Androgens in female pig reproduction: actions mediated by the androgen receptor

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Androgens have potential actions in almost all the organs of males and females. In females, most organs contain some tissues with cells that have androgen receptors. Androgens can regulate cellular functions by binding to androgen receptors or be converted to other hormones. For example, testosterone can bind to the androgen receptor or be aromatised to oestradiol. Treating animals with testosterone, therefore, might elicit some androgenic and oestrogenic effects. Alternatively, testosterone can be converted to other androgens, which in turn, have more or less affinity with the androgen receptor and these new metabolites may or may not be aromatised to oestrogens. This review will highlight the roles of androgens in female mammals other than those as a substrate for oestrogen, with particular emphasis on the actions of the androgen receptors in uteri and ovaries of pigs. Utilising small dosages of an androgen receptor agonist, DHT (5α-dihydrotestosterone) we have observed that some uterine functions were inhibited while ovarian follicular development was augmented. These inhibitory and stimulatory effects of androgen therapy on reproductive organs can potentially be balanced to enhance ovulation rate and litter size in gilts and sows. Perhaps after future experimentation, new uses of androgens or anti-androgens could improve additional aspects of sow performance not presently under consideration.

Introduction

Testosterone and oestradiol are historically aligned with males and females, respectively. Testosterone, the name sake of the testis, was of primary investigative interest to male physiology because testicles are the major site of testosterone synthesis and castration of males resulted in radical alterations of appearance and behaviour. In females, testosterone was associated with its role as a substrate in oestradiol synthesis and non-substrate roles of androgens were not investigated as ambitiously as other more traditional "female" hormones. Typifying this previously held perception of androgens being a "male" hormone, the term "androgen" was defined as compounds enhancing male characteristics, hormones causing masculinisation or chemicals acting like male hormones. No longer gender-orientated in definition, androgens can now be

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considered to be compounds that bind to the androgen receptor (AR). To date, the list of known endogenous and synthetic androgens is extensive.

Fortunately information is available regarding the roles of oestrogens in males and androgens in females. Oestradiol is essential for development of the testis and prostate, maintenance of the skeleton and cardiovascular system, promotion of masculinisation and libido in males (Bakker *et al.*, 2004). In females, endogenous androgens have a wide array of effects and exogenous androgens are prescribed for women to meet a diverse range of therapeutic objectives (Table 1). However, exogenous androgens can have serious consequential effects on many organs and androgen treatment of food producing animals will continue to be a safety concern to human health.

Table 1. Various androgen treatments or therapies in females (references not included)

Women	*Cattle and Sheep*
Sexual dysfunction/state of well-being	Growth promotant (feedlot)
Skin burns	Post natal growth (prenatal treatment)
Wound healing	Reduce fear
Sports/body composition	Block ovulation
Osteoporosis/bone density	Increase ovulation rate by immunisation
Endometriosis	
Post menopausal(with oestrogen)/Hot flushes	*Mice and Rats*
Hereditary angioedema	Growth of mammary ducts/stroma
Breast cancer	Increase synapses in hippocampus
Leukemia	Attenuate seizures
Addison's Disease/adrenal insufficiency	Inhibits non-obese diabetes
Hepatic and kidney failure	
Low lacrimal function/Sjogren's syndrome	*Multiple Animal Models*
Cachexia/anorexia (with AIDS/cancer)	Hypothalamic/behavioural masculinisation
Chronic obstructive pulmonary disease	
Lower cholesterol and HDL	*Pigs*
Dialysis (androgens with erythropoietin)	See Table 2

The role of androgens in females is a timely subject as androgenic disorders are now considered the most common endocrinopathy of women, affecting at least 10 to 20 percent of the US population (Redmond, 1998). Unfortunately, these pathologies remain under reported as women tend to hide hypo- or hyper-androgenic conditions rather than seek medical attention.

Androgens are essential as substrates for oestrogen synthesis, however, androgens also have additional functions in females. For example, utilising a new strategy, the cre-lox knock-out procedure, Yeh *et al.* (2002) demonstrated that in AR knock-out (ARKO) mice, females are fertile but litter size is small. Curiously, the reverse scenario also exists in which androgens have a role only through their conversion to oestrogen. For example, memory in male rats, as qualified in a water radial maze, is enhanced with testosterone but not with the non-aromatisable androgens (Bimonte-Nelson *et al.*, 2003).

