme is present in the liver, kidney, and skin and is highly expressed in the uterus, placenta, and amniotic membrane, where it has an important role in the clearance of circulating thyroid hormones and in regulating placental transfer of maternal thyroid hormones to the fetus. Therefore, as an enzymatic barrier, placental D3 limits the exposure of the fetus to maternal thyroid hormones. In the human placenta, the enzyme activity, and mRNA and protein expression, of D2 are greatest in the first trimester compared with term, but significantly lower than those of D3 at all gestational ages studied (Koopdonk-Kool *et al*. 1996, Chan *et al*. 2003). These findings suggest that local production of T_3 may be important for early placental development, but is unlikely to contribute significantly to circulating T_3 concentrations in the fetus.

The *Dio3* gene that encodes D3 has been shown to be imprinted in the mouse and is preferentially expressed by the paternal allele (Hernandez *et al*. 2002, Tsai *et al*. 2002). However, imprinting does not occur in all fetal tissues and, where it does, expression from the paternal allele varies from 75–85% in fetal tissues to 50–60% of total expression in the placenta (Charalambous & Hernandez 2013). Knockout of the *Dio3* gene causes perinatal thyrotoxicity and partial lethality at or before birth (Hernandez *et al*. 2006). Birth weight is normal in the live mutant pups but there are abnormalities in the pancreatic β-cells, retina, and hypothalamus at birth with a more severe growth-restricted phenotype developing with increasing postnatal age (Hernandez *et al*. 2006, Ng *et al*. 2010, Medina *et al*. 2011, Ueta *et al*. 2012). The tissue-specific patterns of imprinting and expression of *Dio3* suggest that this deiodinase has both paracrine and endocrine actions in preventing feto-placental over exposure to thyroid hormones at critical stages of development.

Another important pathway in thyroid hormone metabolism *in utero* is sulfation, whereby around 80% of T_4 produced by the thyroid gland is metabolized to biologically inactive sulfated forms, such as T_4S, T_3S, and rT_3S (Wu *et al*. 1992, 1993). Thyroid hormones are sulfated by sulfotransferase, primarily in the fetal liver, but also in the kidneys, brain, and intestines (Fig. 1). One significant aspect of this metabolic pathway is that sulfation of thyroid hormones can be reversed by sulfatase enzymes in tissues such as the liver, lung, brain, and placenta (Richard *et al*. 2001, Kester *et al*. 2002). This means that T_3S, for example, can be converted back to T_3, which is likely to be an important source of T_3 especially during hypothyroidism (Fig. 1). In thyroidectomized sheep fetuses, T_3S remains in the circulation for up to 2 weeks while all other thyroid hormones and their metabolites fall below detectable levels (Wu *et al*. 1993). Therefore, during hypothyroidism, T_3S conversion to T_3 in tissues such as the brain maintains a local supply of T_3 essential for normal growth and development. Indeed, the fetal brain employs several mechanisms to maintain normal local concentrations of thyroid hormones in the event of thyroid hormone deficiency. In the thyroidectomized sheep fetus, hepatic D1 activity is downregulated to reduce the endocrine deiodination of T_4 in the fetal liver, while at the same time, cerebral D2 activity is upregulated to enhance local deiodination of T_4 to T_3 in the fetal brain (Polk *et al*. 1988). Therefore, the hypothyroid fetus conserves T_4 for local production of T_3 within the brain, in order to maintain the actions of the thyroid hormones on brain development.

For most of gestation, T_4 is metabolized primarily to rT_3 and a variety of sulfated thyroid hormones that are biologically inactive (Fig. 1). The high ratio of D3 to D1 activity in the fetal liver, and the placental D3 enzyme, maintain a high rate of T_3 clearance and, therefore, concentrations of T_3 are relatively low in the fetal circulation. Toward term, however, there are developmental changes in tissue deiodinase activity and, therefore, plasma T_3 concentration in the fetus (Darras *et al*. 1992, Forhead *et al*. 2006). In fetal sheep, hepatic and renal D1 activities increase, and placental D3 activity decreases, in the 2 weeks before birth (Forhead *et al*. 2006). Overall, preferential deiodination of T_4 to T_3 instead of rT_3 and reduced clearance of T_3 lead to a rise in plasma T_3 concentration in the fetus near term. In fetal sheep, these maturational changes in tissue deiodinase activity have been shown to be induced by the *prepartum* cortisol

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DOI: 10.1530/JOE-14-0025

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surge and can be stimulated prematurely by maternal administration of the synthetic glucocorticoid, dexamethasone (Forhead *et al.* 2006, Forhead *et al.* 2007). Endogenous and synthetic glucocorticoids also increase plasma T_3 conversion via changes in the hepatic D1:D3 ratio in the chick embryo (Darras *et al.* 1996). Therefore, circulating and local concentrations of thyroid hormones in the fetus are regulated developmentally, and in a tissue-specific manner, by the balance between deiodinase and other metabolic enzymes.

