Endocrinology of the mammalian fetal testis

Peter J O’Shaughnessy and Paul A Fowler

College of Medical, Veterinary and Life Sciences, University of Glasgow, Veterinary Research Facility, Bearsden Road, Glasgow G61 1QH, UK and Division of Applied Medicine, Institute of Medical Sciences, Centre for Reproductive Endocrinology and Medicine, University of Aberdeen, Aberdeen AB25 2ZD, UK

Correspondence should be addressed to P J O’Shaughnessy; Email: peter.o’shaughnessy@glasgow.ac.uk

Abstract

The testes are essential endocrine regulators of fetal masculinization and male development and are, themselves, subject to hormonal regulation during gestation. This review focuses, primarily, on this latter control of testicular function. Data available suggest that, in most mammalian species, the testis goes through a period of independent function before the fetal hypothalamic–pituitary–gonadal axis develops at around 50% of gestation. This pituitary-independent phase coincides with the most critical period of fetal masculinization. Thereafter, the fetal testes appear to become pituitary hormone-dependent, concurrent with declining Leydig cell function, but increasing Sertoli cell numbers. The two orders of mammals most commonly used for these types of studies (rodents and primates) appear to represent special cases within this general hypothesis. In terms of testicular function, rodents are born ‘early’ before the pituitary-dependent phase of fetal development, while the primate testis is dependent upon placental gonadotropin released during the pituitary-independent phase of development.

Introduction

The fetal testis is both an endocrine organ and a target for endocrine regulation. Hormones secreted by the testes are critical for masculinization of both the external and internal phenotype, while the fetal testis itself is under regulation by the fetal pituitary in at least some, and probably most, mammalian species. Interestingly, the early critical period of testicular endocrine function does not overlap significantly with the later onset of pituitary regulation of the testis, and in most species, early testis function appears to be autonomous. The endocrine role of the testis during fetal masculinization has been the subject of considerable study, and the mechanisms involved appear to be generally conserved, with some exceptions (Glickman et al. 2005). In contrast, detailed studies of hormonal control of the fetal testis are limited largely to the human and to rodent models, although these two groups are probably not typical of most mammalian species. In this review, we have concentrated largely on control of the fetal testis and propose a general model, which fits, allowing for exceptions, with the limited data available from a number of species.

Fetal testis development

The testes differentiate from the genital ridge at about 12 days post coitum (12 dpc) in the mouse, 30–32 dpc in the sheep, and around 6 weeks of gestation (6 GW) in the human. This process is controlled by the presence of the Y chromosome in the male and, more specifically, the sex-determining region Y (SRY) gene. The presence of SRY initiates the expression of SRY-box containing gene 9 (SOX9), which then stimulates other factors such as fibroblast growth factor 9 and prostaglandin D2. Together, these factors undergo feed-forward loops leading to differentiation of the Sertoli cells (Piprek 2010). The Sertoli cells arise from precursors in the coelomic epithelium and migrate into the developing gonad where they aggregate with the primordial germ cells, which arrived earlier from the yolk sac. Mesonephric endothelial cells also migrate into the developing gonad at this time and enclose the Sertoli cell/germ cell aggregates to form the sex cords (Cool et al. 2008). At 12.5 dpc in the mouse (7–8 GW in the human), as the cords are forming, the fetal Leydig cells start to differentiate from mesenchymal-like stem cells within the interstitial spaces between the cords (Byskov 1986, Huhtaniemi & Pelliniemi 1992, O’Shaughnessy et al. 2006, Ostrer et al. 2007). Differentiation of the fetal Leydig cells is regulated by desert hedgehog (DHH), secreted by the Sertoli cells (Pierucci-Alves et al. 2001), while platelet-derived growth factor α (PDGFA) and the Arx homeobox gene are also involved (Grissold & Behringer 2009). Around 13.0 dpc, the peritubular myoid cells (PMC or PTM) start to develop (Pierucci-Alves et al. 2001), although their origin remains uncertain.
Fetal testicular hormone production

