REVIEW

Emerging role of testosterone in pancreatic β cell function and insulin secretion

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Abstract

One of the most sexually dimorphic aspects of metabolic regulation is the bidirectional modulation of glucose homeostasis by testosterone in male and females. Severe testosterone deficiency predisposes men to type 2 diabetes (T2D), while in contrast, androgen excess predisposes women to hyperglycemia. The role of androgen deficiency and excess in promoting visceral obesity and insulin resistance in men and women respectively is well established. However, although it is established that hyperglycemia requires β cell dysfunction to develop, the role of testosterone in β cell function is less understood. This review discusses recent evidence that the androgen receptor (AR) is present in male and female β cells. In males, testosterone action on AR in β cells enhances glucose-stimulated insulin secretion by potentiating the insulinotropic action of glucagon-like peptide-1. In females, excess testosterone action via AR in β cells promotes insulin hypersecretion leading to oxidative injury, which in turn predisposes to T2D.

Key Words

- ▶ testosterone
- ▶ androgen receptor
- ▶ islet cells
- ▶ diabetes
- ▶ sex dimorphism

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Introduction

The role of sex in metabolic disease is a fundamental issue in endocrinology. Perhaps the most sexually dimorphic aspect of metabolic regulation is the bidirectional modulation of glucose homeostasis and energy balance by the male hormone testosterone in males and females (Navarro *et al.* 2015, Morford & Mauvais-Jarvis 2016, Schiffer *et al.* 2017, Morford *et al.* 2018). It is well established that testosterone deficiency predisposes men to visceral obesity, metabolic syndrome and T2D (Stellato *et al.* 2000, Oh *et al.* 2002, Zitzmann 2009, Navarro *et al.* 2015). In contrast, testosterone excess predisposes women to obesity, metabolic syndrome and T2D (Oh *et al.* 2002, Jones *et al.* 2011, Navarro *et al.* 2015). Considering that men with testosterone deficiency and women with androgen excess represent a large segment of the population (18% of men over 70 years old (Araujo *et al.* 2007) and 5–20% of women of reproductive age (Azziz

et al. 2016), respectively), it is vital to understand the determinants of sex differences in testosterone's effects on metabolic homeostasis (Stellato *et al.* 2000, Zitzmann 2009, Jones *et al.* 2011, Schiffer *et al.* 2017). Although it is established that β cell dysfunction is necessary for hyperglycemia to develop, the role of testosterone in β cell function and insulin secretion is poorly understood. This review discusses how testosterone acts on the AR in the insulin-producing β cells of the pancreas in a sexually dimorphic manner in males and females to promote β cell function or dysfunction, respectively.

Testosterone action in β cells in men

Prostate cancer is the most common cancer in men, and androgen deprivation therapy (ADT), the standard

treatment, promotes severe testosterone deficiency and predisposes patients to metabolic complications (Zitzmann 2009, Faris & Smith 2010, Navarro *et al.* 2015). The metabolic effect of testosterone deficiency in promoting visceral obesity and impairing insulin sensitivity in men is well established (Zitzmann 2009, Navarro *et al.* 2015). In contrast, and surprisingly, the role of testosterone deficiency in predisposing to pancreatic β cell dysfunction and therefore insulin deficiency remains ignored. This is particularly surprising, as observational studies have implicated low testosterone levels in both the development of insulin resistance and the pathogenesis of hyperglycemia and diabetes in men, and hyperglycemia requires β cell dysfunction to develop. In the Massachusetts Male Aging Study, a population-based prospective study that followed over a 1000 men aged 40–70 years for almost 10 years, the authors reported that low serum testosterone concentrations play a role in the development of T2D (Stellato *et al.* 2000). In the Rancho Bernardo study, an observational study of the association between endogenous sex hormones and the prospective development of T2D, the authors also concluded that low testosterone concentrations predicted incident T2D in older men (Oh *et al.* 2002). Consistent with the role of endogenous testosterone in favoring glucose homeostasis in men, two large randomized control trials (RCTs, over 200 subjects) assessing the effect of testosterone therapy on hyperglycemia in hypogonadal patients with T2D revealed a dose-dependent improvement in blood glucose in patients randomized to testosterone (Jones *et al.* 2011, Hackett *et al.* 2014). Smaller RCTs have not consistently reported that testosterone therapy improved glycemic control in hypogonadal men with T2D (Grossmann *et al.* 2015). However, in most of these smaller studies, testosterone deficiency was moderate, diabetes was already well-controlled or the population was heterogeneous, and testosterone deficiency was not the primary driver of T2D development. Overall, systematic reviews and meta-analyses are consistent with a beneficial effect of testosterone therapy in improving glucose homeostasis in men with T2D and primary hypogonadism (reviewed in Harada 2018).

