Published in final edited form as:

Trends Endocrinol Metab. 2016 December ; 27(12): 844–855. doi:10.1016/j.tem.2016.08.008.

Role of sex steroids in β -cell function, growth and survival

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Abstract

The gonads have long been considered as endocrine glands producing sex steroids such as estrogens, androgens and progesterone, for the sole purpose of sexual differentiation, puberty and reproduction. Reproduction and energy metabolism are tightly linked, however, and gonadal steroids play an important role in sex-specific aspects of energy metabolism in different physiological conditions. In that respect, gonadal steroids also influence the secretion of insulin in a sex-specific manner. This review presents a perspective on the physiological roles of estrogen, androgen and progesterone via their receptors in pancreatic β -cells in the gender-specific tuning of insulin secretion. We also discuss potential gender-specific therapeutic avenues that this knowledge may open in the future.

Keywords

Estrogen; androgen; progesterone; islet; β -cells; insulin

Introduction

The pituitary, the thyroid and the adrenal glands are endocrine organs with the sole known function of synthesizing and secreting hormones that act on distant tissues and organs. Other organs have emerged as endocrine peptide secretors that regulate energy homeostasis through secretion of the adipose-derived satiety hormone leptin [1], the incretin glucagon like peptide-1 (GLP-1) produced by intestinal L cells [2], and the bone-derived regulator of energy homeostasis, osteocalcin [3]. The liver can also be considered an endocrine organ that stimulates energy metabolism via production of the fasting hormone fibroblast growth factor 21, and influences pancreatic β -cell function and proliferation by producing kisspeptin [4], and serpin B1 [5]. The list can be extended to include the hunger hormone ghrelin produced by the stomach and the controversial myokine irisin, produced by skeletal muscle during exercise [6]. Historically, the gonads have been viewed as endocrine organs secreting steroids for the sole purpose of sexual differentiation, puberty and reproduction.

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However, because energy stores need to reach a minimum threshold to allow reproduction to occur, reproduction is tightly linked to energy metabolism. Thus, in physiological conditions, gonadal hormones play an important role in sex-specific aspects of energy metabolism [7,8]. For example, secretion of insulin, an anabolic hormone produced by the β -cells of the pancreatic islet of Langerhans that promotes energy storage, is influenced by gonadal steroids in a sex-specific manner. This review discusses the physiological roles of the ovarian- and testicular-islet axes in the biology of insulin-producing β -cells in females and males. We will discuss the roles of estrogens, androgens and progestogens via their receptors, ER, AR and PR, respectively, in the gender-specific tuning of insulin secretion and outline potential gender-specific therapeutic avenues that these signaling pathways open.

Sex steroid biosynthesis in males and females

Pregnenolone, a steroid hormone synthesized from the enzymatic cleavage of cholesterol, is the precursor for the synthesis of gonadal steroids via a reaction catalyzed by the cytochrome P450 side-chain cleavage (P450_{scc}) in the mitochondria (Fig. 1). For review, see [9]. In the adult male, the testicular Leydig cells are the sites of testosterone (T) biosynthesis in response to luteinizing hormone (LH), secreted from the pituitary (Fig. 1). In the female ovary, both granulosa and theca cells contribute to steroidogenesis. Theca cells are the ovarian equivalent of Leydig cells and synthesize androgen in response to LH. Theca cells lack expression of the aromatase enzyme that converts androgen to estrogens, thus they cannot produce estrogens. Aromatase is expressed in granulosa cells, and these cells produce estradiol (E2) and progesterone (P4) in response to LH and follicle-stimulating hormone (FSH) stimulation [9]. Luteinization during early gestation is a process of proliferation and differentiation of the steroidogenic cells of the follicle that become the luteal cells of the corpus luteum producing up to 100-fold greater amounts of P4. In mammals, the outer adrenal cortex also produces androgens such as androstenedione and dehydroepiandrosterone (DHEA) (Fig. 1).