Thyroid hormone transporters and receptors in fetal tissues

Thyroid hormone bioavailability is also determined by the expression of transporters and intracellular receptors in the target tissues. There are several types of thyroid hormone transporters that allow the hormones access to target tissues, including organic anion transporters (OATP), L-type amino acid transporters (LAT1 and LAT2), and monocarboxylate transporters (MCT8 and MCT10; Friesema *et al.* 2005, Jansen *et al.* 2005). A genetic mutation in human *MCT8* (*SLC16A2*) has been identified in families who showed symptoms of hypothyroidism including severe neurological and muscular defects, although the phenotype differs from that observed with congenital hypothyroidism and in mutant MCT8 mouse models (Visser *et al.* 2008, Heuer & Visser 2013). In adult animals, thyroid hormone transporters have been identified in the liver, kidney, brain, lung, and placenta. In the cerebral cortex of the human fetus at 7–20 weeks of gestation, *MCT8* and *MCT10* (*SLC16A10*) mRNA levels are similar to those in the adult brain, and developmental changes in *OATP* (*SLCO1A2*) mRNA have been reported (Chan *et al.* 2011). Thyroid hormone transporter proteins in the brain and other tissues are likely to have an important role in determining tissue-specific bioavailability of the thyroid hormones in fetal as well as in adult life. Thus, variations in thyroid hormone transporter abundance may lead to abnormalities in thyroid hormone exposure even when circulating levels of these hormones are normal. However, to date, the regulation of these transporters in fetal tissues of any species is unknown.

Once transported across the plasma membrane, the bioactivity of thyroid hormones depends ultimately on the expression of intracellular TRs and post-receptor-binding pathways. The various TRα (THRA) and TRβ (THRB) isoforms are expressed in the fetus in a tissue-specific manner by mid-gestation and often at gestational ages earlier than the appearance of thyroid hormones in the fetal circulation (Table 1; Bernal & Pekonen 1984, Nagasawa *et al.* 1997, White *et al.* 2001, Chan *et al.* 2002, 2005). These findings indicate that, for some species, maternal thyroid hormones may contribute to the control of early embryonic growth and development, before the onset of fetal thyroid hormone activity (Obregon *et al.* 2007). In addition, there are developmental changes in TR binding in the fetal brain, lung, skeletal muscle, liver, and heart as term approaches, which are also species specific (Bernal & Pekonen 1984, Perez-Castillo *et al.* 1985, Ferreiro *et al.* 1987, Polk *et al.* 1989, Falcone *et al.* 1994, White *et al.* 2001). In fetal sheep, thyroid hormone binding is present in the liver and brain from 50 days and increases toward term in the liver (Ferreiro *et al.* 1987, Polk *et al.* 1989). Similarly, in fetal pigs, there are decreases in TRα expression in skeletal muscle and increases in TRβ abundance in the heart and skeletal muscle at birth (White *et al.* 2001). In both species, the gestational changes in fetal tissue TR abundance closely parallel plasma cortisol concentrations (Polk *et al.* 1989, White *et al.* 2001); however, the effect of the *prepartum* cortisol surge on the expression of thyroid hormone transporters and receptors *in utero* remains unknown. Furthermore, the developmental expression and potential roles of mitochondrial and plasma membrane receptors that bind thyroid hormones have not been investigated in fetal tissues to date (Chi *et al.* 2013). Tissue bioavailability of the thyroid hormones can, therefore, be varied either systemically by altering hormone secretion by the thyroid glands or at the local level by changes in the tissue transport, metabolism, and receptor milieux of the thyroid hormones.

Placental transfer of maternal thyroid hormones

In all mammalian species, the placenta actively transports iodide from the maternal to fetal circulation to provide iodide for thyroid hormone synthesis (Fig. 1). Gene expression of the sodium–iodide cotransporter is evident from 6 weeks of gestation in the human placenta and also present in the amniotic membrane at term (Li *et al.* 2012, Akturk *et al.* 2013). The transfer of thyroid hormones from the mother to fetus varies between mammalian species and types of placenta and is determined by the placental expression of thyroid hormone transporters, binding proteins, and D3 enzyme activity. The hemochorial placenta in human and rodent species has been shown to be relatively permeable to T_4 and T_3 (Calvo *et al.* 1992, Fisher 1997). A variety of thyroid hormone transporters are expressed in the human placenta and show changes

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DOI: 10.1530/JOE-14-0025

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during normal development and in cases of intrauterine growth restriction (IUGR; Chan *et al.* 2009, Loubiere *et al.* 2010). In isolated microvillous membrane vesicles of human syncytiotrophoblast at term, saturable uptake of T_4 and T_3 across the maternal apical surface occurs by mainly different types of thyroid hormone transporters (Loubiere *et al.* 2012). The thyroid hormone-binding protein, transthyretin (TTR), is expressed by the human placenta from at least 6 weeks of gestation and is upregulated *in vitro* by low oxygen levels (Landers *et al.* 2013). Therefore, placental TTR may facilitate the movement of thyroid hormones from the mother to fetus, especially in the low-oxygen environment of the first trimester.

Before the fetal thyroid gland is functional, the T_4 concentrations measured in the amniotic fluid, and tissues and circulation of the fetus, are derived from the mother by transplacental transfer. Indeed, T_4 has been detected in coelomic fluid from as early as 4 weeks post-conception, which demonstrates that the embryo is exposed to maternal thyroid hormones from early in development (Contempre *et al.* 1993). Once the fetus is able to produce its own thyroid hormones, maternal T_4 makes only a modest contribution to the total concentration in the fetus. In the rat near term, maternally derived T_4 accounts for about 15% of the concentration in the fetal circulation (Morreale de Escobar *et al.* 1990). Therefore, in human and rodent fetuses, maternal thyroid hormones may have an important role in fetal development, especially during the first and second trimesters. Placental transfer of maternal thyroid hormones may become particularly important in conditions of fetal hypothyroidism, when the steep gradient in thyroid hormones from the mother to fetus may aid fetal acquisition of maternal hormones transplacentally. In human fetuses with total thyroid deficiency, cord T_4 concentrations are 20–50% of normal values and decrease rapidly soon after birth (Vulsma *et al.* 1989). By contrast, the epitheliochorial placenta of the sheep appears to be impermeable to maternal thyroid hormones, at least at 0.75 of gestation, and there is negligible materno-fetal transfer, even during fetal hypothyroidism (Hopkins & Thorburn 1972). The effectiveness of the ovine placenta as a thyroid hormone barrier means that the sheep fetus is dependent upon development of its own thyroid hormone axis *in utero*. The thyroidectomized sheep fetus is, therefore, a useful experimental model to examine the effects of thyroid hormones on aspects of fetal growth and maturation, independent of maternal thyroid status.