In contrast to patients with hypogonadism and T2D, patients with prostate cancer treated with ADT exhibit primary testosterone deficiency, allowing studies to prospectively assess the direct role of testosterone depletion on diabetes development. The goal of ADT is to suppress testosterone production by bilateral orchidectomy or by using gonadotropin-releasing hormone (GnRH) analogs (Perlmutter & Lepor 2007).

Alternatively, ADT can also involve blocking the actions of testosterone on the androgen receptor (AR) using AR antagonists. Both treatments, individually or in combination, produce severe cellular testosterone deficiency. Therefore, ADT represents a more rigorous experimental model than hypogonadism to assess the effect of testosterone depletion on the development of hyperglycemia. In a large population-based study of over 70,000 men aged 66 years or older (Medicare enrollees), treated for prostate cancer and without prior diagnosis of diabetes, ADT with GnRH analogs was associated with a 44% increased risk of incident diabetes (34% increased risk for orchidectomy) compared to controls with prostate cancer without ADT (Keating *et al.* 2006). Similarly, an observational study of over 37,000 men treated for prostate cancer in the Veterans Healthcare Administration showed that ADT with GnRH analogs was associated with a 28% increased risk of developing diabetes (16% increased risk for orchidectomy) compared to controls followed for prostate cancer but without ADT (Keating *et al.* 2010). Thus, ADT and the resulting severe testosterone depletion are instrumental in predisposing to hyperglycemia and diabetes in these men. Importantly, neither insulin resistance nor visceral adiposity can induce hyperglycemia without β cell failure to compensate for the insulin resistance (Polonsky 1995, UK Prospective Diabetes Study Group 1995, Weyer *et al.* 1999, Prentki & Nolan 2006). This suggests that the hyperglycemia observed in men treated with ADT is at least partially due to β cell dysfunction, leading to insulin deficiency. Therefore, the increasing reports of hyperglycemia in patients with ADT suggest that severe testosterone deficiency may predispose to β cell failure to compensate for insulin resistance. Consistent with this possibility, one study reported marked hyperglycemia and decreased β cell function following ADT among prostate cancer patients (Inaba *et al.* 2005). In another study performed in obese men with secondary hypogonadism, testosterone therapy improved β cell function (HOMA %B) and glycemic control (Dimitriadis *et al.* 2018). Taken together, these observations suggest that testosterone deficiency, such as that observed during ADT, predisposes to β cell dysfunction and failure in men and that testosterone may improve insulin secretion in these subjects.

To explore this possibility using animal models, we generated mice with selective AR depletion in pancreatic β cells (β ARKO) (Navarro *et al.* 2016). When exposed to a Western diet, male adult β ARKO mice developed fasting and fed hypoinsulinemia leading to hyperglycemia. When challenged with IP glucose, male β ARKO mice exhibited

decreased glucose-stimulated insulin secretion (GSIS), leading to an impaired ability to clear glucose. Consistent with the altered GSIS in β ARKO mice being β cell autonomous, in static incubation, testosterone enhanced GSIS in cultured male islets from human donors and mice, an effect that is not observed in β ARKO islets or in human islets treated with an AR antagonist. Further, during islet perfusion, testosterone enhanced the first- and second-phase GSIS in control mouse islets. In contrast, the increased first phase was absent in β ARKO islets, and they exhibited aberrant early second phase insulin secretion and lower global insulin secretion. Thus, AR in β cells is important to both first- and second-phase GSIS. Together, these observations suggest that testosterone is necessary for normal GSIS in men and that men with androgen deficiency (e.g., those undergoing ADT) develop β cell dysfunction that predisposes them to T2D.

In classical androgen-sensitive tissues, AR is a ligand-activated nuclear receptor that regulates gene expression through binding to an androgen response element on the promoter of target genes (Chang *et al.* 1988, Lubahn *et al.* 1988, Tilley *et al.* 1989). Interestingly, in β cells, AR exhibits a predominant extranuclear location and remains extranuclear following ligand stimulation. Using an androgen dendrimer conjugate that selectively activates extranuclear AR signaling pathways but remains outside the nucleus, we confirmed that extranuclear AR location is sufficient to enhance GSIS in male mouse and human islets (Navarro *et al.* 2016).

