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Impaired estrogen receptor action in the pathogenesis of the metabolic syndrome

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Abstract

Considering the current trends in life expectancy, women in the modern era are challenged with facing menopausal symptoms as well as heightened disease risk associated with increasing adiposity and metabolic dysfunction for up to three decades of life. Treatment strategies to combat metabolic dysfunction and associated pathologies have been hampered by our lack of understanding regarding the biological underpinnings of these clinical conditions and our incomplete understanding of the effects of estrogens and the tissue-specific functions and molecular actions of its receptors. In this review we provide evidence supporting a critical and protective role for the estrogen receptor α specific form in the maintenance of metabolic homeostasis and insulin sensitivity. Studies identifying the ER-regulated pathways required for disease prevention will lay the important foundation for the rational design of targeted therapeutics to improve women's health while limiting complications that have plagued traditional hormone replacement interventions.

Keywords

Metabolic syndrome; Estrogen action; Insulin resistance; Obesity

1. Introduction

The National Vital Statistics report from the Centers for Disease Control indicates that life expectancy has increased by 68% to 80.6 years of age for Caucasian women over the past century, with a noted gender disparity – reduced life expectancy for males of almost 5 years. Considering that menopause occurs at ~51 years (National Institutes of Health, NIA

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www.nia.nih.gov), women in the modern era are challenged with facing menopausal symptoms including hot flashes, sleep and mood disorders, and sexual dysfunction as well as heightened disease risk associated with increasing adiposity and metabolic dysfunction for up to three decades of life. Arming women with knowledge about the health consequences of ovarian failure as well as furthering our understanding of the biological actions of estrogens in reproductive and non-reproductive tissues have become critical endeavors if we wish to improve the health of women around the world. Although many researchers and clinicians have focused on the impact of replacement estrogens to ameliorate clinical symptoms and provide protective health benefit, an incomplete understanding of the tissue-specific effects of estrogen action, and estrogen receptor (ER) distribution and function contributes to our confusion and failure to advance therapeutic strategies to combat female-associated pathologies.

Because of the dramatic increase in life expectancy since the turn of the century, the contribution of sex hormone deficiency to the pathogenesis of metabolic associated diseases has become a therapeutic challenge of the 21st century. Understanding how estrogens and estrogen receptor expression contribute to energy balance, glucose homeostasis, and adipose tissue development promises to yield novel therapeutic applications. Here we review evidence in humans and rodents supporting a role of estrogens and their receptors in regulating fuel homeostasis and insulin sensitivity for the preservation of disease-free health (Fig. 1). We will also present basic research suggesting that the estrogen receptor (ER), specifically the α form of the receptor, ERα, is an important target to combat metabolic dysfunction.

2. Molecular mechanisms of estrogen receptor (ER) action

Early studies in reproductive tissues investigating the actions of estradiol (E_2) led to the paradigm of classical nuclear ERs as ligand-activated transcription factors (Fig. 2) (O'Malley, 1971). Although ERs exist in two main forms, α and β, which have multiple splice variants of unknown function, ERs exhibit tissue specificity in expression and function (Nilsson et al., 2001). The classical, or genomic mechanism of ER action, includes the ligand-activated dissociation of ER from its chaperone, receptor dimerization, and receptor binding either to estrogen response elements (ERE) in target gene promoters or to AP-1 or SP-1 response elements through association/tethering with other transcription factors bound to DNA (Fig. 2) (Safe and Kim, 2008). After binding, ER dimers interact with basal transcription factors leading to activation or repression of target gene expression. Overlap in binding sites for E_2-liganded ERα and ERβ is observed when receptors are expressed individually; however, when both ERs are present, few sites are shared. Each ER restricts the binding site occupancy of the other, with ERα dominating (Charn et al., 2010). Moreover, ligand-activated ER promotes transcription in a cyclic fashion. The repeated cycling of the receptor complex on and off target promoters in the presence of continuous E_2 stimulation may represent a mechanism of continuous sensing and adaptation to the external hormonal milieu to yield the appropriate transcriptional response (Shang et al., 2000).