Thyroid hormones and fetal growth

Thyroid hormone concentrations are low in IUGR and small-for-gestational-age fetuses both in human populations and when fetal growth is restricted in experimental animals by undernutrition and placental insufficiency (Wrutniak & Cabello 1983, Thorpe-Beeston *et al.* 1991*b*, Kilby *et al.* 1998, Rae *et al.* 2002, Pereira & Procianoy 2003). In several of the experimental studies, plasma T_4 concentrations are correlated positively to the body weight of the fetal and/or newborn animals (Wrutniak & Cabello 1983, Fowden & Silver 1995). Similarly, in normal human infants, umbilical T_4 concentrations are positively related to body weight and length at birth (Sack *et al.* 1993, Shields *et al.* 2011). In addition, TR binding in skeletal muscle is lower in newborn runts compared with normal-sized piglets (Dauncey & Geers 1990), and immunostaining for the TR isoforms and thyroid hormone transporter, MCT8, are reduced in the occipital cerebral cortex of IUGR human fetuses (Kilby *et al.* 2000, Chan *et al.* 2014). Collectively, the clinical and experimental findings indicate that bioavailability of thyroid hormones *in utero* regulates fetal growth by acting as a signal of the nutrient and oxygen supply to the fetus (Fowden & Forhead 2009). In addition, when IUGR is progressive or severe, impaired fetal growth *per se* may alter thyroid hormone status by evoking a fetal stress response and secretion of stress hormones such as the glucocorticoids that affect thyroid hormone bioavailability indirectly (Fowden & Forhead 2009).

The growth regulatory effects of the thyroid hormones have been studied more specifically by direct manipulation of thyroid hormone concentrations *in utero* in experimental animals. In species with little, if any, placental transfer of maternal thyroid hormones, such as sheep, goats, horses, and pigs, hypothyroidism induced congenitally or by surgical ablation of the fetal thyroid gland(s) causes growth restriction of the fetus (Table 2; Spencer *et al.* 1989, Piosik *et al.* 1997, Allen *et al.* 1998). These studies show that fetal thyroid hormones are required for both accretion of fetal mass and differentiation of specific cell types, such as the wool or hair follicles, at critical stages of development well before term (Table 2; Hopkins & Thorburn 1972, Hausman 1992). Thus, in sheep, the severity of the developmental abnormalities is related to both the stage of development at the time of thyroidectomy and the duration of thyroid hormone deficiency (Table 2). In animals with greater placental permeability to maternal thyroid hormones, such as rabbits, rodents, and human and non-human primates, the effects of fetal thyroid hormone deficiency

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Table 2 Effects of thyroidectomy *in utero* on the growth and development of the sheep fetus

		Percentage of euthyroid control					
			Length				
Age at surgery	Age at study	Body weight	Crown-rump	Forelimb	Hindlimb	Specific tissue abnormalities	References
73	140	72	–	–	90	Smaller area of type II muscle fibers Decreased force generation in skeletal muscle	Finkelstein *et al.* (1991)
80	135	74	–	–	–	Altered autonomic nervous system function	Walker & Schuijers (1989)
80	145	67	–	–	–	Delayed epiphyseal closure Increased relative brain weight Fewer type II pneumocytes, anemia	Ayromlooi *et al.* (1983)
88	144	67	91	74	76	Delayed bone maturation Reduced relative thymus weight No wool follicle development	Hopkins & Thorburn (1972)
101	135	60	100	100	100	Reduced relative lung weight Reduced protein content in specific tissues Thin skin, abnormal wool development	Erenberg *et al.* (1974)
103	137	72	–	–	–	Increased relative brain weight	Bhakthavathsalan *et al.* (1977)
103	130	91	99	92	86	Altered bone strength and mineral density	Lanham *et al.* (2011)
	144	74	86	82	83	Delayed bone maturation	
105	135	78	89	85	84	Reduced hemoglobin levels	Fowden & Silver (1995)
	139	81	90	88	87	Reduced catecholaminergic response to fasting	Fowden *et al.* (2001*a*)
120	130	100	–	–	–	Reduced relative heart weight Increased relative kidney weight Fewer binucleated cardiomyocytes	Chattergoon *et al.* (2012*a*)
125	132	100	–	–	–	Fewer binucleated cardiomyocytes	Segar *et al.* (2013)
129	145	100	–	–	–	Abnormal neonatal cardiovascular adaptations	Breall *et al.* (1984)

on intrauterine growth are less pronounced (Jost 1979, Fowden & Forhead 2009, Hall *et al.* 2010), which suggests that maternal thyroid hormones compensate, in part, for the fetal deficiency. Human infants with congenital hypothyroidism are often born with a normal bodyweight, although they may have neurological and skeletal abnormalities consistent with the tissue-specific developmental effects of thyroid hormones observed in other animals (Vulsma *et al.* 1989, Patel *et al.* 2011, Shields *et al.* 2011). Certainly, when maternal and fetal hypothyroidism are combined during pregnancy, there are severe consequences for the development of the neuromotor, auditory, cardiovascular, skeletal, and respiratory systems of the human infant (De Zegher *et al.* 1995, Yasuda *et al.* 1999).

