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Estrogen and androgen receptors: Regulators of fuel homeostasis and emerging targets for diabetes and obesity

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Abstract

Because of the increase in life expectancy, the contribution of age-related estrogen or androgen deficiency to obesity and type 2 diabetes will become a new therapeutic challenge. This review integrates current concepts on the mechanisms through which estrogen receptor (ER)s and androgen receptor (AR) regulate energy homeostasis in rodents and humans. In females, estrogen maintains energy homeostasis via ERα, and ERβ by suppressing energy intake and lipogenesis, enhancing energy expenditure and ameliorating insulin secretion and sensitivity. In males, testosterone is converted to estrogen and maintains fuel homeostasis via ERs and AR, which share related functions to suppress adipose tissue accumulation and improve insulin sensitivity. We argue that ERs and AR are targets to prevent age-related metabolic disorders.

Contribution of sex hormones to metabolic diseases

Increased food supply and decreased physical activity have resulted in a worldwide epidemic of obesity. As a consequence of these environmental changes, the incidence of type 2 diabetes (T2D) is on the rise [1]. In addition, a disorder involving increased visceral adipose tissue, hyperlipidemia, insulin resistance, and hypertension, namely, the metabolic syndrome, has emerged [2]. There is a concerted interaction between sex/reproduction and energy metabolism [3]. First, extreme conditions of disrupted energy balance such as obesity on one hand of the spectrum, or anorexia leading to cachexia on the other, both negatively impact fertility. Second, there are fundamental aspects of energy metabolism that are regulated differently in males and females [4]. To cite one critical example, female mammals bearing the burden of gestation and lactation have been favorably affected during evolution to resist the loss of body energy stores during prolonged periods of food scarcity and therefore deposit adipose tissue in the lower subcutaneous area, with lower lipolytic activity. Conversely, males deposit adipose tissue in visceral areas, with greater lipolytic activity to be able to mobilize energy stores promptly for muscle activity. It is believed that the circulating gonadal hormones, specifically androgen and estrogen, control these sex differences in energy balance between the onset of puberty and menopause. Because of the dramatic increase in life expectancy, women will spend the second half of their life, after

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menopause, in estrogen deficiency which predisposes to the metabolic syndrome and T2D [5]. Men will also spend a significant part of their life in age-related androgen deficiency.

Although no clear relationship exists between the gradual loss of T production and T2D, androgen deficiency clearly predisposes men to the metabolic syndrome [6]. Therefore, the contribution of sex hormone deficiency to metabolic diseases will become a new therapeutic challenge of the 21st century. Understanding how estrogen and androgen contribute to fuel homeostasis via their receptors promises to yield critical therapeutic applications. This review integrates current concepts on the role of estrogen, androgen and their receptors in regulating energy homeostasis in male and female rodents and humans. We also discuss how estrogen receptor(ER)s and androgen receptor (AR) are important targets for age-related metabolic disorders.

Estrogen receptors

Mechanism of ER action

In healthy premenopausal women, 17β-estradiol (E2) is produced by the ovaries by the aromatization of androstenedione to estrone, followed by conversion to E2. In these women, E2 functions as a circulating hormone that acts on distant target tissues. In post-menopausal women, however, when the ovaries fail to produce E2 and in men, E2 is produced in extra gonadal sites, mainly adipose tissue, bone, vessels and brain from the local tissue aromatization from circulating testosterone (T) [7]. Therefore, in males and females, T should be considered a circulating prohormone that is locally converted to either E2 acting on ERs, but also to 5α-dihydrotestosterone (DHT), the main ligand of the AR. Although DHT cannot be aromatized to estrogen, the situation is complicated by the fact that DHT can still be converted to a “second estrogen”, 5alpha-androstane-3beta,17beta-diol that acts on ERs [8]. The ER exists in two main forms, ERα and ERβ, which have multiple isoforms and exhibit distinct tissue expression patterns and functions [9]. In the classical ER signaling pathway, E2-activated ER binds as a homodimer to an estrogen response element (ERE) in target promoters or indirectly to an AP-1 or Sp-1 response element through association with other transcription factors, like Fos/Jun, that tether the activated ER to DNA [9]. This classical, “genomic” mechanism typically occurs within hours, leading to up- or down-regulation of gene transcription. E2 can also activate rapid signals, acting within minutes or seconds via extranuclear and membrane-associated forms of ERs and the G protein-coupled estrogen receptor (GPER), leading to activation of ion channels and protein kinases [10]. Although reproductive functions are mostly mediated via classical nuclear ERs acting as ligand-activated transcription factors, a large component of ER actions related to energy metabolism also involves extranuclear ERs, indirectly modulating gene expression or acting independently of nuclear events [11].