The fetal testis secretes three hormones essential for normal masculinization; anti-Mullerian hormone (AMH), which causes degeneration of the Mullerian (paramesonephric) ducts, androgens, which act to stabilize the Wolffian (mesonephric) ducts and to masculinize the external genitalia, and insulin-like 3 (INSL3), which acts with testosterone to induce masculinization; anti-Mullerian hormone (AMH), which causes degeneration of the Mullerian ducts, androgens, which act to masculinize the external genitalia, and insulin-like 3 (INSL3), which acts with testosterone to induce testicular descent (Hutson 1985, Nef & Parada 1999, Zimmermann et al 2008). Shortly after 13.0 dpc in the mouse (35 dpc in the sheep and 8 GW in the human), therefore, the essential structure of the testis is in place (Fig. 1), and it very rapidly starts to secrete the hormones required to masculinize the fetus.

Endocrine regulation of the fetal and neonatal testis

In the post-pubertal male, testicular function is critically dependent on pituitary gonadotropins. LH stimulates testosterone production by the Leydig cells, and FSH, along with testosterone, regulates Sertoli cell function, inhibin secretion, and, indirectly, spermatogenesis (Zhang et al 2001, Abel et al 2008, Verhoeven et al 2010). In the fetus, however, the role of pituitary-derived hormones is much less clear and appears to be limited to the latter part of gestation. There are also significant species differences in control of the fetal gonad. In particular, the rodent testis is apparently independent of pituitary hormones throughout gestation, while placental gonadotropin is critical for normal fetal testicular development in primates and possibly the horse (Knospe 1998, Gromoll et al 2000, O’Shaughnessy et al 2006, Scott et al 2009). For the remainder of this review, we report what is known about regulation of the major cell types of the mammalian testis through fetal development.

**Figure 1** Fetal testis histology. (A) Fetal mouse: low magnification of a semi-thin section showing seminiferous tubules (ST), which have developed from the sex cords and interstitial tissue (I). (B) Fetal mouse: higher magnification of (A) showing gonocytes (G) in the central part of the sex cord with the Sertoli cells (S) around the periphery. The peritubular myoid cells (PMC) form a concentric layer around the cord, and Leydig cells (L) are present within the interstitium. (C) Fetal human: immunohistochemically labeled for the androgen receptor (AR) which is clearly expressed in PMC and in some interstitial cells. (D) Fetal sheep: immunohistochemically labeled for anti-Mullerian hormone (AMH) which is strongly expressed in fetal Sertoli cells. (E) Fetal human: immunohistochemically labeled for 3β-hydroxysteroid dehydrogenase (HSD3B) which is localized exclusively in the Leydig cells. In all photomicrographs, the bar represents 50 μm.
**Leydig cells**

In all eutherian mammals so far studied, two or three populations of Leydig cells arise during development. The fetal Leydig cell population is the predominant source of circulating androgen in the fetus and is replaced after birth by the ‘adult’ population of cells which gives rise to the pubertal surge in testosterone (O’Shaughnessy et al. 2006). These two Leydig cell populations appear to be distinct both functionally and morphologically, and while they arise separately, a connection between the precursor stem cells is possible but unknown (O’Shaughnessy et al. 2006, Griswold & Behringer 2009). It has also been suggested, on the basis of a post-natal rise in androgens, that there is a third ‘neonatal’ population of Leydig cells in a number of species, including humans (Prince 2001). It remains to be determined, however, whether this represents a distinct population or reactivation of the fetal population.