In fetal sheep, thyroidectomy reduces bodyweight, individual organ weights, and skeletal growth of the vertebrae and limbs (Table 2). The changes in the body weight and vertebral and limb length of thyroidectomized fetuses can be ameliorated by T_4 replacement (Fowden & Silver 1995, Fowden *et al.* 2001*a*). The protein content of fetal tissues such as the heart, lung, and skeletal muscle is also reduced by fetal thyroidectomy (Erenberg *et al.* 1974). The growth restriction of thyroidectomized fetuses is asymmetrical with greater effects on the weight of soft tissues than on the length of bones, although brain sparing occurs as observed in other types of IUGR (Table 2). The appendicular skeleton is also more adversely affected than the axial skeleton of thyroidectomized fetuses (Table 2). The abnormalities in bone structure and mechanical properties after fetal thyroidectomy are associated with a reduction in the circulating levels of osteocalcin, a marker of osteoblast activity, without any change in the plasma concentrations of total calcium or markers of osteoclast activity (Hopkins & Thorburn 1972, Lanham *et al.* 2011). These findings suggest that hypothyroidism delays bone development by reducing normal bone deposition rather than by changing the rate of bone degradation or

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DOI: 10.1530/JOE-14-0025

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calcium homeostasis *in utero* (Lanham *et al*. 2011). Thyroid hormones, therefore, promote both general body growth and the development of individual tissues of the fetus.

Metabolic effects of the thyroid hormones

Thyroid hormones act on fetal growth via direct and indirect mechanisms. First, thyroid hormones have direct actions on fetal metabolism, particularly on the consumption of oxygen (O_2) and glucose. Infusion of T_3 into fetal sheep for 5 days increases fetal O_2 consumption by 28% in association with increases in fetal cardiac output and umbilical blood flow (Lorijn & Longo 1980, Lorijn *et al*. 1980). Conversely, the weight-specific rates of fetal O_2 consumption and oxidation of glucose carbon are reduced by 20–30% by thyroidectomy of fetal sheep and restored to normal values by T_4 replacement (Fowden & Silver 1995). Availability of T_4 has also been shown to regulate glucose oxidation in adipose tissue of fetal pigs (Hausman *et al*. 1996). In addition, fetal hypothyroidism prevents the normal fall in fetal glucose oxidation observed in response to short-term fasting of pregnant ewes (Fowden *et al*. 2001*a*). The reduced O_2 consumption of thyroidectomized sheep fetuses occurs without any alteration in the weight-specific rate of umbilical blood flow but is accompanied by fetal anemia and a reduction in blood O_2 content (Fowden & Silver 1995). The causes of the changes in fetal O_2 consumption, therefore, appear to differ between hypothyroidism and hyperthyroidism although this may reflect, in part, the duration of exposure to abnormal thyroid hormone concentrations. Overall, circulating T_4 and T_3 concentrations correlate positively with the whole-body rate of O_2 consumption in the fetus (Lorijn & Longo 1980, Lorijn *et al*. 1980, Fowden & Silver 1995). However, there are no changes in O_2 consumption by the liver, kidney, brain, or placenta of thyroidectomized fetuses, which suggests that the primary oxidative action of the thyroid hormones is on fetal fat and skeletal muscle (Bhakthavathsalan *et al*. 1977, Klein *et al*. 1983, Polk *et al*. 1987, Fowden & Silver 1995, Herpin *et al*. 1996). Certainly, in fetal sheep, there is an increase in the proportion of the anaerobic type II muscle fibers in several muscles after fetal thyroidectomy consistent with the more limited oxidative capacity observed in these circumstances (Finkelstein *et al*. 1991, Fowden & Silver 1995).

At the cellular level, thyroid hormones can influence oxidative metabolism either by changing expression and activity of the electrogenic Na^+–K^+ ATPase pump or by acting on the mitochondrial electron transport chain (ETC) and oxidative phosphorylation *per se* (Wrutniak *et al*. 1998, Ramminger *et al*. 2002, Patel *et al*. 2011). *In vitro* studies have shown that T_4 and T_3 increase the amount and activity of Na^+–K^+ ATPase pumps in cultured skeletal myotubes and pulmonary epithelial cells from fetal rats close to term (Brodie & Sampson 1988, Ramminger *et al*. 2002). However, no changes in Na^+–K^+ ATPase pump activity are observed in the liver, kidney, or brain of thyroidectomized fetal sheep during late gestation (Klein *et al*. 1983). Mitochondrial contents of total protein and cytochrome *c* oxidase, a component of the ETC, are reduced by prenatal hypothyroidism in skeletal muscle and liver of fetal and newborn pigs (Herpin *et al*. 1996). Similarly, cerebral cytochrome *c* oxidase is reduced in hypothyroid rat fetuses without a change in mitochondrial DNA content (Vega-Nunez *et al*. 1995). In addition, in fetal sheep, plasma T_3 concentrations are positively related to adipose tissue expression of the mitochondrial uncoupling proteins 1 and 2 (UCP1 and UCP2), which dissipate the mitochondrial proton gradient and reduce the efficiency of ATP production (Mostyn *et al*. 2003, Gnanalingham *et al*. 2005). Taken together, these observations suggest that thyroid hormones affect mitochondrial respiration, biogenesis, and ATP generation in a tissue-specific manner. However, whatever the specific mechanisms involved, hypothyroid fetuses will derive less ATP from oxidative metabolism than euthyroid fetuses and, thus, have less energy available for growth of non-essential tissues. Thyroid hormones, therefore, stimulate fetal growth through oxidative actions on fetal metabolism (Fig. 2).