In β cells, GSIS is driven by glucose metabolism through glycolysis and oxidative phosphorylation, which generate ATP (Ashcroft 1980) and trigger intracellular $[Ca^{2+}]_i$ influx. Interestingly, testosterone activation of AR in β cells potentiates GSIS independently of increases in cellular ATP, membrane depolarization and $[Ca^{2+}]_i$ influx. Rather, testosterone enhances GSIS from cultured islets by increasing cAMP accumulation (Navarro *et al.* 2016). Interestingly, the insulinotropic effect of testosterone alone observed in mouse and human islets is not observed in insulin-secreting INS-1 cells, even though these cells express AR. This observation suggests that the insulinotropic effect of testosterone requires a secreted factor, produced by islet non- β cells and acting on β cells, to facilitate the effect of testosterone in a paracrine manner. For that reason, we explored the possibility that AR action in β cells amplifies GLP-1R signaling to increase cAMP production. We reasoned that because GLP-1 is secreted by α cells (Liu *et al.* 2011, Marchetti *et al.* 2012), testosterone would enhance GSIS in cultured islets but not in cultured INS-1 cells (which do not secrete GLP-1). This led to the

discovery that the insulinotropic effect of testosterone via AR in islet β cells is dependent on activation of the GLP-1 receptor (GLP-1R) by islet-derived GLP-1, as it is abolished in the presence of a GLP-1R antagonist (Navarro *et al.* 2016). This is consistent with the observation that male β ARKO mice exhibit blunted GSIS and glucose intolerance in response to parenteral glucose, which does not activate gut GLP-1 secretion. It also suggests that testosterone amplifies the insulinotropic effect of islet-derived GLP-1 *in vivo*. Further, in cultured mouse and human islets, testosterone also amplifies the insulinotropic effect of exogenous GLP-1. This paracrine model is consistent with studies showing that in mice, gut GLP-1 acts locally in a paracrine manner through a gut-brain-islet axis to enhance insulin secretion (Smith *et al.* 2014). Therefore, a model is emerging in which testosterone provides fine-tuning of insulin secretion in males by enhancing the β cell insulinotropic actions of GLP-1 (Fig. 1). Morimoto *et al.* reported that testosterone stimulates islet insulin synthesis (Morimoto *et al.* 2001). However, because they used testosterone (which, unlike dihydrotestosterone, is converted into estrogens), the effect on insulin synthesis was likely due to testosterone aromatization to estrogen acting on ERs (Wong *et al.* 2010).

Surprisingly, male rats with castration-induced testosterone deficiency exhibit a decrease in β cell mass due to increased apoptosis and decreased proliferation, but this is not observed in castrated male mice (Harada *et al.* 2018). Similarly, male β ARKO mice show no alteration in β cell mass (Navarro *et al.* 2016).

The evolutionary and biological basis for testosterone stimulation of insulin secretion in males is likely to promote anabolism, since both testosterone and insulin are anabolic hormones. Testosterone secretion is pulsatile and is acutely stimulated by mating and dominance (Archer 2006), both of which require optimal energy stores. Likely, testosterone pulses have enduring actions to sensitize β cells by raising the basal level of cAMP. Therefore, the integration of androgenic and metabolic signals could be an evolutionary strategy to enhance muscle anabolism and glycogen storage in males when food is available. Thus, pulsatile testosterone secretion could constitute another layer of regulation that affects β cell function (Wortham & Sander 2016).

The AR is also important for male β cell health. The AR-dependent gene network was investigated in β cells following a high-throughput whole transcriptome sequencing (RNA-Seq) in islets from male β ARKO and control mice (Xu *et al.* 2017). AR-deficient islets exhibited altered expression of 214 genes (DEGs)

Figure 1

Mechanism of testosterone insulintropic action in β cell. Testosterone action on an extranuclear AR in β cell amplifies the insulintropic action of islet-derived GLP-1 by increasing cAMP production and PKA activation.