Evidence of local islet steroidogenesis

The brain also synthesizes steroids *de novo* from cholesterol that are referred to as neurosteroids [10]. Evidence suggests that the pancreas also has the machinery to synthesize steroids. Cytochrome P450_{scc}, responsible for the first limiting step in steroid biosynthesis (Fig. 1) was detected in dog pancreas mitochondria [11]. The enzymatic activities of 17 β -hydroxysteroid dehydrogenase (17 β -HSD), which produces testosterone from androstenedione and E2 from estrone (E1) (Fig. 1), have been reported in rat, human [12] as well as canine pancreases [13]. In fact, the mRNA of type 1 17 β -HSD is expressed in human pancreas [14], and the type 12 form was exclusively observed in the islets of Langerhans [15]. P-450_{scc}, and P-450_{17 α} , which has 17 α -hydroxylase activity and C17–C20 lyase activity, the latter a prerequisite for androgen biosynthesis, were found to be co-localized in rat islet β -cells (Fig. 1). This suggests that P4 is intracellularly produced and is converted to androstenedione [16]. Co-localization of P-450_{scc} and 3 β -hydroxysteroid dehydrogenase (3 β HSD), which converts pregnenolone to P4 and DHEA to androstenedione (Fig. 1) was also found in rat β -cells [16]. This indicates that P4 is intracellularly produced in rat β -cells and converted to androstenedione. Similarly, the activity of 3 β HSD was demonstrated in the

mitochondrial fraction of dog pancreas homogenates [17]. Aromatase and 5 α -reductase activities were identified in human pancreatic carcinoma and in normal adult or pooled fetal pancreatic tissue [18]. Thus, β -cells could in theory produce testosterone, dihydrotestosterone (DHT), and E2, which would act as local steroids in the islets. In the case of neurosteroids, their local concentration is thought to exceed that of the steroids in plasma [10]. Thus, locally-produced islet steroids could directly and efficiently interact with ER and AR in the same or neighboring cells in a paracrine or intracrine manner, and would be inactivated locally at the same place that they were formed [19]. Since venous blood from the islets showers the liver via the portal vein, where drug-metabolizing cytochrome P-450 enzymes rapidly inactivate steroids, the local islet-derived steroids should not produce effects on distant tissues.

Role of estrogens

The role of female hormone E2 and related estrogens via ER α , ER β and the G protein-coupled ER (GPER) in islet biology has been recently reviewed [20] and can be summarized as follows (See Fig. 2): ER α is involved in survival, insulin biosynthesis, and nutrient homeostasis, while ER β enhances GSIS. The G-protein coupled ER is implicated in GSIS and islet survival. Unlike the classical nuclear ERs, which acts as a ligand-activated transcription factor in breast and uterine cells, β -cell ERs reside mainly in extranuclear locations. They exert their effect via cytosolic interactions with kinases such as Src, ERK, and AMPK, or via transcription factors of the STAT family. These ER actions are relevant to human islet function and survival. Here, we will focus on recent developments.

Type 1 diabetes

Common autoimmune diseases usually show a female predominance with the exception of type 1 diabetes (T1D) [21] which is characterized by a male predominance in European populations (ratio: 1.7) [22]. In support of a protective role of ovarian hormones, the male predominance develops after puberty, while puberty is associated to a decreased incidence in girls [23,24]. Additionally, the residual β -cell function at diagnosis (measured by C-peptide) is also high in girls [25,26]. Therapeutic strategies focused on restoring immune tolerance remain the main avenue to prevent T1D. One promising approach is enhancing the immunoregulatory properties of the lymphocyte population of invariant natural killer T (iNKT) cells [27]. For many years, estrogen-based therapies have been considered promising immunoregulatory strategies in autoimmune diseases such as multiple sclerosis [28–30]. E2 therapy protects female non-obese diabetic (NOD) mice from autoimmune T1D by preventing islet insulinitis [31]. The protective effect of E2 administration was decreased in NOD mice deficient in iNKT cells. E2 treatment of NOD mice enhanced the immunoregulatory functions of iNKT lymphocytes and enhanced their production of the cytokines IL-4 and IFN- γ which dampened the auto-immune islet destruction. E2 treatment was efficient not only in preventing insulinitis when administered early, but also in protecting from T1D development when E2 treatment was initiated after the onset of insulinitis [31]. Further studies are needed to determine if estrogen ligands could increase the efficiency of therapeutic strategies aimed at promoting iNKT cell immunomodulatory functions in T1D.