ERs control of energy intake and expenditure

The documented anti-obesity effects of E2 *in vivo* are centrally mediated. Surprisingly, the major models of estrogen deficiency and resistance do not exhibit hyperphagia. Thus, mice of both sexes lacking the aromatase enzyme, that cannot synthesize E2, develop obesity but show no hyperphagia or reduced energy expenditure. Rather, they exhibit a reduced spontaneous physical activity and a decrease in lean body mass [12]. Similarly, ERα deficiency in male and female mice causes obesity without hyperphagia but with decreased energy expenditure [13,14]. In male and female rats, Debbie Clegg made the observation that E2 enhances the ability of centrally administered leptin to suppress food intake [15]. This “leptino-mimetic” function of E2 is best observed in leptin-deficient (ob/ob) and leptin resistant (db/db) mice of both sexes, in which E2 decreases food intake and increases energy expenditure, resulting in a reduction in body weight [16]. The anorectic function of

exogenously-administered E2 is present in female WT mice and is lost in female ERα-deficient mice, demonstrating that ERα activation is anorexigenic [17]. Thus, loss of ERα action produces a predominant decrease in energy expenditure while conversely, increasing ERα signaling by raising serum E2 concentrations both suppresses energy intake and increases energy expenditure. E2 also suppresses food intake through ERβ food intake since the anorectic effect of intracerebroventricular injection of E2 is blocked by co-administration of ERβ antisense oligodeoxynucleotides in female rats [18].

The precise anatomic site of ER suppression of body weight in the brain is still unknown. The arcuate nucleus (ARC) is a key hypothalamic area for mediating leptin's inhibition of food intake. It contains first-order, leptin-responsive, anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons. Tamas Horvath and coworkers showed that E2 triggers excitatory inputs to POMC neurons in the ARC of female rodents [16]. However, E2 does not seem to suppress food intake via action on ERs in ARC POMC neurons. In fact, it was recently suggested that E2 anorexigenic function in female mice is mediated via a decrease in hypothalamic orexigenic NPY and AgRP, but independent of ER action on ARC NPY and AgRP neurons, since these cells do not express ERα [19]. Most importantly, E2, acting via ERα in nucleus tractus solitarius neurons of the brainstem, is sufficient to inhibit feeding in female rats, suggesting that E2 anorectic function could originate in the hindbrain [20]. E2 stimulation of energy expenditure could involve both ERα and ERβ since silencing of ERα in the hypothalamus of female rodents reduces energy expenditure and produces obesity without hyperphagia [21], while the administration of an ERβ-selective agonist to high fat diet (HFD) fed female mice increases expression of the thermogenic uncoupling protein-1 in brown adipose tissue and reduces obesity [22]. Evidence points toward a site of action in the ventromedial nucleus of the hypothalamus (VMH) for ERα, since silencing of ERα in the VMH reduces energy expenditure [21]. Unlike in the case of ERα and ERβ, the role of G protein-coupled ER (GPER) in body weight regulation still needs validation. In one study, female mice lacking GPER developed obesity [23]. However, the obesity phenotype was observed in only one of the four GPER mutant mouse lines studied [24]. The signaling mechanisms of ER actions in hypothalamic neurons are not fully elucidated, but available evidence suggests that it involves extranuclear ERs. First, E2 triggers a rapid increase in excitatory inputs to POMC neurons in the ARC *in vivo*, consistent with rapid, extranuclear or membrane initiated actions [16], and accordingly, E2 can suppress NPY in clonal hypothalamic neurons via a membrane form of ERα [25]. Second, an E2-responsive, Gq-coupled membrane receptor (Gq-mER) is involved in mediating the anorectic effects of E2 on food intake and body temperature in hypoestrogenic female rodents [26,27].