with a fold change >2 . A third of these genes code for proteins involved in inflammation and cellular stress, demonstrating that islets lacking AR are adapting to injury. These include *Fgf21* (Wente *et al.* 2006), *Lcn2* (Chang *et al.* 2013), osteoprotegerin (Maruyama *et al.* 2006, Reid & Holen 2009), chemokine ligands 5 and 10 (Schulthess *et al.* 2009, Nunemaker *et al.* 2014), several interferon-gamma-induced guanylate-binding proteins (Kim *et al.* 2016), intra-islet proinflammatory cytokines and associated receptors like interleukin-1 β , the interleukin 22 receptor- α 1 (Shioya *et al.* 2008), the interleukin-1 receptor antagonist (Dayer-Metroz *et al.* 1989) and interleukin-10. A fifth of dysregulated genes are involved in β cell function. These include genes coding for G-protein-coupled receptors such as *Gpr161* (Bachmann *et al.* 2016), *Gpr126* (Mogha *et al.* 2013), *Gpr26* (Zhang *et al.* 2011), ion channels altering membrane polarization like the potassium inwardly-rectifying channel, subfamily J, member 5 (*kcnj5*), the potassium voltage-gated channel, subfamily Q, member 1 (*kcnq1*) (33) and *trpc4* (Islam 2011). Dysregulated genes also code for proteins involved in β cell exocytosis machinery such as synaptotagmin-10 (Cao *et al.* 2011), rabphilin 3a (Arribas *et al.* 1997) and enzymes involved in glucose metabolism, hexokinase 2, hexokinase domain containing 1 (Ludvik *et al.* 2016) and glucokinase-binding protein 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (Arden *et al.* 2008).

Taken together, the studies described above demonstrate that testosterone action via AR is necessary for β cell health and normal GSIS in male mice, and probably also in men. Therefore, we propose that moderate androgen deficiency in men promotes adiposity and insulin resistance, but with moderate β cell dysfunction, and the incidence of T2D is mild. However, during severe androgen deficiency resulting from ADT, men display a more profound β cell dysfunction that further accelerates the progression toward T2D (Fig. 2).

These findings have clinical and therapeutic implications. Selective androgen receptor modulators (SARMs) are in development to provide androgen therapy for age-related frailty with androgenic anabolic activity in muscle and bone, but without androgenic stimulation of the prostate (Mohler *et al.* 2009). Obviously, the design of SARMs with AR agonistic action in β cells represents a therapeutic avenue to prevent androgen deficiency-related diabetes in men.

Surprisingly, despite AR protein expression in islets and β cells, and functional studies described earlier demonstrating the importance of AR in GSIS *in vivo*, genome wide transcriptome analyses of mouse islets have failed to detect appreciable levels of AR mRNA (Xu *et al.* 2017). This discrepancy is likely related to tissue-specific AR mRNA instability (Krongrad *et al.* 1991, Yeap *et al.* 1999, 2004) or the high glucose-induced AR mRNA degradation under islet culture conditions (Harada *et al.* 2018).

Figure 2

Mechanism of diabetes in men with androgen deficiency. Moderate androgen deficiency during aging predisposes men to increased adiposity and insulin resistance leading to metabolic syndrome. During severe androgen deficiency such as androgen depletion therapy (ADT), the additional β cell dysfunction predisposes to diabetes.

Testosterone action in β cells in women

The association between testosterone excess and the development of hyperglycemia in women has been known for nearly a century (Achar & Thiers 1921). Polycystic ovarian syndrome (PCOS), the main cause of testosterone excess, predisposes women to T2D (Ehrmann *et al.* 1999, Legro *et al.* 1999, Rubin *et al.* 2017). In syndromes of extreme insulin resistance, and in obese women with PCOS, insulin resistance is the driver of the ovarian production of androgens (Spiegelman & Flier 1996); however, in the most common form of PCOS, androgen excess is instrumental in promoting hyperglycemia. As discussed in the previous section for males, the development of hyperglycemia in women with PCOS suggests that androgen excess promotes β cell dysfunction in women. In fact, clinical evidence suggests that this is the case. First, women with hyperandrogenemia exhibit either higher basal insulin secretion and decreased post-prandial insulin secretion (O'Meara *et al.* 1993) or exaggerated acute insulin response to glucose (Dunaif & Finegood 1996). These alterations in β cell function are not explained by insulin resistance. Rather, they are closely associated with testosterone levels (Holte *et al.* 1994). Finally, there is a robust relationship between β cell dysfunction and testosterone concentrations in these women (Goodarzi *et al.* 2005, Zhang *et al.* 2018). Since the AR is expressed in β cells in females, this raises the possibility that excess testosterone produces insulin hypersecretion and β cell dysfunction. Consistent with this possibility, Mishra *et al.* observed that female rats exposed to androgen excess using dihydrotestosterone