After the onset of T1D, pancreatic islet transplantation (PIT) is the most physiological treatment [32–34]. The female sex is a predictor of insulin independence after total pancreatectomy and islet cell autotransplantation, suggesting that E2 improves PIT in women [35]. In fact, it was recently shown that a transient treatment with E2 at the time of PIT improves the engraftment of a marginal dose of human islets in diabetic nude mice of both sexes [36]. The protective effect of E2 was secondary to 1) an acute protection of islet graft functional mass from hypoxia, oxidative stress and apoptosis and 2) chronic induction of islet revascularization. These effects were mediated via ER α and ER β with a predominant ER α effect.

Silencing the inflammatory protein inducible nitric oxide synthase (iNOS) in islets is another strategy to promote the survival of transplanted islets [37]. Hwang et al. used peptide micelles that co-deliver small interfering RNA (siRNA)-iNOS and E2 loaded in the hydrophobic core. The delivery of these peptide micelles improved the engraftment of a marginal dose of islet transplanted in male diabetic syngeneic mice. Obviously, further studies are needed to assess the effect of local estrogen delivery to improve islet engraftment during PIT. However, the concept that estrogen ligands could help increase the efficiency of therapeutic strategies aimed at restoring iNKT cell immune function while at the same time promoting islet engraftment is appealing.

Type 2 diabetes

The targeting of E2 to islets using GLP-1 as a vector has been proposed as another mean to protect functional β -cell mass in both forms of diabetes, without the undesirable effects of general estrogen therapy. Indeed, islet β -cells express both ERs and GLP-1 receptors (GLP-1R), and conjugates of GLP-1 stably linked to E2 were synthesized and tested. When given to male diet-induced obese mice, GLP1-E2 conjugates had a synergistic anti-obesity effect above that observed by a single agonist, and without inducing the adverse systemic E2 effects. The effect was centrally mediated, as GLP-1 provided targeted E2 delivery to the hypothalamus that resulted in suppressing food intake [38]. The effect of the GLP1-E2 conjugates was also efficient in preventing type 2 diabetes (T2D) in male New Zealand obese mice [39]. However, the islet protection in these mice was not a consequence of E2 targeting to the islet, but to the hypothalamic targeting and prevention of obesity described above [27]. Further, in male mouse and cultured human islets, the GLP1-E2 conjugates did not enhance the insulinotropic effect of GLP-1 [40]. Studies are ongoing to determine the relationship between GLP1-E2 peptides and β -cell survival [41].

Another approach to ER targeting for islet protection without reproductive effects consists of pairing estrogens with a selective estrogen receptor modulator (SERM) that has antagonistic action in breast and uterus. For example, pairing conjugated equine estrogens (CE) with the SERM bazedoxifene [42] is a new menopausal hormone therapy providing the benefits of CE by treating menopausal symptoms while at the same time protecting the uterus and breast from estrogen stimulation with bazedoxifene [43]. The combination CE/bazedoxifene and bazedoxifene alone reduced the severity of β -cells destruction and resulting insulin-deficient diabetes induced by streptozotocin (STZ) in female mice [44]. The prevention of STZ-induced insulin-deficient diabetes in mice is a marker of estrogen agonist activity in

preventing β -cell apoptosis [45]. Thus, the prevention of STZ-induced diabetes by bazedoxifene demonstrates that in female mice, bazedoxifene acts as an estrogen agonist in β -cells. Preliminary studies in the Akita mouse model of endoplasmic reticulum (ER) stress in β -cells also suggest that the combination of CE/ bazedoxifene acts as a pharmacological ER stress mitigator. In the islet of male Akita mice, the accumulation of unfolded insulin promotes ER stress which induces the expression of the pro-apoptotic transcription factor CCAAT-enhancer-binding protein homologous protein (CHOP). In these mice, treatment with CE/bazedoxifene reduced islet CHOP expression, and prevented islet destruction and the development of insulin-deficient diabetes [46]. Therefore, the combination CE/ bazedoxifene used for menopausal hormone therapy could protect women from estrogen deficiency-induced β -cell dysfunction and damage.