Thyroid hormones and the insulin-like growth factors

A second, indirect mechanism by which thyroid hormones may influence fetal development is through interactions with other endocrine systems involved in regulating intrauterine growth (Fowden & Forhead 2013). Through changes in tissue or plasma levels and/or receptor abundance, manipulation of thyroid hormone concentrations *in utero* has been shown to affect the fetal bioavailability of several hormones and growth factors including the renin–angiotensin system, catecholamines, leptin, prostaglandins, growth hormone (GH), and the insulin-like growth factors (IGFs; Walker & Schuijers 1989, Richards *et al*. 1993, Forhead *et al*. 1998, 2000*a*,*b*, Fowden *et al*. 2001*a*, Forhead & Fowden 2002, Chen *et al*. 2005, 2007, Liu *et al*. 2005, O'Connor *et al*. 2007, Carey *et al*. 2008). For instance, thyroid hormones are known to be involved in the neonatal epigenetic modifications of the hippocampal glucocorticoid receptors that have long-term

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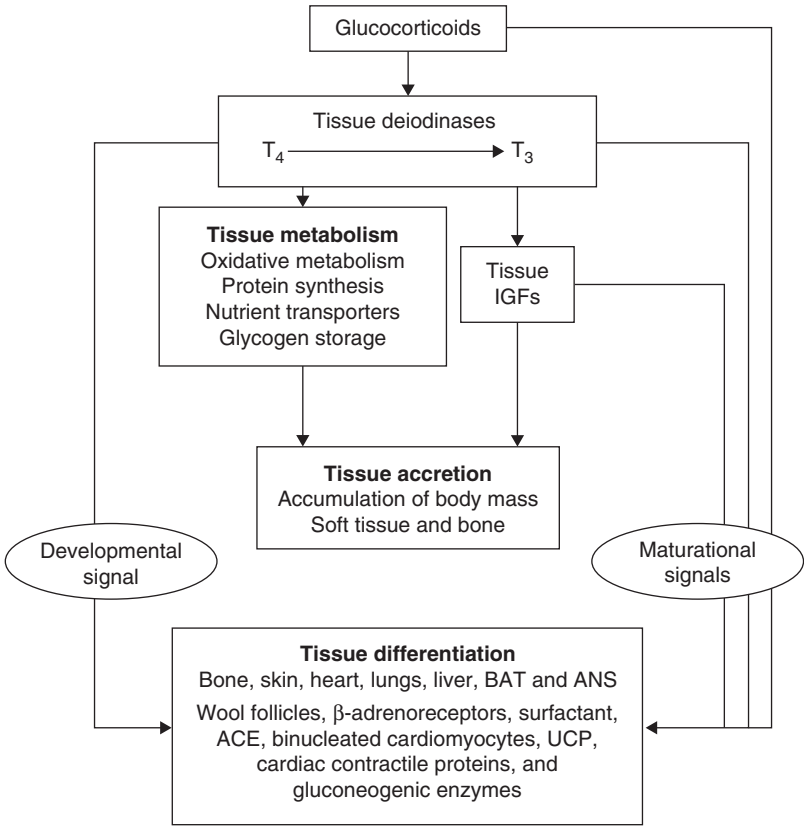

Figure 2

Schematic diagram showing the role of the thyroid hormones in the growth and development of the fetus during the second half of gestation. T_4, thyroxine; T_3, triiodothyronine; BAT, brown adipose tissue; ANS, autonomic nervous system; ACE, angiotensin-converting enzyme; UCP, uncoupling protein.

consequences for the function of the adult hypothalamic–pituitary–adrenal axis (Champagne 2013). In particular, their role in regulating the somatotropic axis and local tissue expression of the IGFs is likely to have important implications for growth and development *in utero*.

The IGFs are expressed widely in fetal tissues and are known to have an important role in fetal and placental growth (Fowden 2003, Forbes & Westwood 2008). Their expression *in utero* also varies with gestational age and nutritional state in a tissue-specific manner (Fowden & Forhead 2009). In fetal sheep and pigs, plasma IGF1 but not IGF2 concentrations are reduced by hypothyroidism and restored to normal values by T_4 treatment (Mesiano *et al.* 1987, Latimer *et al.* 1993). These changes are accompanied by alterations in tissue expression of the *IGF1* but not the *IGF2* gene (Fowden *et al.* 2006). In hypothyroid fetal pigs, the reduction in tissue IGF1 content is widespread whereas, in thyroidectomized fetal sheep, changes in *IGF1* mRNA expression are tissue specific with decreases in skeletal muscle and increases in the liver (Latimer *et al.* 1993, Forhead *et al.* 1998, 2000*a*,*b*, 2002). Manipulation of thyroid hormone levels in fetal sheep also alters plasma GH concentrations and hepatic expression of the GH receptor (GHR; Richards *et al.* 1993, Forhead *et al.* 2000*a*,*b*). Furthermore, prevention of the normal *prepartum* rise in T_3 concentrations by thyroidectomy of fetal sheep modifies the normal ontogenic pattern of expression of the *GHR* and *IGF* genes in both liver and skeletal muscle toward term (Forhead *et al.* 1998, 2000*b*, 2002). Thus, thyroid hormones appear to regulate not only general tissue accretion but also terminal differentiation of fetal tissues in preparation for extrauterine life (Fig. 2).