This review will focus on the effects of androgens in females beyond their role as a substrate for oestrogen synthesis. The steroid, DHT is an endogenous androgen that is synthesised by the enzyme 5α-reductase. DHT can not be aromatised to oestrogen (Wilson, 1975) and fortuitously, experimentation utilising DHT allows androgen's role as a substrate for oestrogen to be distinguished from AR-mediated events. Therefore, investigational use of DHT to alter aspects of female reproduction will be frequently cited in this review. Additionally, inclusion of the location and activity of 5α-reductase will offer information about sites of DHT action. Information specific to swine will be considered noteworthy and at times will supersede earlier discov-

eries in other species. In the forthcoming paragraphs, the general actions of androgens in females will be highlighted followed by a more specific discussion of the uterus and ovary. The last section will summarise known and potential areas of pig reproduction that might be enhanced with androgen treatment of females.

General actions of androgens in females

The physiological actions of androgens in females are complex, as androgens induce physiological effects via combinations of a variety of mechanisms and pathways. Androgens can bind to their cognate nuclear AR (genomic effects). Classical AR belongs to the family of nuclear receptors, a group of proteins that influence gene transcription. The AR gene is located on the X chromosome (Seifert *et al.*, 1999) and its associated polymorphisms have been identified in pigs (Trakooljul *et al.*, 2004). Androgens may also bind to membranous receptors and elicit non-genomic effects (Revelli *et al.*, 1998). Gorczynska and Handelsman (1995) observed non-genomic effects when freshly isolated Sertoli cells experienced increased intracellular concentrations of calcium within 20 seconds of DHT treatment. A less known pathway is the ligand-independent pathway (Buchanan *et al.*, 2001). Kim *et al.* (2005) suggested that enhanced phosphorylation and formation of a novel bridging ("enhanceosome cooperation") action of p300/CBP (CREB-binding protein) between unbound AR and CREB (cAMP responsive element-binding protein) allowed continued transcription of target genes even in the absence of the ligand (androgen).

Many androgens can be enzymatically converted to other active androgens, a process called intracrinology (Labrie *et al.*, 2003). When these additional intracrine pathways for androgen were evaluated, Labrie *et al.* (2003) estimated that women synthesise approximately two thirds the amount of total androgens synthesised by men. Newly converted androgens may have more or less affinity with the AR. One such pertinent pathway in females is the rather widespread conversion of testosterone to DHT. A forthcoming discussion of the location of 5α-reductase will support the widespread nature of this pathway. As an AR agonist, DHT has a greater affinity for the AR than testosterone (Grino *et al.*, 1990) and throughout the body, the conversion of testosterone to the more potent androgen, DHT, can be considered a mechanism of "androgen amplification" (Roy and Chatterjee, 1995).

Androgens can also influence oestrogenic responses in gilts, not necessarily through the oestrogen-substrate role but, by altering amounts of oestrogen receptors (ERα and ERß; Cárdenas and Pope, 2004). Androgens can interact with numerous other receptors and growth factors. For example, DHT can be reduced by 3α-hydroxysteroid oxidoreductase to 3α-androstanediol (Martini *et al.*, 1993). Although 3α-androstanediol has no affinity for the AR (Cunningham *et al.*, 1979) it does bind to steroid recognition sites of the GABA receptor (Marrow *et al.*, 1990). As another example of interactions with other receptors and growth factors, androgens can enhance or attenuate FSH or IGF-1 responses in follicles (deMoura *et al.*, 1997; Vendola *et al.*, 1999). Finally, androgens can cause differentiation of several organs or responses (i.e. virilism of hair distrubtion, abnormal oestrous behaviour and liver function) in females but the mechanism(s) controlling several of these permanent changes remain unclear.