Leydig cell-derived androgens are essential for masculinization of the fetus (Geissler et al. 1994, Kremer et al. 1995, Caron et al. 1997) during a critical ‘masculinization programming window’, which extends from 15.5 to 17.5 dpc in the rat and from about 8 to 12 GW in the human (Welsh et al. 2008, Scott et al. 2009). This means that both circulating androgen and masculinization can be used to assess Leydig cell function in the early phases of testicular development (Scott et al. 2009), although only fetal androgen levels are a reliable indicator of Leydig cell function in later gestation. On this basis, it is clear that, in those mammals for which data are available (human, pig, cattle, sheep, dog, rat and mouse), both fetal masculinization and increasing plasma androgens occur before the hypothalamic–pituitary–gonadal (HPG) axis is likely to be functional (Fig. 2). This would suggest that pituitary-derived gonadotropins are not required for initial fetal Leydig cell activity, although the cells are responsive to LH from an early stage (Pointis & Mahoudeau 1977). The data are, perhaps, clearest for rodents in which circulating or testicular androgens are present and increasing before LH is detectable (Habert & Picon 1982, El Gehani et al. 1998b, O’Shaughnessy et al. 1998). Additionally, in the hypogonadal (hpgr) mouse, which lacks GNRH because of a gene mutation, circulating androgen levels in the fetus are normal at the end of gestation, although only 10% of normal pituitary LH is present (O’Shaughnessy et al. 1998). Confirmation that the fetal Leydig cells in the mouse are independent of pituitary LH has since come from animals engineered to lack the LH receptor (LHR; LuRKO mice) or the LHβ subunit (LHβ-null; Lei et al. 2001, Zhang et al. 2001, Ma et al. 2004). These mice have normal androgen levels and a normal testicular phenotype at birth, although, predictably, there is failure of post-natal Leydig cell development (Zhang et al. 2001, 2004). Apart from the human, this level of detailed study is missing from other species. Nevertheless, older evidence, from fetal hypophysectomy or fetal decapitation in rabbits, sheep, and pigs, suggests that the Leydig cells become LH-dependent in the second half of gestation in these species (Jost 1951, Liggins & Kennedy 1968, van Vorstenbosch et al. 1982, 1984a). This is not necessarily at variance with the more detailed rodent data, however, since gestation is short in rats and mice and the HPG axis does not develop until close to parturition. In contrast, in other species with a longer gestation, the HPG axis generally becomes active early in the second half of pregnancy (Fig. 2). Thus, as a general rule across species, the fetal Leydig cells appear to become LH-dependent at the same time or shortly after the development of the HPG axis. The mechanism involved in this change in sensitivity has not been studied, but it appears unlikely that it is caused simply by induced dependence on LH following exposure to the hormone. The best evidence for this being the marked post-natal drop in testosterone levels in the hpgr mouse (caused by lack of neonatal LH) despite, presumably, little or no fetal exposure to LH (O’Shaughnessy et al. 1998). Similarly, developmental acquisition of LHRs appears unlikely to be responsible as fetal Leydig cells express LHR transcripts and are responsive to LH soon after differentiation (Pointis & Mahoudeau 1977, Zhang et al. 1994, Derecka et al. 1999).