ERs suppress lipogenesis in white adipose tissue and liver

E2 also suppresses white adipose tissue (WAT) accumulation by decreasing fatty acid and triglyceride synthesis or lipogenesis. Greenberg and coworkers showed that *in vivo* treatment with E2 reduces adipocyte size in ovariectomized female mice by reducing fatty acid uptake (down-regulation of lipoprotein lipase), reducing lipogenesis (down-regulation of acetyl-coA carboxylate and fatty acid synthase), and increasing catecholamine-stimulated lipolysis [28]. Similarly, E2 suppresses lipogenic genes and triglyceride accumulation in WAT and liver in HFD-fed [29] and leptin-resistant female mice [30]. Interestingly, this effect is reproduced by ERβ, but not ERα, selective agonists [22,31]. ERs are expressed in adipocytes and hepatocytes of both sexes, and extensive evidence demonstrates that E2 has direct effects on cultured adipocytes with the overall effect of inhibiting adipogenesis and lipogenesis [32]. Thus, the E2 effects described above could result from ER action in peripheral tissues. Still, the exact contribution of E2 anti-lipogenic effects *in vivo* resulting from direct ER action in WAT and liver or from central ER action affecting adipose and

liver via the autonomous system is still unknown. Although the overall effect of E2 is to decrease WAT accumulation, E2 favors subcutaneous WAT accumulation via central [15] and peripheral mechanisms in both sexes [32]. ERβ is anti-lipogenic and anti-adipogenic. ERβ-deficiency favors WAT accumulation in female mice during high fat feeding by increasing PPARγ signaling in WAT, thus demonstrating that ERβ acts directly on adipocytes *in vivo* and is a negative regulator of PPARγ [33]. In addition, ERβ–selective ligands show PPARγ antagonistic actions in adipocytes mediated though a mechanism involving ERβ competing with PPARγ for peroxisome-proliferator-activated receptor-γ coactivator 1 (PGC1)α [22].