Despite dramatic behavioural differences between the sexes, few anatomical and molecular markers have been identified to further differentiate between the male and female brain (Cooke *et al.*, 1998). Shah *et al.* (2004) modified the AR gene in mice to co-express two reporter molecules, lacZ and placental alkaline phosphatase (PLAP). Adding ß-galactosidase to the tissue sections allowed labelling of AR containing nuclei while the addition of PLAP resulted in visualisation of neuronal processes. Less than 10 percent of the neurones within the mouse

brain contained AR. In addition to the three known sexually dimorphic areas of the brain, the preoptic area of the hypothalamus, the bed nucleus of the stria terminalis and the nucleus of the bulbocavernosus, new dimorphic "islands" in the basal forebrain were observed to contain AR-stained neurones (Shah *et al.*, 2004). A closer examination of the three dimorphic areas revealed that the dorsal raphe nucleus, an area of the brain that innervates projections to the cerebral cortex and limbic system, is devoid of AR in female rats and mice, in contrast to males with modest-to-abundant amounts of AR (Sheng *et al.*, 2004).

Testosterone exerts many of its effects on the brain of females after conversion to DHT or oestrogens. Two different genes encode for 5α-reductase-1 and -2 (5α-R-1 and 5α-R-2, respectively; Wilson and Russell, 1994). Both these isoforms reduce androgens and are present throughout the body, including the major divisions of the brain (Callard *et al.*, 1978). Genes encoding for 5α-R-1 are positively controlled by DHT while 5α-R-2 genes are negatively regulated by DHT in the brain (Torres and Ortega, 2003). Neurones and glial cells have 5α-reductase but neurones apparently have greater activity than glial cells (Celotti *et al.*, 1991). These authors suggested that neurones also have, but glial cells lack, the ability to convert testosterone to oestradiol. Finally, the feedback of steroids on GnRH secretion might be through intermediate GABA neurones, as AR is not found in GnRH neurones (sheep, Herbison *et al.*, 1996). Sullivan and Moenter (2004) suggested that DHT can affect GnRH release by stimulating release of GABA and increasing the number of synaptic contacts from GABAergic to GnRH neurones.

Expression of female-type behaviour in female mice is highly dependent on ER activity and independent of AR function (Sato *et al.*, 2004) but this dependency is not evident in rhesus monkeys (Thorton and Goy, 1986). Sato *et al.* (2004) hypothesise that sexual dimorphism differs between rodents and primates. In swine, adult sexual activity after treatment of male foetuses with androgens changed more dramatically than similarly treated females. Treatment of pregnant sows with testosterone proprionate on days 29 to 50 resulted in a wide range of effects in female offspring. These post-treatment effects of testosterone proprionate included; delayed age at puberty, aberrant oestrogen feedback on LH secretion, unchanged tonic LH secretion, some, but not complete virilised genitalia and only a slight reduction in the extent of their female-type behaviour (Elsaesser and Parvizi, 1979; Ford and Christenson, 1987; Petric *et al.*, 2004). It remains unknown if these effects in gilts are via the AR or are the result of conversion to oestrogens or other hormones.

The presence of hepatic AR was first detected in rabbits (Sheets *et al.*, 1985) and has subsequently been identified in the liver of females of a number of mammals. The activity of 5α-reductase in the liver of adult females is 5- to 10- fold greater than in male rats (Yates *et al.*, 1958). There are hypothetically two periods or events during development that establish gender differences in hepatic 5α-reductase activity. The first is during the neonatal period when testicular androgens imprint a masculine potential on an otherwise feminine activity (McEwen, 1976). The second period of hepatic maturation of 5α-reductase activity is at puberty (Pak *et al.*, 1985), when androgen treatment of males further decreases 5α-reductase activity. The "female" pattern of GH secretion (more continuous than the typical pulsatile pattern of males) stimulates 5α-reductase in the liver (Waxman *et al.*, 1989) perhaps explaining the cause of gender differences in 5α-reductase activity. A resulting greater 5α-reductase activity in the female liver as compared to the male, might be a mechanism for females rats to metabolise more Δ^4-3-keto-steroids (Yates *et al.*, 1958). Alternatively, female rats might increase the regulatory impact of androgens on hepatocyte function through androgen amplification, in lieu of lesser concentrations of androgens in their blood than males. Finally, liver weight is positively correlated with ovulation rate in gilts (Wise and Ford, 1998), perhaps due to an altered feedback system involving differences in metabolic clearance of steroids and subsequent secretion of gonadotrophins.