Thyroid hormones and fetal maturation

Toward term, there are maturational changes in a wide range of fetal tissues in preparation for extrauterine life, which are dependent on the *prepartum* rise in fetal cortisol concentrations (Fowden *et al.* 1998). These changes ensure

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activation of physiological processes essential for survival immediately at birth such as pulmonary gas exchange, adaptations in cardiac function, hepatic glucogenesis, and thermogenesis. The cortisol-induced maturational changes include the ontogenic changes in tissue D3 and D1 deiodinase activities and the concomitant increase in circulating T_3 concentration in the fetus toward term (Forhead *et al*. 2006, Fowden & Forhead 2009). In turn, the *prepartum* increase in T_3 bioavailability in the fetus may mediate, at least in part, the maturational effects of both endogenous cortisol and exogenous synthetic glucocorticoids given as a clinical treatment to improve neonatal viability in threatened pre-term delivery.

The lungs and respiratory function

Ventilation of the lungs and gas exchange in the newborn animal depend on a number of structural and functional changes, including removal of lung liquid and production of surfactant (Olver *et al*. 1981, Wilson *et al*. 2007, Hillman *et al*. 2012). Thyroid hormones have an important role in determining the sensitivity of the fluid absorption system to catecholamines released during birth (Barker *et al*. 1988, 1990, 1991). Toward term, the ability of epinephrine and cAMP to switch lung liquid secretion to absorption increases progressively (Barker *et al*. 1988). This maturational process is impaired in thyroid-deficient sheep fetuses, but can be restored by replacement infusion of T_3 or T_4 (Barker *et al*. 1990). Antenatal T_3 administration can also improve pulmonary function in newborn lambs delivered prematurely (Chan *et al*. 1998). However, both cortisol and T_3 are required for epinephrine-induced lung liquid absorption and act synergistically via mechanisms that depend on protein synthesis (Barker *et al*. 1991, Ramminger *et al*. 2002). These effects are probably mediated by upregulation of the pulmonary β-adrenergic receptors (Das *et al*. 1984, Warburton *et al*. 1988), but as thyroid hormones influence cAMP responsiveness, they may also involve intracellular signaling pathways downstream of the receptors (Barker *et al*. 1988, Wilson *et al*. 2007). Thyroid hormones are known to increase the expression of pulmonary β-adrenergic receptors and apical Na^+ channels in the fetus and can stimulate the expression and activity of the Na^+/K^+ ATPase in the basolateral membrane of the alveolar epithelium (Das *et al*. 1984, Warburton *et al*. 1988, Wilson *et al*. 2007).

Maturation of surfactant synthesis and release by the type II pneumocytes also depends, in part, on the increasing T_3 bioavailability toward term (Mendelson & Boggaram 1991, Hillman *et al*. 2012). Thyroidectomy of fetal sheep reduces the number of type II pneumocytes in the lungs at term as well as the number of surfactant-containing lamellar bodies in these cells (Ayromlooi *et al*. 1983). *In vitro* and *in vivo* studies have shown that thyroid hormones affect synthesis of both the phospholipid and protein components of surfactant in fetal mice, rats, sheep, monkeys, and human infants (Ballard *et al*. 1984, Das *et al*. 1984, Torday & Dow 1984, Warburton *et al*. 1988, Romaguera *et al*. 1993, Gilbert *et al*. 2001, van Tuyl *et al*. 2004). In particular, thyroid hormones promote synthesis of surfactant proteins B and C. They also increase the phospholipid content of lung liquid, although this effect may be mediated via upregulation of pulmonary β-adrenergic receptor expression and, hence, enhanced epinephrine-stimulated surfactant release (Das *et al*. 1984, Warburton *et al*. 1988). Similar to lung liquid resorption, the effects of T_3 and cortisol on surfactant production appear to be synergistic with greater effects on lung stability when the two hormones are given together than when either hormone is given alone (Warburton *et al*. 1988, Mendelson & Boggaram 1991, Hillman *et al*. 2012).

Finally, thyroid hormones can affect lung maturation via actions on the expression of angiotensin-converting enzyme (ACE) in the pulmonary vascular endothelium. In postnatal lungs, angiotensin I is activated to angiotensin II by ACE as the cardiac output circulates through the pulmonary vasculature. However, before birth, the fetal lungs are poorly perfused and pulmonary ACE levels are relatively low. In fetal sheep toward term, there is a rise in pulmonary ACE concentration, in association with the *prepartum* changes in plasma cortisol and T_3, which is abolished by thyroidectomy and can be stimulated prematurely by T_3 infusion (Forhead *et al*. 2000*a*, Forhead & Fowden 2002). Upregulation of pulmonary ACE by T_3 may activate the fetal renin–angiotensin system near term and may have implications for the maturation of cardiovascular and renal function as well as for local pulmonary development.