**Figure 2** Schematic representation summarizing species differences and similarities in timing of critical events in testis development during gestation. The diagram focuses on elements of endocrine production and action in the testis. Figure adapted from Klonisch et al. (2004), with modification and updates based on new findings since 2004 or additional publications located in the literature (Attal 1969, O’Shaughnessy et al. 2007, Fowler et al. 2008, 2009). Note that in most species, the HPG axis becomes functional at about 50–70% of gestation, after the period of critical masculinization.
While study of the hpg and LuRKO mice shows that LH is not required for fetal Leydig cell function during gestation, even after development of the HPG axis, this does not rule out the possibility that the cells may be responsive to stimulation by other hormones at this time. This concept was given support by data from NKX2-1-null mice, which suggested that pituitary hormones are essential for fetal Leydig cell activity in late gestation. These mice lack a pituitary gland, a thyroid gland, and essential lung parenchyma in addition to suffering other defects in the forebrain (Pakarinen et al. 2002). At the end of gestation in these animals, there is a significant decrease in testicular testosterone levels. Since LH is not required for fetal Leydig cell function, results from the NKX2-1-null mouse suggest that another pituitary hormone is critical for maintaining Leydig cell activity at this time. Shortly after the testicular phenotype of the NKX2-1 null mice was described, we reported that fetal mouse Leydig cells express the melanocortin type 2 receptor, the receptor for ACTH. Furthermore, we showed that ACTH would stimulate androgen production in fetal and neonatal testes but not in adult testes in these mice (O’Shaughnessy et al. 2003, Johnston et al. 2007). Study of proopiomelanocortin (POMC)-null mice (which lack ACTH) and compound POMC-null/LuRKO mice showed, however, that neither ACTH nor LH is essential for Leydig cell function during fetal development in the mouse (O’Shaughnessy et al. 2009). Evidence for a role of other pituitary hormones in fetal Leydig cell function is scant. Pituitary hormones, other than the gonadotropins, can affect post-natal Leydig cell function (Amir et al. 1978, Weiss-Messer et al. 1996, Colon et al. 2005), but there is little evidence of effects on the fetal Leydig cells. In the human fetus, the second trimester pituitary secretes prolactin (PRL), and the PRL receptor is expressed in the testis, but there is no correlation between PRL and testosterone (Fowler et al. 2008, 2009). There are also no reported abnormalities of masculinization in PRL receptor-null mice or, indeed, in GH receptor-null mice or TSH receptor (TSHR)-null mice, while adult males are partially or wholly fertile in all three cases (Ormandy et al. 1997, Zhou et al. 1997, Marians et al. 2002). In conclusion, therefore, it appears that fetal Leydig cells in the mouse are responsive to LH and ACTH but are not critically dependent on them, or any other pituitary hormone, at any time during gestation – unless there is extensive redundancy in the effects of different pituitary hormones. Reduced Leydig cell function in NKX2-1-null mice remains unexplained, currently, but may be related to other effects of NKX2-1 depletion, such as defects in brain development. Failure of thyroid development may affect Sertoli cell development, but we have no evidence that it would alter fetal Leydig cell function in the fetus (cf. TSHR-null above).

The evidence is, therefore, strong that Leydig cell function during gestation is not dependent on pituitary hormone control in the mouse. In other non-primate species, evidence from both the timing of HPG axis development (Fig. 2) and early fetal decapitation (van Vorstenbosch et al. 1982) suggests that in many, if not all, species, there is an early period (late first to second third of pregnancy) of Leydig cell function which is independent of LH action and which coincides with a critical period of androgen-dependent fetal masculinization (Welsh et al. 2008). It is likely that Leydig cell activity is regulated during this period by local growth factors secreted within the testis or that constitutive activity within the Leydig cells is sufficient to ensure adequate androgen production. Local factors that may be involved include DHH, PDGFA, insulin-like growth factor 1, vasoactive intestinal polypeptide, pituitary adenylate cyclase-activating polypeptide, natriuretic peptides, and the transforming growth factor-β superfamily (El Gehani et al. 1998a, 2000, 2001, Griswold & Behringer 2009, Scott et al. 2009, Sarraj et al. 2010). Realistically, the role that each of these factors plays in fetal Leydig cell activity is only likely to be determined once a fetal Leydig cell-specific Cre mouse model is developed.