Androgen action(s) in the uterus and ovary

Uterus

The AR is found in the nuclei of many cell types in pig uteri. However, some differences exist among species in the patterns and proportions of AR within various cell types of the uterus. Utilising immunohistochemistry techniques, we observed strong AR staining in the luminal and glandular epithelium with approximately 40% less staining in the myometrium of gilts (Cárdenas and Pope, 2003). Androgen receptor staining was also evident in the subepithelial stroma, while AR staining was less in stromal cells that were located deeper in the endometrium. Neither stage of the oestrous cycle nor events during early gestation appeared to alter the amount of AR staining (Cárdenas and Pope, 2003).

The potential for endocrine control of AR gene expression in the uterus was examined by utilising an ovariectomised gilt model followed with replacement therapy of oestradiol or DHT alone or the combination of oestradiol and DHT. Treatment with DHT alone did not change the amounts of AR mRNA from those of gilts in the vehicle group. However, oestradiol administration alone did increase mRNA for AR but this increase was partially blocked with DHT and oestradiol co-treatment (Cárdenas and Pope, 2004).

Considering multi-cell type (whole) cultures of endometrial tissues, 5α-reductase activity has been known to exist in gilts for a considerable period of time (Henricks and Tindal, 1971; Gadsby, 1978; Fischer *et al.*, 1985) but cell specific localisation has not yet been determined. The enzyme 5α-reductase has been localised in the human endometrium, specifically in epithelial, but not in stromal (Ito *et al.*, 2002) nor myometrial (Bulun *et al.*, 1994) cells.

Androgens might antagonise several uterine functions in gilts, perhaps through attenuation of the ERs and, therefore, inhibition of oestrogen-sensitive genes. Co-treatment of ovariectomised gilts with oestradiol and DHT reduced amounts of immunoreactive ERα in myometrial and stromal cells, and tended to decrease the amounts of ER in the luminal epithelium. Curiously, the glandular epithelia expressed a unique, cell-type, specific response as the amounts of immunoreactive ERα remained unchanged from those of gilts treated with oestradiol alone (Cárdenas and Pope, 2004). The inhibitory actions of androgens, when administered during the preceding follicular phase, on the ability of the uterus to support early conceptus development are dose and duration of treatment dependent (Cárdenas and Pope, 1997; Cárdenas *et al.*, 2002). Other inhibitory actions of androgens, specifically during the follicular phase of the oestrous cycle, range from marginal (uterine wet weight and cell proliferation) to significant (amount of complement component C3 message; Cárdenas and Pope, 2005). Finally, the effects of androgens in intact, cycling gilts are possibly modulated differently than those of ovariectomised gilts (Cárdenas and Pope, 2005).

As uterine stromal cells are sensitive to androgenic antagonism of oestrogenic effects, understanding the nature of this interaction might be valuable. Apparently, AR and ERα can be co-expressed in the same uterine cell types, but the mechanism(s) influencing their interactions is not clear. For example, the presence of androgen-response element(s) in the ER gene has not been reported. Collectively, these observations have led us to suggest that bound AR in endometrial stromal cells attenuates oestrogenic action(s) in the uterus of gilts. Specifically, stromal cells of the endometrium down-regulate the ERs in response to androgens, and those down-regulated stromal cells in turn might alter other factors required by juxtapositional epithelia. This cell-to-cell interaction between stroma and epithelia has been hypothesised to exist in other species (Clark *et al.*, 1985; Buchanan *et al.*, 1999).

Ovarian synthesis of androgens

Androgens common to females of other species, testosterone, DHT, dehydroepiandrosterone

(DHEA), DHEA sulphate and androstenedione, have also been observed in gilts (Stone and Seamark, 1985). Androstenedione is actively synthesised by theca cells of growing follicles, as concentrations in follicular fluid are several fold greater than testosterone (Evans *et al.*, 1981; Tsang *et al.*, 1985). Androstenedione exceeds testosterone concentrations in blood from the utero-ovarian vein by 2- to 20-fold (Ciereszko *et al.*, 1989). Although, porcine gonadal aromatase converts testosterone into oestrogens slower than androstenedione (Corbin *et al.*, 1999), androstenedione is metabolised through the intermediate oestrone, in the pathway to oestradiol (Peters and McNatty, 1980). In contrast, testosterone can be directly aromatised to oestradiol and the AR has more affinity for testosterone than androstenedione (Wilson, 1996). In summary, androstenedione probably has a major role as a substrate for oestrogen synthesis rather than as an agonist for the AR. Our laboratory has focused initially on testosterone and DHT effects in the ovary and, to date, we have done little experimentation with androstenedione.