The heart and cardiovascular function

Thyroid hormones are also essential for the normal maturation of cardiomyocytes and the cardiovascular system (Thornburg *et al*. 2011). They promote a switch from proliferation to hypertrophy and differentiation of the cardiomyocytes both at term and earlier in gestation (Chattergoon *et al*. 2012*a*,*b*). In a series of *in vivo* and *in vitro* studies in fetal sheep, T_3 has been shown to increase the cardiomyocyte size and the population of terminally differentiated binucleated cells in association

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with downregulation of cell cycle promoters by 50% or more and upregulation of cell cycle suppressors and various molecular mechanisms of cell growth by up to 500% (Chattergoon *et al.* 2007, 2012*a*,*b*). Conversely, thyroidectomy of the sheep fetus reduces the number of binucleate cardiomyocytes by 27% and the relative weight of the heart by 10–15% near term (Chattergoon *et al.* 2012*a*, Segar *et al.* 2013). In rodents, T_3 has been shown to have anabolic effects on the fetal heart with increases in cardiac protein synthesis and expression of the insulin-sensitive glucose transporter, GLUT4 (Crie *et al.* 1983, Castello *et al.* 1994). These thyroid hormone-dependent changes in cardiomyocyte growth and differentiation are accompanied by alterations in expression of contractile proteins, mechano-signaling proteins, and various genes coding for cardiac pacemaker, potassium channels, and sarcoplasmic reticulum calcium pump proteins (Edwards *et al.* 1994, Mai *et al.* 2004, van Tuyl *et al.* 2004, Kruger *et al.* 2008, Chattergoon *et al.* 2012*a*, Segar *et al.* 2013). In particular, the thyroid hormones have an important role in the perinatal switch from β- to α-myosin heavy chains in the sacromeres (Edwards *et al.* 1994, van Tuyl *et al.* 2004). Many of these maturational effects of T_3 on cardiac contractility appear to be mediated via the phosphatidyl-inositol-3-kinase/AKT and mTOR pathways (Kruger *et al.* 2008, Chattergoon *et al.* 2012*a*). Thyroid hormones also affect the atrial natriuretic peptide content of the fetal heart and have an important role in coordinating maturation of the absolute and relative abundance of the multiple adrenergic receptor subtypes in the fetal heart (Birk *et al.* 1992, Metz *et al.* 1996, Mai *et al.* 2004, Chattergoon *et al.* 2012*a*). In particular, they are essential for *prepartum* upregulation of the β-adrenergic receptors and, thus, cardiac responsiveness to β-agonists (Birk *et al.* 1992, Chen *et al.* 2005).

The cellular changes induced in the fetal heart by thyroid hormones have major implications for cardiac function both *in utero* and during the transition to extrauterine life. At birth, the two sides of the heart have to switch from pumping in parallel to pumping in series and, on the left side, this has to occur against a greater pressure caused by the loss of the low resistance placental pathway. Indeed, recent studies have shown that thyroid hormones are essential for the adaptation and growth of the fetal ovine heart in response to a pressure overload during late gestation (Segar *et al.* 2013). Fetal blood pressure and heart rate are reduced by about 10–25% by thyroidectomy of fetal sheep depending on the gestational age at surgery and the duration of hypothyroidism (Breall *et al.* 1984, Walker & Schuijers 1989, Chen *et al.* 2005, 2007, Segar *et al.* 2013). Conversely, T_3 infusion into euthyroid fetal sheep near term causes tachycardia accompanied by increases in fetal cardiac output and pulmonary blood flow (Lorijn & Longo 1980). Fetal thyroidectomy abolishes the inotropic effect of the β-adrenergic agonist, isoprenaline, and prevents the fetal bradycardia and hypertension normally observed in response to hypoxemia, despite elevated basal circulating concentrations of norepinephrine in the fetus (Walker & Schuijers 1989, Birk *et al.* 1992, Chen *et al.* 2005). Fetal hypothyroidism also prevents the increases in heart rate, cardiac output, blood pressure, and systemic blood flow normally observed in newborn lambs in the hours after delivery (Breall *et al.* 1984). In part, the lack of an appropriate cardiovascular response to fetal hypoxemia and delivery *per se* is due to the paucity of cardiac β-adrenergic receptors and may also reflect abnormalities in functioning of the baroreflex and autonomic nervous system more generally (Walker & Schuijers 1989, Chen *et al.* 2005). Changes in perinatal cardiovascular function in response to manipulation of thyroid hormone levels may, therefore, involve more than cardiac adaptations alone. Certainly, there are changes in catecholamine content and abundance of receptors for vasoactive agents such as the angiotensin II and the catecholamines in several fetal tissues after fetal thyroidectomy (Walker & Schuijers 1989, Forhead & Fowden 2002, Chen *et al.* 2005, 2007, Liu *et al.* 2005). Indeed, a poor catecholaminergic response to hypoglycemia appears to be a contributory factor to the metabolic abnormalities observed in thyroidectomized fetuses of fasted ewes (Fowden *et al.* 2001*a*).