In primates, including the human, the fetal Leydig cells also go through an early phase of independence from hormonal stimulation, but, unlike other species, this is relatively short. After this period, the cells rapidly become dependent upon the activity of choriionic gonadotropin (CG), which acts through the LHR (termed LHCGR in primates). The clearest evidence for both the hormone-independent and CG-dependent phases comes from humans with inactivating mutations in genes encoding the LHCGR or LHß subunit (Weiss et al. 1992, Kremer et al. 1995). In the absence of LHCGR activity, XY individuals have an external female phenotype, indicating loss of testicular androgen production during the critical period of sexual differentiation (Welsh et al. 2008). However, some androgen-dependent Wolffian duct derivatives are present (epididymis and ductus deferens) demonstrating an early period of fetal Leydig cell activity in these individuals (Kremer et al. 1995). In contrast, in the absence of active pituitary-derived LH, fetal masculinization appears normal (presumably maintained by human CG (hCG)) and it is post-natal masculine development that fails (Weiss et al. 1992). Fetal Leydig cells from those species so far studied are sensitive to LH soon after differentiation but are not normally exposed to stimulation through the LHR. Given the massive stimulation by CG early in fetal primate Leydig cell development, it is perhaps not surprising that the cells have evolved to become dependent upon it. In humans, hCG levels peak at around week 10 (Fowler et al. 1998) and fetal androgen levels mirror those of hCG, consistent with a primary Leydig cell dependence on hCG (Fowler et al. 2009). As hCG levels decline, however, towards the end of the second trimester, fetal LH may become more important in maintaining Leydig cell function (Fowler et al. 2007, 2009). Interestingly, in anencephalic human fetuses, studied in the late second...
and third trimesters, there is an apparent loss of fetal Leydig cells (Baker & Scrimgeour 1980), and the external genitalia are often small in newborns (Scott et al. 2009). Similarly, hypophysectomy in the last third of gestation reduces the overall percentage of Leydig cells at term in the rhesus monkey (Gulyas et al. 1977). In the human, in the third trimester, Leydig cells are no longer proliferating (O’Shaughnessy et al. 2007), and cell numbers are declining (Waters & Trainer 1996). These data from human and monkey imply, therefore, that Leydig cell survival in the late gestation primate is dependent upon pituitary LH, in common with other species, though confirmation of these early studies using modern stereological techniques is required.

**Sertoli cells**

The fetal Sertoli cells play an essential role in the initial differentiation and development of the testis (Palmer & Burgoyne 1991). Crucially, Sertoli cells also secrete AMH, which acts to prevent Müllerian duct development in the developing male. In the testis, the Sertoli cells induce differentiation of the fetal Leydig cell population (Griswold & Behringer 2009) and act to maintain the gonocytes and, depending on species, the early spermatogonia. This is initially through expression of CYP26B1, which acts to metabolize retinoic acid and, thereby, prevents the entry of cells into meiosis (Li et al. 2009). Later, the Sertoli cells act to ensure survival of the germ cells through expression of factors such as Kit ligand and generation of the germ cell stem cell niche (Payne et al. 2010). Lastly, germ cell number and fertility in the adult animal are dependent upon the final numbers of adult Sertoli cells. Sertoli cell proliferation occurs throughout fetal and prepubertal development, and changes in proliferation in the fetus could have significant consequences for the adult animal. Post-natal compensation for a decline in fetal Sertoli cell proliferation has been reported in the rat (Auharek et al. 2010), but this may not be relevant to the later fetal period in other species if, as we suggest here, the rodent is an example of ‘early’ parturition (Fig. 3).