ERs improve insulin sensitivity

E2, at physiological concentrations, favors insulin sensitivity, and E2 deficiency and/or resistance provokes insulin resistance. Perhaps the best evidence is that men lacking E2 production secondary to mutations in the aromatase gene or men harboring E2 resistance secondary to genetic ERα deficiency develop insulin resistance and/or glucose intolerance [34,35]. Accordingly, male and female mice with E2 deficiency or E2 resistance by elimination of the aromatase or ERα genes develop insulin resistance [12,13]. The cause of insulin resistance induced by E2 deficiency or resistance is probably multifactorial. In one study, female mice lacking ERα did not show insulin resistance in skeletal muscle but exhibited decreased insulin suppression of hepatic glucose production (HGP) during a euglycemic, hyperinsulinemic clamp in anesthetized mice, suggesting that ERα deficiency provokes hepatic insulin resistance [36]. Andrea Hevener and coworkers, however, reported that ERα-deficient female mice accumulate pro-inflammatory lipid intermediates in skeletal muscle leading to marked muscle insulin resistance with minor alterations in liver insulin sensitivity during euglycemic, hyperinsulinemic clamp conditions in conscious mice [14]. In addition, decreased expression of the insulin-sensitive glucose transporter GLUT4 is observed in skeletal muscle of male ERα-deficient mice, which may contribute to the muscle insulin resistance observed in these mice since GLUT4 is essential to insulin-sensitive glucose transport in skeletal muscle and WAT [37]. E2 treatment improves insulin resistance in female mice fed a high fat diet [29,38] and in obese female mice with genetic leptin resistance [30] through a pathway at least partially dependent on ERα [31,38]. E2 treatment also reduces HFD-induced insulin resistance in skeletal muscle by fifty percent during hyperinsulinemic euglycemic clamp in an ERα-dependent manner [38]. However, as discussed, E2 also suppresses lipogenesis and steatosis in liver of HFD-fed [29] and leptin resistant mice [30] suggesting that it protects from insulin resistance by preventing ectopic lipid accumulation (lipotoxicity). In summary, ERα deficiency decreases GLUT4 expression in skeletal muscle and impairs lipid homeostasis in skeletal muscle and liver of rodents, thus decreasing insulin's ability to suppress HGP and to promote skeletal muscle glucose utilization. Accordingly, activation of ERα during HFD and genetic leptin resistance improves insulin resistance induced by ectopic lipid accumulation in skeletal muscle [29,30,31,38]. Still, the effect of ERα in mediating insulin sensitivity via central mechanisms remains to be determined. In absence of ERα signaling, ERβ could promote insulin resistance in skeletal muscle. Ovariectomy in hyperestrogenic female ERα-deficient mice (which suppresses E2 action though ERβ), improves glucose tolerance and insulin sensitivity [39] and administration of an ERβ-selective agonist in male E2 deficient ArKO mice decreases skeletal muscle GLUT4 expression [37]. Accordingly, administration of tamoxifen, acting as an ERβ antagonist in male ERα-deficient mice, increased GLUT4 expression and improved insulin sensitivity [40]. Interestingly, ERs modulate GLUT4 expression in WAT and skeletal muscle in a tissue-specific way. While ERβ-mediated repression of GLUT4 predominates in skeletal muscle, ERα-mediated induction of GLUT4 predominates in WAT [40].

Finally, recent evidence indicates that ERβ-deficiency protects against diet-induced insulin resistance in male mice by increasing PPARγ signaling in adipose tissue, which indirectly improves skeletal muscle insulin action by promoting lipid accumulation away from muscle and into adipose tissue [33].

The physiological and genetic evidence argues that E2 and ERα favor insulin sensitivity in rodents and humans of both sexes when E2 concentrations stay within a tight physiological window. Conversely, high doses of estrogens provoke insulin resistance [41,42]. In fact, two recent studies have reported that in postmenopausal women, higher plasma levels of E2 (associated with higher T levels) were strongly and prospectively related to increased risk of developing T2D [43,44].

ERs favor β-cell function and survival

The beneficial effect of estrogens on β-cell function in humans and rodents has been recently reviewed [11]. We will focus on the most important and recent developments. There are gender dimorphisms in rodent models of β-cell failure that helped us identify the function of ERs in β-cells. A classical sexually-dimorphic model of T2D is the transgenic mouse overexpressing human amyloid polypeptyde (hIAPP) in pancreatic β-cells. The hIAPP is a classical late β-cell injury in T2D. Steven Kahn and co-workers initially reported that overexpression of hIAPP in islets predisposes mice to the development of islet amyloid and hyperglycemia with a strong male predominance [45]. This led to the paradigm that suppression of E2 production by ovariectomy enhanced islet amyloid formation in female mice [46] and that conversely, E2 treatment prevents amyloid formation and β-cell failure in males [47]. In order to study the anti-apoptotic action of E2 on islets *in vivo*, we used the mouse model of β-cell injury induced by streptozotocin (STZ) and showed that circulating E2 acts as a protective hormone, preventing β-cell apoptosis *in vivo* in both sexes and at physiological concentrations [48]. ERα and ERβ are expressed in rodent and human β-cells in both sexes where they exhibit a predominant extranuclear localization [48,49,50]. E2-activated ERα prevents islet apoptosis in males and females via an ERE-independent pathway [50]. This is mediated via activation of extra-nuclear ERs with a predominant ERα effect [50]. Although the precise signaling pathways are still under investigation, it appears that ERα and ERβ prevent apoptosis via distinct pathways, independently of gene transcription or *de novo* protein synthesis suggesting that this cytoprotection happens independently of nuclear events [50,51].