The pattern of testosterone secretion during the porcine oestrous cycle has been examined previously (Fitko *et al.*, 1998; Jana *et al.*, 2000; Wise and Ford, 1998; Jana *et al.*, 2004). Concentrations of DHT in peripheral blood were lower than testosterone and did not change during the oestrous cycle (Fig. 1; E.Routman, E. Jimenez, H. Cárdenas and W. Pope, unpublished). Testosterone increased ($P < 0.05$) from oestrus to the luteal phase and then followed a transient trend of decreasing from the expected time of luteolysis (days 14 to 16; day 0 = first day of oestrus; gilts averaged a 19.5 day cycle) to increasing again at oestrus. It is possible that the increase in systemic testosterone during the luteal phase reflects corpora lutea secretion (Gregoraszczuk and Oblonczy, 1996). Blood samples collected from additional gilts on days 0, 5, 10 and 17 (n = 4) from the jugular and ovarian vein demonstrated that the concentration of testosterone was less in the jugular compared with the ovarian vein but the concentration of DHT was not affected by site of venepuncture (data not shown, E.Routman, E. Jimenez, H. Cárdenas and W. Pope, unpublished). These latter observations suggest that the ovary is a significant source of peripheral testosterone but not DHT.

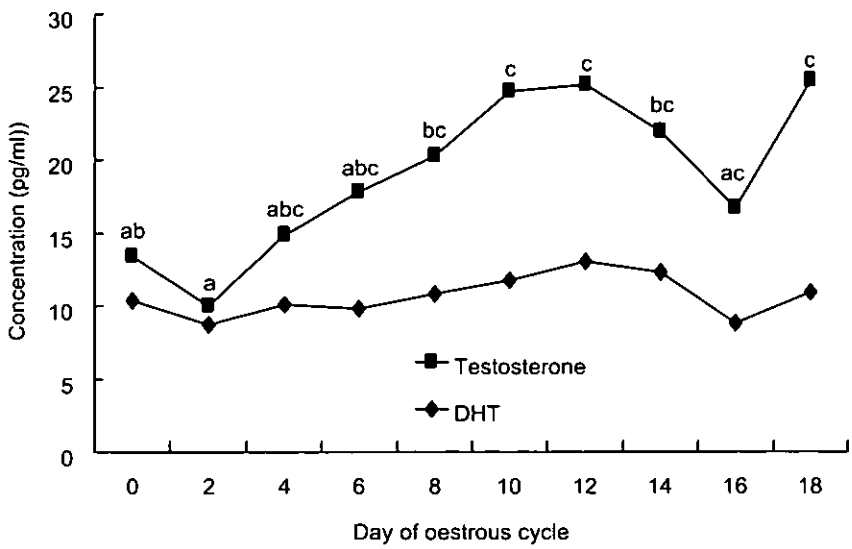

Fig. 1 Mean concentration of testosterone and dihydrotestosterone in plasma from the jugular vein of gilts (n = 6) sampled on even numbered days of the oestrous cycle. SEM for concentrations of testosterone and DHT in plasma were 10 and 2, respectively. Mean concentrations of testosterone with different superscripts (a, b or c) are different ($P < 0.05$).

Through genetic selection, the University of Nebraska has developed a line of pigs with an increased ovulation rate (Johnson *et al.*, 1999). Analysis of some physiological differences between these lines has indicated that more oestrogen-active follicles were present in the larger ovulation-rate line, two to three days before ovulation, and that these follicles were selected over a longer period than follicles of control gilts (Yen *et al.*, 2005). Microarray analysis allowed Caetano *et al.* (2004) to observe 59 unique genes from follicular tissues that were differentially expressed between the select and control line. Some of these differentially expressed genes were related to the transport of cholesterol to follicular cells, other genes were associated with steroidogenic enzymes (side chain cleavage, 17-α-hydroxylase, aromatase and cytochrome C oxidase), and others with the steroidogenic acute regulatory (StAR) protein. Noteworthy, is the upregulation of 17-α-hydroxylase during the final days of follicular maturation in the high ovulating gilts as this enzyme catalyses the conversion of progesterone to androgens.