β -cell regeneration

The role of ERs in promoting β -cell proliferation remains a matter of controversy. GPER has been implicated in the expansion of functional β -cell mass observed during pregnancy. In female rodents, GPER expression is markedly upregulated during pregnancy, which is associated with decreased expression of the islet microRNA miR-338-3p [47]. In rodents, downregulation of miR-338-3p promoted β -cell proliferation, while increased miR-338-3p expression decreased β -cell mass. In isolated rat islets, exposure to E2 or the GPER agonist G1 also decreased miR-338-3p to levels observed in gestation, a level that was associated with increased β -cell proliferation. These E2 effects depend on cAMP and protein kinase A. Although E2 exposure also reduced the level of miR-338-3p in cultured human islet cells [47], neither E2 nor silencing of miR-338-3p elicited replication of human β -cells in culture [22]. Likewise, neither E2 or G1 treatments produced any proliferation of human β -cells transplanted in male mice [36]. Thus, the impressive effect of GPER activation and the resulting suppression of miR-338-3p observed in rodent β -cell proliferation are not observed in human β -cells.

Partial duct ligation (PDL) is another rodent model of β -cell expansion due to pancreatic injury. Following PDL, cells expressing the endocrine specification factor Neurogenin3 (NGN3+) are generated near the duct and can then differentiate into β -cells [48]. In PDL, β -cells are mostly generated via replication. They can also derive from neogenesis via a NGN3+ stage [48]. Treatment with the ER α antagonist tamoxifen or genetic elimination of ER α in male mice similarly decreased NGN3 expression and β -cell proliferation in the PDL model, suggesting that ER α is involved in this process [49]. PDL increased E2 in the ligated portion of the pancreas and stimulated nuclear localization of ER α in β -cells (ER α is cytosolic β -cells under normal conditions). ER α inhibition with tamoxifen in the embryonic pancreas, or its deletion as in the ER α -deficient mouse, also decreased NGN3 expression and NGN3+ progenitors at the end of gestation [49]. Thus, the generation of NGN3+ cells and the subsequent β -cell mass expansion in developing or injured mouse pancreas are both stimulated by ER α [49].

The transgenic (Tg) mouse model with β -cell-directed expression of the inducible cAMP early repressor-I γ exhibits decreased β -cell replication, severe loss of β -cell mass, leading to diabetes. This manifests itself in a sexually dimorphic manner, because only male mice

suffer from hyperglycemia throughout life. Treatment of orchidectomized male Tg mice with E2 enhanced β -cell proliferation by inducing the neogenesis of new β -cells in the ducts and the replication of existing β -cells in the islets [50]. The authors did not investigate whether ER α or ER β were involved in this process. However, E2 stimulation of β -cell proliferation occurred concomitantly with an increased expression of pancreatic duodenal homeobox-1 (PDX-1).

Thus, in these two rodent models of β -cell regeneration, E2 can induce β -cell mass expansion via ER α signaling by inducing the replication of existing β -cells or the neogenesis of new β -cells via activation of NGN3 or PDX-1 respectively. Still, validity of these findings to human β -cells has not been established [51].

The ER β could also be involved in β -cell regeneration. A selective ER β agonist (WAY200070) was shown to increase β -cell proliferation in male normal C57BL6 mice, mice rendered diabetic with STZ and in the diabetic db/db mice [52].

In summary, ERs activation in β -cells promotes survival and mass expansion in rodents as well as immunomodulation. Selective activation of ERs in islets is a strategy to protect functional β -cell mass if we can harness their beneficial properties.

Role of androgens

Males

AR has long been considered a classical ligand-activated nuclear receptor that regulates the expression of target genes in reproductive tissues through binding to cognate response elements on the DNA [53–55]. Although the function of T and AR in adiposity and insulin sensitivity in males is known, the role of AR in islet function has been poorly explored [8,56]. This is surprising, because large observational studies have reported that among prostate cancer patients, androgen depletion therapy (ADT), which produces profound androgen deficiency, was associated with an increased risk of T2D [56]. This raises the possibility that testosterone is important for insulin secretion in males. This paradigm was explored in mice with β -cell-selective AR deficiency (β ARKO). Adult male β ARKO mice exhibit decreased glucose-stimulated insulin secretion (GSIS) leading to glucose intolerance [57]. When exposed to a Western diet, these mice developed fasting and fed hypoinsulinemia and hyperglycemia, respectively. Testosterone enhances GSIS in cultured male human and mouse islets, an effect that was blocked in β ARKO islets and in human islets treated with the AR antagonist flutamide. Thus, T enhances GSIS via direct action on AR in islet β -cells. Importantly, in β -cells, unlike in prostate cells, AR exhibits an extranuclear location and enhances GSIS by increasing cAMP production and activating the cAMP-dependent protein kinase A in a manner similar to GLP-1 [57]. In fact, in cultured islets, the insulinotropic effect of T depends on activation of the GLP-1 receptor by islet-derived GLP-1, as it was abolished in the presence of a GLP-1R antagonist. Further, in cultured mouse and human islets, T amplifies the insulinotropic effect of exogenous GLP-1. Interestingly, β ARKO mice exhibit blunted GSIS and glucose intolerance in response to parenteral glucose, suggesting that T also amplifies the insulinotropic effect of islet-derived GLP-1 *in vivo*. This is consistent with studies showing that in mice, gut GLP-1 acts locally