GPER is present in β-cells and in one study, GPER-deficient mice displayed altered insulin release from isolated islets stimulated with pharmacological concentrations of E2. In this study, impaired glucose-stimulated insulin secretion (GSIS) was observed in GPER-deficient mice but the mice were chronically treated with E2 and insulin sensitivity was not assessed [52]. In another GPER-deficient mouse, however, we did not observe any alteration in GSIS [50]. Thus, the role of GPER in GSIS remains controversial.

Elimination of GPER predisposes to STZ-induced islet apoptosis in female mice, but not in males [50]. We and others observed that pharmacological activation of GPER by the agonist, G1, prevents oxidative stress and cytokine-induced apoptosis in cultured mouse and human islets [50,53]. G1 has recently been shown to induce the expression and to activate a small 36kDa ERα isoform lacking transcriptional activity and mediating rapid estrogen signaling, suggesting that GPER signals as an inducer of ERα36 [54]. However, the observation that G1 cytoprotection is lost in cultured GPER deficient islets further supports the functional significance of GPER itself in islet survival [50]. Recently, Nadal and co-workers reported that E2 activation of ERβ enhances GSIS in cultured islets by suppressing the ATP-sensitive potassium channel through effects on the membrane atrial natriuretic peptide receptor [55]. This finding shed new light on the role of ERβ in islet function.

The Zucker Diabetic Fatty (ZDF) rat is a classical model of T2D and a critical example of sex dimorphism. Male ZDF rats develop pancreatic β-cell failure to compensate for insulin resistance leading to overt T2D [56]. Fifteen years ago Roger Unger reported that β-cell failure in male ZDF rats is secondary to islet triglyceride accumulation leading to β-cell apoptosis, and the concept of lipotoxicity was born [57]. β-cell failure occurs almost exclusively in male ZDF rats, while female ZDF rats remain normoglycemic [57]. Interestingly, islet triglyceride content in the adult ZDF female is 70% lower than that of males [57] suggesting that E2 prevents islet lipid accumulation. Indeed, we recently reported that E2 treatment of male ZDF rats suppresses islet lipogenesis and prevents β-cell failure probably via ERα action in islets [58].

ERα is also important for insulin biosynthesis. We and others have shown that exposure to physiological concentrations of E2 increases β-cell insulin gene expression and insulin content via an extranuclear ERα-dependent mechanism involving Src and ERK kinases [49,59] and an increase in NeuroD-1 binding to the insulin promoter [59]. Thus, the elevated E2 concentration during pregnancy may participate in the islet adaptation to the increased metabolic demand by enhancing insulin biosynthesis and release via ERα and ERβ [49,55,59]. In conclusion, E2 at physiological concentrations increases insulin production and protects the pancreatic β-cells against major β-cell injuries encountered in diabetes, such as lipotoxicity, hIAPP, oxidative stress, and apoptosis.

Most ERα actions that control body weight, insulin sensitivity, and β-cell biology [12,13,14,15,[32],[34],[35],37,40,48,50] are present in both sexes, demonstrating that T aromatization in E2 acting on ERα is important to energy homeostasis in males. However, the role of ERβ has been studied in both sexes for β-cell survival only [50], and for either females for body weight regulation [18,22,33] or males for insulin sensitivity [37,40]. Therefore it is assumed that ERα and ERβ share similar metabolic function in both sexes. Figures 1 and 2 summarize these actions in women and men, respectively.

Androgen Receptor

Mechanism of AR action

Androgens influence gene transcription through the activation of the androgen receptor (AR), a ligand-activated transcription factor that subsequently binds as a homodimer with specific DNA motifs in its target genes [60]. These DNA motifs, called androgen response elements (AREs), can be classified as classical AREs, which are recognized by glucocorticoid or progesterone receptors and AR-specific AREs, which display selectivity for the AR [61]. As in the case of estrogens, over the past two decades evidence has accumulated to implicate rapid responses to androgens, dependent or independent of the AR [62].