Ovary – AR and 5α-reductase activity

The porcine adrenal, uterus, liver and pituitary gland contain 84, 62, 44 and 1%, respectively, of the amounts of AR mRNA in the ovary (Trakooljul *et al.*, 2004). Within the ovary, the AR has been detected in nuclei of most cell types of follicles (pigs, Garrett and Guthrie, 1996; Cárdenas *et al.*, 2002a; Hickey *et al.*, 2004), corpora lutea (Carrizo *et al.*, 1994), stroma (Otala *et al.*, 2004) and surface epithelia (Edmonson *et al.*, 2002). Within the porcine follicle, a greater density of AR has been detected in the granulosa cells of preantral, small and medium sized follicles than larger follicles (Garrett and Guthrie, 1996; Slomczyñnska and Tabarowski, 2001; Cárdenas and Pope, 2002a). During late follicular development, the amount of AR remains rather constant in preovulatory follicles (Tetsuka *et al.*, 1995; Hillier and Tetsuka, 1997; Cárdenas and Pope, 2002a). Recently, we noted that the intensity of staining for the AR protein in cells of pre-antral and small follicles remained constant during the oestrous cycle and only decreased before the onset of oestrus (H. Cárdenas and W. Pope, unpublished data). Theca cells contain 40 to 60% less AR than granulosa cells and, unlike granulosa cells, AR in theca cells are not influenced by day of the oestrous cycle (H. Cárdenas and W. Pope, unpublished data). Although the location and relative intensities of staining for the AR have been determined within the ovary, to date, the likely functional activity for these receptors has not been proposed.

In rats, the activity of 5α-reductase peaks in the ovary coincident with CL formation (Lephart *et al.*, 1992). Perhaps related, within the human ovary, 5α-reductase is more prevalent in the CL than stroma or follicles (Haning *et al.*, 1996). Luteinising hormone stimulated theca 5α-reductase activity (Aono *et al.*, 1981), while the relatively smaller amounts of 5α-reductase in granulosa cells were inhibited by FSH (Payne *et al.*, 1992). In rat granulosa cells, IGF-1 slightly elevated 5α-reductase activity whereas FSH did not alter the activity of the enzyme (deMoura *et al.*, 1997).

Ovary - Effects of DHT on porcine follicles

Exogenous DHT from days 13 to oestrus increases ovulation rate (Cárdenas *et al.*, 2002), and increases FSH receptor mRNA (FSHR; Cárdenas and Pope, 2002a), but does not change the amount of immunostaining of AR in thecal and granulosa cells (Cárdenas and Pope, 2005). *In vitro*, DHT suppresses FSH induced progesterone production but induces granulosa cell proliferation, particularly in cells in close proximity to the oocyte (Hickey *et al.*, 2004) and inhibits FSH induced aromatase activity (Chan and Tan, 1986). Continuing this list of DHT effects with observations in rats includes: augmenting FSH induced progesterone synthesis (Armstrong and Dorrington, 1976), stimulating growth of follicles primed with PMSG (Daniel and Armstrong, 1980), inhibiting FSH induced stimulation of LH receptor synthesis (Jia *et al.*, 1985) and augmenting FSH-stimulated utilisation of lipoproteins by granulosa cells (Schreiber *et al.*, 1984).

Considering the novel effects of DHT on ovulation rate, partitioning the treatment with DHT from days 13 to oestrus into shorter periods of days 13 to 16 or days 17 to oestrus, resulted in similar increases in ovulation rates to those treated with DHT from days 13 to oestrus (Cárdenas et al., 2002). It is possible that effects of exogenous androgen occur during the first two or three days of treatment and that smaller, more critical, windows of drug administration may offer an alternative to the more common, day 13 to oestrus regime.