in a paracrine manner via a gut/brain/islet axis to enhance insulin secretion [58]. Therefore, a model is emerging in which T provides fine-tuning of insulin secretion in males by enhancing the action of GLP-1 (Fig. 2). The biological basis for androgen stimulation of insulin secretion in males is likely to promote anabolism, since both testosterone and insulin are anabolic hormones.

Females

In contrast to males, AR deficiency in β -cells of female mice did not alter glucose homeostasis, probably a consequence of females' lower dependence on androgens [59]. However, androgen excess in women predisposes to pancreatic β -cell dysfunction [60–63]. In some studies of women with polycystic ovary syndrome (PCOS), β -cell dysfunction was proportional to testosterone concentrations independent of insulin resistance, suggesting that excess testosterone action in β -cells produces dysfunction. This hypothesis was explored in female β ARKO mice. When female control mice were exposed to chronic androgen excess, they developed hyperinsulinemia and insulin resistance. However, the phenotype was not observed in littermate female β ARKO mice lacking AR selectively in β -cells [64]. Thus, in female mice, excess AR activation in β -cells may produce insulin hypersecretion leading to secondary insulin resistance. Unlike T, the androgen DHEA has beneficial effect on female rat islet. DHEA supplementation in ovariectomized female rats improves glucose-stimulated insulin secretion impaired by a high-fat diet [65].

In addition to the effect of T excess in adult β -cell function, T also has developmental effects on female islets. Prenatal maternal exposure to T in mice programs β -cell dysfunction in female offspring with increased fasting glucose in absence of insulin resistance but impaired insulin secretion in response to glucose *in vivo* and in cultured islets [66]. In an ovine model, prenatal T exposure increased insulin secretion in adult female offspring in the absence of glucose intolerance [67]. In this model, prenatal T disrupted female fetal islet development, increasing β -cell numbers and area per islet leading to hyperinsulinemia in adult offspring [68]. The female fetal androgenized islets expressed AR, and showed increased transcript expression for PDX-1 and IGF-1 receptor, potentially explaining the increased β -cell mass in adult offspring. In addition, cultured total pancreas extracts from these androgenized female fetuses showed increased insulin secretion under euglycemic conditions, but no response to increased glucose concentration. Thus, fetal androgenic stimulation of female β -cells may predispose to β -cell dysfunction in adults characterized by hyperinsulinemia in response to normal glucose concentrations in the absence of insulin resistance.

In nonhuman primates, maternal androgen exposure also programs β -cell alterations in early post-natal life of female offspring, leading to hyperinsulinemia and increased insulin secretion in response to glucose challenge, relative to insulin sensitivity [69]. Androgenized female primate infants exhibited altered islet morphology suggestive of enhanced β -cell proliferation and mass expansion. However, changes in the adult islet morphological alteration were more subtle, suggesting islet post-natal adaptation that would predispose to diminished insulin response to glucose in the insulin resistant mature PCOS phenotype [70].

Thus, developmental androgen excess programs female β -cells *in utero* via AR. This alters insulin secretion in adult females leading to basal hyperinsulinemia (independent from

insulin resistance) but reduced insulin secretion in response to glucose. In addition, in adult females, excess T produces hyperinsulinemia. Thus, the combination of developmental and postnatal androgen excess in females may program the β -cell dysfunction observed in adult females with PCOS (Fig. 3).