AR prevents visceral fat accumulation in males

T deprivation in men contributes to the development of the metabolic syndrome. There is an inverse relationship between total serum testosterone and the amount of visceral adipose tissue and the metabolic syndrome [63]. This is observed in the context of age-related hypogonadism [64], inherited T deficiency [65], and androgen deprivation during treatment of prostate cancer [66].

Accordingly, in men, high T is linked to insulin sensitivity [67]. Evidence discussed in the ER section demonstrates that aromatization of T into E2 is critical to energy homeostasis in males, suggesting that T acts as a prohormone in men to provide E2 for tissue energy homeostasis. Indeed, orchidectomized male rodents treated with either T or E2 remain lean, while those treated with the pure androgen DHT (that is not aromatized to E2), develop

obesity [68]. Several lines of evidence demonstrate, however, that T has anti-obesity actions that are mediated via AR. First, men with genetic androgen resistance linked to CAG repeats in the AR gene, which decreases AR-mediated gene transcription, have elevated visceral fat [69]. Second, male mice lacking AR develop late onset visceral obesity with increased lipogenesis in WAT and liver [70,71]. Furthermore, AR is involved in adiponectin biology. Adiponectin is high in hypogonadal men and reduced by T therapy [72]. T infusion also decreases adiponectin in mice [73], an effect that is at least partially mediated via AR since adiponectin is increased in AR-deficient mice [70]. Whether AR suppression of adiponectin reflects increased adiponectin sensitivity or a decreased adipocyte number remains to be determined.

The suppressing effect of T on WAT mass in males may be indirectly mediated via AR signaling in skeletal muscle. Several lines of evidence support this scenario. First, *in vitro*, T promotes the commitment of pluripotent mesenchymal stem cells into myogenic lineage while inhibiting the adipogenic lineage via an AR-dependent mechanism [74] mediated via non-canonical Wnt signaling [75]. This androgenic anabolism involves an induction of IGF1, leading to nuclear accumulation of beta-catenin, a pro-myogenic, anti-adipogenic stem cell regulatory factor [76]. Accordingly, selective overexpression of AR in muscle cells of transgenic male rats increases lean mass with hypertrophy of type IIb fibers, increasing oxidative metabolism thus decreasing adipocyte size and WAT mass [77]. Conversely, and consistent with this model, male mice lacking AR in adipose tissue are not obese. These mice show an increased WAT production of leptin without leptin resistance [78]. Thus, activation of AR in skeletal muscle may indirectly decrease WAT mass by increasing muscle oxidative metabolism or through the release of a circulating factor.

AR action in skeletal muscle promotes insulin sensitivity in males

Apart from increasing visceral WAT, the mechanism of AR deficiency-induced insulin resistance probably involves a decrease in the transcription factor PGC1α in skeletal muscle. Indeed, PGC1α stimulates mitochondrial biogenesis and skeletal muscle oxidative fibers and is thus a molecular marker of muscle insulin sensitivity. A decrease in PGC1α expression in skeletal muscle of T2D subjects is associated with insulin resistance [79]. Similarly, in men, low T levels are associated with low PGC1α expression levels in muscle [67] and AR-deficient mice have low levels of PGC1α in tissues [70]. Thus, T deficiency promotes insulin resistance at least partially via an AR-dependent mechanism involving a decrease in PGC1α-mediated oxidative and insulin sensitive muscle fibers as well as increased visceral WAT and liver steatosis.

Central AR actions favor energy homeostasis in males

AR is expressed in the brain more abundantly in males [80]. Male AR-deficient mice develop obesity without hyperphagia but with reduced locomotor activity and energy expenditure associated with decreased brown adipose tissue thermogenesis [70]. AR suppresses lipogenesis in males, and male AR-deficient mice exhibit unsuppressed lipogenesis in muscle and liver [70,71]. AR also functions in the male hypothalamus to favor central leptin signaling. AR-deficient male mice exhibit a failure of leptin to promote STAT3 nuclear localization in ARC neurons and to suppress food intake and reduce body weight even before the onset of overt obesity [80]. In summary, in males, AR is involved in the control of WAT mass via central and peripheral effects.