At the time of this review it remains unknown how DHT increases ovulation rate in gilts. We have observed that treatment of gilts with DHT increased the mRNA for FSHR (Cárdenas and Pope, 2002a) and hypothesised that an increase in FSHR might be associated with the increase in ovulation rate (Cárdenas and Pope, 2005). FSH has many positive influences on ovarian follicular growth which could explain some of the effects of DHT including the stimulation of; granulosa cell division (Babu *et al.*, 2000), anti-apoptotic factors (Kaipia and Hsueh, 1997), aromatase activity (Hickey *et al.*, 1988), progesterone synthesis (Ford and Howard, 1997) and increasing the amounts of LH receptors (Channing, 1975; LaBarbera and Ryan, 1981). Guthrie *et al.* (1998) suggested that FSH functions as a primary element in regulating follicular atresia. Guthrie and Bolt (1990) noted that selection of ovulatory follicles occurs coincident with decreasing FSH and several laboratories have suggested that LH might be responsible for initiating final maturation of ovulatory follicles (Nakano *et al.*, 1977; Foxcroft and Hunter, 1985; Liu *et al.*, 1998). Perhaps increasing the amounts of FSHR coincident with the normal decrease of FSH (ligand) is a mechanism(s) to delay the loss of FSH "influence" in follicles.

Potential uses of androgens in female pigs

Treatment of pigs with androgens will continue to be a marketing, and in some cases a health, concern for consumers. Any favourable use of androgens to improve reproductive performance of gilts or sows would have to fully address any public concerns. Documented areas for androgen therapy to improve gilt performance are illustrated at the top of Table 2, while more speculative uses of exogenous androgens are listed at the bottom. It is probable that few of the therapies listed in Table 2 are exclusive of androgen's role as a substrate for oestrogens.

Table 2. Potential uses for androgen to improve reproductive performance in female pigs.

Production parameter	Observed or theoretical effect	Reference
Litter size	Increased one pig/litter	Cardenas and Pope, 2002b
Litter size	Increased ovulation rate	Cardenas and Pope, 1994
Neonatal rate of gain	One day old at treatment	Dvorak, 1981
Juvenile rate of gain	Androgen and oestradiol implant	DeWilde and Lauwers, 1984
Potential or speculative applications		
Number of teats	Prenatal antiandrogen therapy	Drickamer *et al.*, 1999
Herd conception rate	Prenatal antiandrogen therapy	Drickamer *et al.*, 1997
Mammary growth	Duct and stroma development (rats)	Zhang *et al.*, 2004
Birth weight	Prenatal androgens, before d104	Wise and Christenson, 1992
In vitro fertilisation	First attempt failed to improve	Herrick and Pope., 2002
Oestrous detection	Improve boar libido, prenatal	Rohde Parfet, *et al.*, 1990

The speculative uses of androgens are based on hypothetical application of some recent observations and require further elaboration (Table 2, bottom). The number of teats and conception

rate of gilts is another important trait to swine production but these phenotypes are reduced in gilts from litters with a greater proportion (> 67 %) of males (Drickamer *et al.*, 1997; Drickamer *et al.*, 1999). Treatment with anti-androgens at a critical stage of gestation might reverse the negative affects of androgens or androgen induced factors from neighbouring foetal males. Likewise, further experimentation perhaps to determine a more precise window of treatment or to examine a better source or dosage of androgen, could be utilised in a therapy to enhance birth weights. Finally, many of the androgen therapies listed in Table 2 might have to be partitioned within a large swine operation to treatment of those pigs (foetuses) dedicated for growth as compared with replacement females.

Conclusion

Androgens are endogenous to normal female reproduction but their specific functions remain, for the most part, to be determined. One of the difficulties in investigating the role of androgens is the multiple pathways by which these steroids alter cellular function. In addition to being a substrate for oestrogen synthesis, androgens can bind to AR, be metabolised to other hormones, alter amounts and actions of other receptors, interact with growth factors and possibly other pathways still undiscovered. Although investigations have surveyed the body for the location of the AR and 5α-reductase, and other experimentation has allowed concluding circumstances that facilitate some changes in these proteins, the science of what androgens do in the normal physiological events of female reproduction is glaringly absent. This review, even with its focus on AR actions in the uterus and ovary, can offer little more to this "survey". Under experimental conditions some aspects of uterine function were attenuated by androgens through interactions with oestrogenic pathways. Specific to the ovary, recent observations indicate that the AR exists in various cell types of porcine follicles and binding of androgens to the AR can have a positive influence on events during final maturation of follicles. The potential exists for many aspects of pig production to be influenced by androgen treatments. Understanding basic mechanisms of how androgens directly or indirectly alter reproductive performance in sows and gilts probably will prove valuable to improving swine production.

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