Progestogens

Progestogens are named for their function in maintaining pregnancy (i.e., progestational) and activate PR. The most important progestogen is P4. Historically, P4 was shown to enhance insulin response to glucose, suggesting that P4 promotes islet adaptation to gestational insulin resistance [71]. The discovery of PR in the primate and human endocrine pancreas suggested a direct role of P4 on islet function [72,73]. Treatment of female rats with a combination of E2 and P4 increased GSIS and ameliorated glucose tolerance, suggesting that the increased GSIS was a primary event rather than a consequence of insulin resistance [74]. In addition, ex vivo cultures of islets of these same female rats revealed increased islet size and GSIS [74]. However, when E2 and P4 were acutely added to female cultured islets, no increase in GSIS was observed, suggesting that the P4 insulinotropic effect on islets was due to chronic islet stimulation by P4. In fact, P4 exposure of cultured islets for 2 weeks increased islet GSIS by increasing glucose sensitivity [75]. In MIN6 β -cells, P4 was reported to enhance GSIS, in part by increasing glucose metabolism via an increase in the activity of the rate limiting enzyme, glucokinase [76]. However, in the same cells, P4 used at pharmacological concentrations was also shown to inhibit the stimulatory effect of E2 on GSIS via PR [77].

The effects of P4 on islet function need to be investigated in the full hormonal milieu of pregnancy [78]. To mimic pregnancy, Sorenson et al cultured rat islets with P4, E2 and prolactin (PRL, to mimic placental lactogen). Exposure to P4 alone for a week had no effect on GSIS or islet cell proliferation. However, after 4 days of stimulation, P4 opposed the effects of PRL on GSIS and β -cell proliferation. This suggests that in late pregnancy P4 inhibits PRL [79]. This is consistent with the observation that in pregnant rats, P4 treatment increases islet-cell proliferation on day 14, but not on day 21 (when placental lactogen is high) [78]. In contrast, in both cases P4 treatment increased islet proliferation in cyclic rats [78]. Further, treatment of cycling female and male rats with P4 stimulated β -cell proliferation. This effect was not observed in gonadectomized mice [80] or cultured rat islet cells [79], suggesting that P4 requires intact gonadal function to induce islet cell proliferation. Similarly, in perfused pancreas of ovariectomized rats, E2 increased insulin release but P4 alone did not, although P4 enhanced the effect of E2 [81].

Surprisingly, female mice deficient in PR exhibit enhanced β -cell proliferation with increased β -cell mass resulting in improved β -cell function [82]. Increased β -cell proliferation is not associated with changes in islet expression levels of the cell cycle regulator (p21, p27, cyclin D1, cyclin B1, and cyclin E). However, PR-deficient islets showed decreased expression of the tumor-suppressor p53, which may enhance islet proliferation [82]. Therefore, P4 can induce β -cell proliferation, but at the same time, PR deficiency enhances β -cell proliferation. This suggests that *in vivo* P4 acts on more than one receptor. Indeed, the progesterone receptor membrane component 1 (PGRMC1), a

membrane-associated PR composed of a single transmembrane protein, is known to mediate P4-associated membrane signaling in mammalian cells. Zhang et al reported that PGRMC1 is a component of the GLP-1R complex, which potentiates GLP-1-induced cAMP accumulation and insulin secretion [83]. The mechanism underlying PGRMC1 enhancement of GLP-1-induced insulin secretion is not clearly understood. It is proposed that PGRMC1 acts as an membrane adaptor protein in β -cells to enhance GLP-1R transactivation of the epidermal growth factor receptor, thus increasing GSIS via calcium influx [84–86].

Finally, P4 has been shown to induce β -cell apoptosis in cultured rat islets and clonal insulin-secreting cells [87]. Since the sex of the cells was not mentioned, the translational relevance of these findings is unknown

Concluding remarks and future perspectives

Receptors for estrogens, androgens and progestogens are expressed in male and female β -cells. Although male and female mammals exhibit the same overall mechanism of nutrient-induced insulin secretion, evidence presented here demonstrates that the fine-tuning of insulin secretion can be regulated in a sex-specific manner by gonadal steroids. Thus, ERs are targets to improve functional β -cell mass and modulate immune function in T1D. However, AR enhances GLP-1-stimulated insulin secretion in the male. In contrast, excess AR activation in female fetal and adult β -cells produces β -cell dysfunction in the adult. The role of the PR in female is more complex and depends on the reproductive status.