AR and β-cells in males

Early studies reported that T accelerates the hyperglycemic decompensation via an AR-dependent mechanism in male mouse models of insulin-deficient diabetes in which β-cell destruction is induced by streptozotocin [81,82]. Recently, however, it was reported that

testosterone protects early apoptotic damage induced by streptozotocin in male rat pancreas and via an AR dependent mechanism [83,84]. In the later study, however, the effect of T on diabetes incidence was not reported. Therefore the role of the AR in male β-cell survival and function needs clarification. Figure 3 summarizes AR's effects on energy homeostasis in men.

Role of AR in females

The role of AR in female energy metabolism is not well characterized. While AR deficiency is reported to have no effect on body weight in female mice [85], women with complete androgen insensitivity syndrome have increased total fat mass compared to both female and male age-matched control subjects [86]. Therefore further studies are needed to determine the role of AR in female energy metabolism.

Although the consequence of AR deficiency in females in not well studied, the association between hyperandrogenicity and diabetes in women has been known for almost a century [87]. It has been postulated that excess androgen provokes insulin resistance. In women, hyperandrogenism is a risk factor for the metabolic syndrome independently of obesity and insulin resistance [88]. Furthermore, T infusion in healthy women decreases insulin-stimulated whole body glucose uptake [89]. The role of excess T in promoting skeletal muscle insulin resistance with fiber type switch has also been confirmed from studies in female rodents [90]. Hyperandrogenemia is also associated with pancreatic β-cell dysfunction [91,92,93]. In some studies of women with PCOS, β-cell dysfunction is closely associated with the degree of androgenicity, independent of insulin resistance, raising the possibility that excess T may predispose to secondary β-cell failure [92,93]. Consistent with this hypothesis, in mice, T accelerates the hyperglycemic decompensation in experimental models of insulin-dependent diabetes in which β-cell destruction is induced by oxidative stress or inflammation [81,94]. In addition, hyperandrogenemia in women with PCOS is accompanied by systemic oxidative stress [95], and excess T in female mice similarly provokes systemic oxidative stress via an AR-dependent mechanism [94]. We showed that in the presence of a prior β-cell injury, excess T predisposes female mice to β-cell failure via an AR-dependent mechanism [94] that could involve an AR present in β-cells [96]. Thus, excess AR activation in β-cells may participate in β-cell dysfunction observed in women with androgen excess.

Despite accumulated evidence that T excess alters metabolism in females, it is not clear whether T excess initiates metabolic abnormalities or perpetuates them. Indeed, treatment with AR antagonists or suppression of ovarian androgen production with GnRH analogues in hyperandrogenic women does not always improve insulin resistance [97], thereby suggesting that excess androgen in women may not be instrumental in the metabolic abnormalities but rather an aggravating factor. Further studies in this area are needed.

Conclusions and perspectives

E2 and T are critical hormonal signals maintaining energy homeostasis in both sexes, and the impact of E2 treatment on obesity and diabetes prevention is one of the most powerful observations of rodent physiology. Although men have lower circulating E2 concentrations than premenopausal women, aromatization of circulating T to E2 in target metabolic tissues equilibrates cellular E2 concentrations, and ER activation is similarly critical in both sexes in promoting fuel homeostasis. Conversely, and probably reflecting the lower circulating and cellular T and DHT concentrations in females, AR activation is weak in females and thus AR is less important. Indeed, if androgen concentrations increase in females to the level of males, this provokes excess AR activation leading to metabolic disturbances. The mechanism of this bi-directional modulation of metabolism by AR between males and

females is unknown. Because of this sex-specific stoichoimetry of ERs/AR activation, AR is primarily a male drug target, while ERs are sex non-specific drug targets to improve metabolic diseases. The major obstacle to the development of ER and AR ligands to treat metabolic diseases is the fear of hormone-dependent cancer. Further studies are thus needed to identify and develop new ligands that prevent diabetes and obesity that lack the mitogenic actions predisposing to hormone-dependent cancers. This can be achieved by targeting E2 or T to the appropriate cells or developing novel selective ER/AR modulators that retain the beneficial effects of their ligand in selected tissues while lacking the mitogenic actions in reproductive organs.