In the adult, the primary hormones regulating Sertoli cell activity are FSH and androgen. In the rat, full-length FSH receptors (FSHRs) are first detected in the testis at 16.5 dpc (Rannikki et al. 1995), just before development of the HPG axis. Sertoli cell function must, therefore, be FSH-independent during the first few days after differentiation, and there is little evidence to suggest that FSH becomes of importance in later fetal life, at least in rodents. A number of years ago, studies suggested that antiserum to FSH could reduce the number of Sertoli cells proliferating at the end of gestation in the rat (Orth 1984). More recent studies have shown, however, that FSHR knockout (FSHRKO) mice have normal numbers of Sertoli cells at birth, with most markers of Sertoli cell activity (e.g. Dhh, Pdgfa and Amh) similar to those in the wild-type up to 5 days post-natally (Johnston et al. 2004). In contrast to FSH, androgens appear to play a significant role in the establishment of Sertoli cell number during fetal development. In androgen-insensitive testicular feminized (Tfm) mice (Johnston et al. 2004) and in androgen receptor-knockout (ARKO) mice (Tan et al. 2005), there is a reduction in Sertoli cell number at birth and this has been further confirmed by the effects of treatments designed to reduce fetal androgen levels in vivo (Scott et al. 2007). In contrast to the effect of ubiquitous ARKO, Sertoli cell numbers are normal at birth in mice lacking ARs only in the Sertoli cells (SCARKO mouse; De Gendt et al. 2004). Combined with the observations that Sertoli cells do not express ARs during fetal development in the rodent or human (Shapiro et al. 2005, Chemes et al. 2008, Willems et al. 2010), these data indicate that the effects of androgens must be mediated through another testicular cell type in the fetus. Immunohistochemical data suggest that it is mostly PMC (and some interstitial cells) that express the AR in the testis during fetal development (Majdic et al. 1995, Shapiro et al. 2005, Chemes et al. 2008; Fig. 1), and it appears likely that androgen action on the Sertoli cells is mediated through the PMC. Recent evidence that androgen action through the PMC is required for normal Sertoli cell function in the adult animal would support this hypothesis (Welsh et al. 2009).
The role of FSH in regulating Sertoli cell function or proliferation in non-rodent species is uncertain, partly because it is difficult to dissociate the effects of FSH from those of androgen. Fetal hypophysectomy, for example, will reduce testis size and tubule diameter in the newborn sheep, while testis size is reduced in the hypophysectomized rhesus monkey fetus and anencephalic human (Liggins & Kennedy 1968, Gulyas et al. 1977, Baker & Scrimgeour 1980). A reduced testis size in these species is consistent with reduced Sertoli cell number, but, in each case, the procedure used, or condition studied, will inevitably remove both FSH and LH and, thus, probably reduce testicular androgen levels. Treatment of fetal lambs with octylphenol, a putative endocrine disrupting chemical, will reduce FSH and Sertoli cell number without significantly affecting LH levels (Sweeney et al. 2000), consistent with a requirement for FSH in the fetal testis. Unfortunately, testicular androgen levels were not measured in this study, and a direct effect of octylphenol on the Sertoli cell cannot be ruled out. Interestingly, it has been reported that, in the pig, fetal decapitation does not appear to affect Sertoli cell number (reported as Sertoli cells per cross-sectioned tubule) at birth (van Vorstenbosch et al. 1984b), despite a probable reduction in Leydig cell function. This would suggest that fetal Sertoli cell development in this species is independent of both FSH and androgen. However, the effects of decapitation on overall testis size are not reported, and the study needs to be confirmed with direct measurements of fetal testicular androgen levels and Sertoli cell numbers.

Thyroid hormone has been shown to be an important regulator of Sertoli cell differentiation and proliferation in the neonatal/prepubertal rodent (Wagner et al. 2008). Nevertheless, fetal hypothyroidism does not appear to affect Sertoli cell development (Francavilla et al. 1991, Hamouli-Said et al. 2007), despite the presence of thyroid hormone receptors on the fetal Sertoli cells (Jannini et al. 1994). Since rodents are born ‘early’, relative to development of the HPG axis, however, this may not mean that fetal thyroid hormone activity is unimportant in other species. Unfortunately, direct studies of fetal hypothyroidism in other mammalian species are currently lacking, although there is a correlation between fetal thyroid hormone levels and Sertoli cell numbers in two different breeds of boar (McCoard et al. 2003). In the human, hypothyroidism in boys leads to testicular enlargement, which is consistent with the effects on Sertoli cell number seen in rodents (Jannini et al. 1995). The thyroid hormone receptor α1 has been reported to be expressed in Sertoli cells at week 17 (Jannini et al. 2000), and our preliminary data indicate expression of both protein and transcript as early as week 12 (S Flannigan 2010, unpublished observations) when Sertoli cells are proliferating exponentially (O’Shaughnessy et al. 2007). This raises the possibility of early thyroid hormone effects on subsequent Sertoli cell numbers in the human, although there is, as yet, no direct evidence for this.