The liver and glucogenesis

At birth, there is activation of hepatic glucogenesis to maintain a glucose supply to neonatal tissues during the period between placental separation and the onset of nutritive suckling (Fowden *et al.* 2001*b*, Hillman *et al.* 2012). This depends on adequate glycogen stores and gluconeogenic enzyme activities in the liver (Fowden *et al.* 1998, 2001*b*). The normal developmental increments in hepatic glycogen, and hepatic and renal gluconeogenic enzymes, are abolished in hypothyroid sheep fetuses (Forhead *et al.* 2003, 2009). Fetal thyroidectomy also prevents activation of fetal glucogenesis in response to maternal fasting during late gestation, which is accompanied by low hepatic glycogen levels and a failure to increase key gluconeogenic enzyme activities (Fowden *et al.* 2001*a*). Both fasting-induced fetal glucogenesis and the normal *prepartum* increases in hepatic glycogen

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and gluconeogenic enzyme activities are dependent on the increase in cortisol secretion by the fetal adrenal glands (Fowden *et al*. 1998). As cortisol but not T_3 levels rise normally in thyroidectomized fetuses (Forhead *et al*. 2002, 2003), the reduced glucogenic capacity of these fetuses suggests that the effects of *prepartum* cortisol surge are mediated by the concomitant increase in T_3 production. Certainly, the normal positive correlations observed between fetal cortisol concentrations and the hepatic activities of the rate-limiting gluconeogenic enzymes, glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), are absent in thyroidectomized fetuses in late gestation (Fowden *et al*. 2001*a*). Furthermore, T_3 treatment of immature euthyroid sheep fetuses causes an increase in hepatic G6Pase and PEPCK activities in the presence of low cortisol concentrations (Forhead *et al*. 2003). Thyroid hormones, therefore, have an important role in ensuring that hepatic gluconeogenesis can be activated at birth.

Adipose tissue and thermogenesis

At birth, the mammalian neonate must maintain its body temperature for the first time. This requires more heat production than *in utero*, so, depending on the species, shivering and/or non-shivering thermogenesis are initiated at birth (Silva 2011). Activation of non-shivering thermogenesis, in particular, requires thyroid hormones. In sheep, thyroidectomy *in utero* reduces body temperature after birth and prevents the neonatal increase in O_2 consumption by the lamb as a whole and by certain of its tissues such as the liver, brain, and brown adipose tissue (Klein *et al*. 1983, Breall *et al*. 1984, Polk *et al*. 1987, Schermer *et al*. 1996). It also reduces thermogenic activity of the perirenal brown adipose tissue used for non-shivering thermogenesis, coincident with an increase in the incidence of shivering to help maintain core temperature (Schermer *et al*. 1996). In addition, norepinephrine is less effective at stimulating O_2 consumption by brown adipose tissue from newborn lambs thyroidectomized *in utero* 2 weeks before delivery (Polk *et al*. 1987). Similarly, inactivating the D2 deiodinase that produces T_3 in brown adipose tissue impairs the oxidative capacity and heat production of newborn mice (Hall *et al*. 2010).

The thermogenic actions of the thyroid hormones are due, in part, to upregulation of UCP abundance and other mitochondrial proteins in brown adipose tissue and the uncoupling of the mitochondrial proton-motive force from ADP phosphorylation to release the energy as heat (Guerra *et al*. 1994, Schermer *et al*. 1996, Gnanalingham *et al*. 2005). However, direct administration of T_3 to fetal sheep before birth does not activate thermogenesis by brown adipose tissue, even when the fetus is cooled (Schroder *et al*. 1987, Power *et al*. 1989), although it does augment thermogenesis and O_2 consumption in response to catecholamines and cAMP by fetal brown adipose tissue *in vitro* after T_3 infusion *in vivo* (Klein *et al*. 1984). This has lead to the suggestion that placental factors inhibit activation of thermogenesis by brown adipose tissue until after delivery (Power *et al*. 1989, Symonds *et al*. 2003). However, by upregulation of β-adrenergic receptor abundance and/or downstream components of the signaling pathway in brown adipose tissue as occurs in fetal lung and other tissues, thyroid hormones may increase the effectiveness with which the sympathetic nervous system can stimulate thermogenesis in the neonate (Symonds *et al*. 2003, Hillman *et al*. 2012). Thus, thyroid hormones appear to have a maturational role in enhancing the thermogenic capacity of brown adipose tissue toward term but may not be the direct stimulus for initiating non-shivering thermogenesis immediately after birth.

Conclusions

Thyroid hormones have an essential role in fetal development. They stimulate intrauterine growth during the second half of gestation through anabolic actions on fetal metabolism and effects on growth regulatory factors and endocrine systems (Fig. 2). They also have discrete actions in triggering specific developmental events such as differentiation of the wool follicles and binucleated cardiomyocytes (Fig. 2). In addition, the *prepartum* rise in T_3 bioavailability has an important role in mediating several of the maturational effects of the glucocorticoids in late gestation. Often, T_3 and cortisol act synergistically to switch the cell cycle from accretion to differentiation in a range of fetal tissues essential for neonatal survival (Fig. 2). Several of the *prepartum* maturational changes induced by the thyroid hormones increase the functionality of the sympathetic nervous system. In turn, this improves the response of the neonate to the stress of delivery and aids its adaptation to the new extrauterine environment. Indeed, the effects of an altered thyroid hormone status during intrauterine development may have lifelong consequences through permanent changes in the structure and function of tissues and organ systems. However, the extent to which thyroid hormones alter development of the tissues, such as the autonomic nervous system, either prenatally or in the long term

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and the mechanisms by which these hormones act at the cellular and molecular levels *in utero* still remain largely unknown.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding
This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements
The authors would like to thank all members of the staff of the Department of Physiology, Development and Neuroscience who have helped with our studies over the years. Some of the research by the authors described here was funded by the BBSRC.

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Received in final form 26 February 2014
Accepted 18 March 2014
Accepted Preprint published online 19 March 2014

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-14-0025

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