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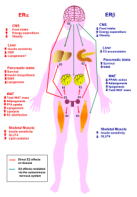

Figure 1. Metabolic effects of ERα and ERβ activation in females

Activation of ERα in the central nervous system (CNS) suppresses food intake, increases energy expenditure and decreases body weight. In addition, activation of ERα improves peripheral energy and glucose homeostasis in multiple ways by 1) preventing liver steatosis, suppressing hepatic glucose production and improving insulin sensitivity, 2) enhancing skeletal muscle lipid oxidation, GLUT4 expression and insulin sensitivity, 3) enhancing subcutaneous white adipose tissue (WAT) distribution while decreasing overall WAT mass by decreasing WAT free fatty acid (FFA) uptake, lipid synthesis and increasing lipolysis, 4) favoring pancreatic β-cell survival and function by preventing pro-apoptotic injuries and lipotoxicity, and increasing insulin biosynthesis and glucose-stimulated insulin release (GSIS). Activation of ERβ in the central nervous system (CNS) also suppresses food intake and increases energy expenditure and prevents obesity on a high fat diet. In addition, activation of ERβ affects peripheral energy and glucose homeostasis by 1) favoring pancreatic β-cell survival and function by preventing pro-apoptotic injuries and increasing GSIS, 2) preventing obesity and decreasing WAT mass, 3) promoting insulin resistance in absence of ERα activation. ERα and ERβ metabolic actions on peripheral tissues result from direct activations of ERs in these tissues or from a central ER action affecting peripheral tissues via the autonomous system CNS ERs.

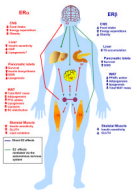

Figure 2. Metabolic effects of ERα and ERβ activation in males

Activation of ERα in males has similar effect than in females. In the central nervous system (CNS), ERα suppresses food intake, increases energy expenditure and decreases body weight. In addition, activation of ERα improves peripheral energy and glucose homeostasis in multiple ways by 1) preventing liver steatosis, suppressing hepatic glucose production and improving insulin sensitivity, 2) enhancing skeletal muscle lipid oxidation, GLUT4 expression and insulin sensitivity, 3) enhancing subcutaneous white adipose tissue (WAT) distribution while decreasing overall WAT mass by decreasing WAT free fatty acid (FFA) uptake, lipid synthesis and increasing lipolysis, 4) favoring pancreatic β-cell survival and function by preventing pro-apoptotic injuries and lipotoxicity, and increasing insulin biosynthesis and glucose-stimulated insulin release (GSIS). Activation of ERβ in the central nervous system (CNS) also suppresses food intake and increases energy expenditure and prevents obesity on a high fat diet. In addition, activation of ERβ affects peripheral energy and glucose homeostasis by 1) favoring pancreatic β-cell survival and function by preventing pro-apoptotic injuries and increasing GSIS, 2) preventing obesity and decreasing WAT mass, 3) promoting insulin resistance in absence of ERα activation. ERα and ERβ metabolic actions on peripheral tissues result from direct activations of ERs in these tissues or from a central ER action affecting peripheral tissues via the autonomous system CNS ERs.

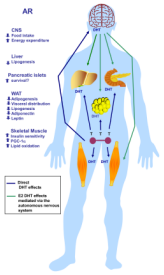

Figure 3. Metabolic effects of AR activation in males

Physiological activation of AR in the central nervous system (CNS) suppresses food intake, increases energy expenditure and decreases body weight. In addition, physiological activation of AR improves peripheral energy and glucose homeostasis by 1) preventing liver steatosis 2) enhancing skeletal muscle insulin sensitivity by increasing PGC1α expression, mitochondrial biogenesis and skeletal muscle oxidative fibers, thus increasing lipid oxidation, 3) decreasing WAT lipogenesis and visceral WAT mass. AR activation also decreases WAT adiponectin and leptin production.