(DHT) exhibit hyperinsulinemia through an increase in the transcription of the insulin gene in pancreatic β cells (Mishra *et al.* 2018). Testosterone excess may predispose women to T2D via chronic AR activation in pancreatic islet β cells, producing insulin hypersecretion and secondary β cell failure. To explore this hypothesis, we generated female mice with testosterone excess and conditional AR deletion in β cells (β ARKO) (Navarro *et al.* 2018). Under conditions of Western diet feeding, control mice with chronic testosterone excess developed abnormalities characteristic of early T2D. They displayed fasting and fed hyperinsulinemia associated with exaggerated GSIS and insulin resistance. Accordingly, these mice developed compensatory β cell hyperplasia with increased β cell mass. However, they also developed secondary β cell failure due to a failed attempt at compensation for insulin resistance, leading to hyperglycemia in the fasting and fed state and during a glucose challenge. In contrast, in female β ARKO mice, testosterone did not produce fasting hyperinsulinemia. These mice remained normoglycemic in the fasting and fed states and during a glucose challenge, demonstrating that, during testosterone excess, AR activation in β cells is necessary for the development of hyperglycemia in female mice. Although testosterone activation of AR in neurons produced peripheral insulin resistance in these mice, evidence supports the role of AR activation in β cells in the development of β cell failure. First, acute testosterone exposure produces insulin hypersecretion in an AR-dependent manner in cultured female mouse and human islets incubated in high glucose. In addition, testosterone enhanced both first- and second-phase insulin secretion during female mouse islet

Figure 3

Summary of the bidirectional modulation of β cell function in males and females. In males, testosterone action in β cells increases GSIS by enhancing GLP-1 insulinotropic action, prevents inflammation and promotes β cell health. In females, testosterone excess in β cells promotes insulin hypersecretion, mitochondrial dysfunction, oxidative stress and predisposes to β cell dysfunction and failure.

perfusion. *Second*, testosterone enhances mitochondrial respiration and oxygen consumption in female mouse cultured islets, and accordingly, chronic testosterone excess *in vivo* produces islet oxidative injury via AR in β cells. Female mice exposed to chronic testosterone excess become more susceptible to additional islet oxidative stress induced by either a Western diet or streptozotocin, in a manner dependent on AR in β cells (Navarro *et al.* 2018). Further, female rats exposed to DHT excess exhibit significant mitochondrial dysfunction with decreased mitochondrial DNA copy number, increased reactive oxygen production and downregulation of mitochondrial biogenesis (Mishra *et al.* 2018). Together, these studies suggest that, in the presence of prior or additional islet metabolic stress, the deleterious effect of chronic AR activation by testosterone causes β cell hyperfunction, oxidative stress and mitochondrial dysfunction, which predisposes to secondary β cell demise in female mice. Additionally, hyperglycemia-induced inflammation further deteriorates β cell function in women with PCOS (Malin *et al.* 2015).

In addition to adult androgen excess, developmental androgen excess in female mammal fetuses programs female β cells *in utero* via AR (Mauvais-Jarvis 2016). The developmental effect of testosterone alters insulin secretion in adult female offspring, leading to basal hyperinsulinemia (independent from insulin resistance) but reduced insulin secretion in response to β cell dysfunction, as observed in adult females with androgen excess.

Conclusion and future perspectives

The studies reviewed here demonstrate that testosterone acts in β cells to differentially modulate β cell function in males and females. In males, physiological concentrations of testosterone enhance GSIS in a physiological manner, and loss of AR action in β cells produces insulin deficiency, which predisposes to diabetes. In contrast, in females, increasing circulating testosterone concentrations to levels observed in males activates AR in β cells to enhance GSIS in a non-physiological manner, leading to mitochondrial dysfunction, oxidative stress and ultimately resulting in β cell dysfunction that predisposes to diabetes. Further studies are needed to unravel the molecular determinants of this bidirectional modulation of β cell function in male and females. The actions of testosterone in male and female β cells are summarized in Fig. 3.

Declaration of interest

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

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