**Germ cells**

In rodents, pituitary factors do not appear to be important for gonocyte survival or development, and numbers are normal at birth in both hpg (Baker & O’Shaughnessy 2001) and FSHRKO mice (P J O’Shaughnessy 2009, unpublished observations). Gonocyte numbers are, however, reported to be increased in the Tim mouse towards the end of gestation suggesting an inhibitory role for androgen (Merlet et al. 2007). In other species, there are few direct studies of gonocyte numbers, although following hypophysectomy in the fetal rhesus monkey, there is a significant reduction in germ cell number (Gulyas et al. 1977). In hypophysectomized fetal sheep, the resulting reduction in testis size and tubule diameter (Liggins & Kennedy 1968) would also be consistent with reduced gonocyte numbers. Similarly, in anencephalic humans, it is reported that gonocyte/prespermatogonial numbers appear reduced (Baker & Scrimgeour 1980). Therefore, it is likely that gonocyte proliferation and survival during fetal development in most species are pituitary-dependent in the latter parts of gestation, although this effect is likely to be mediated through Sertoli cell number and activity.

**Peritubular myoid cells**

The PMC have been postulated for some time to have a role in regulation of Sertoli cell activity, but knowledge of PMC cell control and function remains extremely meager, particularly in the fetus. PMC express the AR in the adult animal, and recent studies have begun to show how important androgen actions, via the PMC, are for normal adult testicular function (Welsh et al. 2009). In the fetus, the PMC are the main cell type expressing the AR (Majdic et al. 1995, Shapiro et al. 2005, Chemes et al. 2008), and Sertoli cell number is reduced in ARKO and Tim mice (Johnston et al. 2004, Tan et al. 2005), suggesting a role for the PMC in fetal Sertoli cell development. In PMC-ARKO mice (lacking AR on the PMC only), the testes appear largely normal at post-natal day 12, suggesting that fetal Sertoli cell development is largely unaffected (Welsh et al. 2009). However, Cre expression, and therefore AR ablation, is variable in PMC-ARKO mice used in this study, averaging about 40% of the PMC, and this may be insufficient to induce a fetal phenotype.

**Conclusions**

Data from a number of studies indicate that, in general, the mammalian fetal testis goes through an early period of independence from hormonal control and then becomes LH- (and possibly FSH-) dependent in the latter part of gestation (Fig. 3). Two of the more notable variants to this theme are our own species, the human and the mouse. It is perhaps unfortunate, therefore, that
much of our understanding of endocrine regulation of the fetal testis has come from spontaneous genetic mutations in the mouse or the human and from manipulation of the mouse genome. Undeniably, rodents, and the mouse in particular, offer enormous advantages in the mechanistic study of testicular development. However, the life span of these species is brief, and for them, it is clearly advantageous, in terms of reproductive efficiency, to have a short gestation which allows the mother to carry more pups and to become pregnant again more quickly. Gestation in rodents appears, therefore, to primarily represent only the pituitary-independent phase of fetal gonad development seen in other mammals. On the other hand, primates are also an exception to the general rule because the fetal testes have come to depend on CG, although the later part of gestation, after CG falls to low levels, may be pituitary-dependent, in common with other species. Currently, there is a dearth of information about this later, pituitary-dependent phase of fetal testicular development. It may be that larger species, such as the sheep or the pig, are more appropriate models for the study of fetal testicular control and such as the sheep or the pig, are more appropriate for the study of fetal testicular control and function, both because they appear to show a pituitary-dependent phase and also because it is technically possible to regulate (or ablacte) the fetal pituitary either surgically or chemically.

Declaration of interest

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

Funding

We gratefully acknowledge the European Community’s Seventh Framework Programme (FP7/2007–2013) funding under grant agreement no. 212885.

Acknowledgements

S Cassie, S Flannigan, and M Fraser (University of Aberdeen) performed the immunohistochemistry shown in Fig. 1.

References


Orth JM 1984 The role of follicle-stimulating hormone in controlling Sertoli cell proliferation in testes of fetal rats. Endocrinology 115 1248–1255. (doi:10.1210/endo-115-4-1248)


Welsh M, Saunders PT, Fiskin M, Scott HM, Hutchison GR, Smith LB & Sharpe RM 2008 Identification in rats of a programming window

www.reproduction-online.org

Reproduction (2011) 141 37–46


Received 2 August 2010
First decision 16 September 2010
Accepted 18 October 2010