Obviously, because of their systemic side effects, general estrogens and androgens therapies cannot be used for β -cell therapy. Thus, it is critical to elucidate the precise molecular pathways used by sex steroids and their receptors to promote these actions in order to better extract and harness these beneficial effects without reproductive side effects. Additional studies are needed to unravel the mechanisms behind estrogen, androgen and progestin, as they represent avenues for gender-specific protection of β -cell functional mass in diabetes and therefore precision medicine.

Acknowledgments

This work was supported by grants from National Institutes of Health (RO1 DK074970), and the American Diabetes Association (7-13-BS-101).

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OUTSTANDING QUESTIONS BOX

- Can estrogen-based treatments be used to enhance immune therapy and protect β -cell functional mass in T1D? Can estrogens induce β -cell proliferation in humans as they do in rodents?
- How can we harness the insulinotropic effect of testosterone in male β -cells for the prevention or treatment of T2D in hypogonadal men but without the side effects of general testosterone therapy?
- Since in utero testosterone programs the development of islet β -cells, are male islet β -cells that are naturally exposed to a prenatal testosterone surge in human males, different in architecture and function than that of females?

TRENDS BOX

- The steroid receptors for estrogen (ERs), androgen (AR) and progesterone (PR) are expressed in islet β -cells and they are involved in survival, insulin secretion and mass expansion.
- ERs are targets to improve functional β -cell mass in type 1 diabetes by protecting from pro-apoptotic stimuli and enhancing the immunomodulatory function of iNKT lymphocytes.
- AR enhances GLP-1 stimulated insulin secretion in the male and represents a novel target to prevent diabetes in aging and androgen-deficient men
- Excess AR activation in the female fetal and adult β -cells produces β -cell dysfunction in the adult by producing insulin hypersecretion leading to secondary failure.
- PR is important to β -cell adaptation to pregnancy by increasing insulin secretion and opposing the late effect of PRL on proliferation.

Tissue specific biosynthetic pathways

Figure 1. Steroidogenesis of sex hormones in classical steroidogenic tissues

Steroids are synthesized in the gonads and adrenal glands from cholesterol. The first reaction catalyzed by cytochrome P450 side-chain cleavage (P450_{scc}) in the mitochondria produces pregnenolone. Progestagens are the first steroids synthesized. In the Leydig cells of the testis, the cytochrome P-450_{17α} catalyses two key steps in the biosynthesis of androgens from pregnanes, the 17α hydroxylation step and the subsequent 17–20 lyase reaction and produces dehydroepiandrosterone (DHEA). Leydig cells express high levels of 3β-hydroxysteroid-dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-

HSD), and DHEA is converted to the final product, testosterone, via the intermediates androstenediol and androstenedione. In target tissues, testosterone is converted to dihydrotestosterone (DHT) by the action of 5 α -reductase (5 α -R). In thecal cells of the ovary, pregnenolone is converted to P4 by the 3 β -HSD. Cytochrome P-450_{17 α} then catalyzes P4 transformation into androstenedione. Aromatase is expressed by granulosa cells (as well as adipose tissue and bone in both sexes), and produces estradiol (E2) and estrone (E1) from testosterone and androstenedione.

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Figure 2. Effect of estrogens and ERs on β-cell function, growth and survival

17β-estradiol binds ERα, ERβ and the GPER in islet β-cell to promote the effects described.

Selective ligands for the three receptors have the same effect of their cognate receptor.

Figure 3. The testicular/islet axis in insulin secretion

Testosterone secreted by the testicles binds AR in β -cells, which amplifies (+) the insulintropic effect of the β -cell GLP-1 receptor (GLP-1R) that is activated by islet-derived GLP-1 and GLP-1R agonists (GLP-1RA). Gut GLP-1 acts in a paracrine manner on GLP-1Rs in the gut's portal vein to relay signals via the vagal nerve to the brain which then signals to the islets (gut/brain/islet axis) to enhance insulin secretion (+).

Fetal testosterone excess

Adult testosterone excess

Figure 4. Effect of androgen excess in fetal and adult female islets

Testosterone excess in the adult female activates AR in β -cells leading to insulin hypersecretion and hyperinsulinemia. Fetal testosterone excess programs β -cells *in utero* via AR: This leads to basal hyperinsulinemia but decreased insulin secretion in response to glucose in adult females. Thus, the combination of fetal and adult androgen excess in females may result in the β -cell dysfunction observed in adult females with PCOS.