In addition to classical signaling, E_2-ERα can act within minutes or seconds via extranuclear and membrane-associated forms of the receptor (Fig. 2) (Hammes and Levin, 2007).

Membrane-associated receptors are localized to caveolae where they congregate with other signaling molecules, including G proteins, growth factor receptors, tyrosine kinases (Src), linker proteins (MNAR), and orphan G-protein coupled receptors (GPCRs). In a variety of cell types, membrane and extranuclear pools of ERs activate protein kinases that phosphorylate transcription factors to promote their nuclear translocation and transcriptional action (Filardo et al., 2000; Hammes and Levin, 2007; Tiano and Mauvais-Jarvis, 2012a). The G protein-coupled estrogen receptor (GPER), or GPR30, has been reported to respond to E_2; however, its role as an ER is still controversial and thus will not be discussed in this review. Although it is thought that estrogen effects on reproductive function are almost exclusively mediated via classical nuclear ERs acting as ligand-activated transcription factors, a proportion of ER action related to energy metabolism may also involve extranuclear ERs (Fig. 2) (Liu and Mauvais-Jarvis, 2010). A central issue in the field pertaining to the tissue-specific sites of ERα action and the molecular mechanisms by which the receptor selectively activates or represses target genes remains to be resolved.

3. The impact of brain estrogen action in the regulation of energy intake and expenditure

Studies in humans and animal models have established important roles for estrogens in the regulation of metabolism. As estrogen levels decline during and following menopause, the prevalence of obesity escalates markedly (Carr, 2003; Flegal et al., 2002; Freedman et al., 2002). Ovariectomy (OVX), i.e. removal of the ovaries, leads to increased adiposity in rodents (Blaustein and Wade, 1976; Drewett, 1973; Wallen et al., 2001), that is prevented by estrogenization typically by subcutaneous implantation of a time-release estrogen pellet (Geary et al., 2001). Although OVX induces a transient increase in food intake, prevented by E_2 normalization (Clegg et al., 2003a; Gao et al., 2007), hyperphagia cannot solely account for the changes in metabolism and the development of obesity (Wallen et al., 2001). Furthermore, mice of both sexes lacking the enzyme CYP19, aromatase (aromatase catalyzes the synthesis of estradiol), develop obesity in the absence of hyperphagia. Instead, aromatase-deficient mice exhibit reduced physical activity and diminished lean body mass (Jones et al., 2000). Similarly, mice of both genders with a homozygous null mutation for Esr1 (ERα) develop obesity in the absence of hyperphagia (Heine et al., 2000; Ribas et al., 2009). This work suggests that although endogenous E_2 favors body weight homeostasis by increasing energy expenditure (Rogers et al., 2009a), exogenous estrogens may promote energy balance by influencing both energy intake and expenditure. Thus, loss of ERα action produces a predominant decrease in energy expenditure, while conversely, increasing ERα signaling by raising serum E_2 concentrations both suppresses energy intake and increases energy expenditure as illustrated in Fig. 3 and will be discussed later.

For over a century we have known that specific regions of the CNS control food intake, energy expenditure and weight gain, as lesioning of specific hypothalamic nuclei within the ventral medial hypothalamus (VMH) (Louis-Sylvestre, 1980; Smith, 2000) or lateral hypothalamus (LH) caused dramatic changes in these biological processes (Danguir and Nicolaidis, 1980; Milam et al., 1980). ERα is highly expressed in the rodent brain including the ventrolateral portion of the VMN, the ARC, the medial preoptic area (MPOA), and the

paraventricular nuclei (PVN) (Merchenthaler et al., 2004; Osterlund et al., 1998; Shima et al., 2003; Simerly et al., 1990; Simonian and Herbison, 1997; Voisin et al., 1997; Wilkinson et al., 2002). ERβ is expressed in the same hypothalamic nuclei but at significantly lower levels by comparison. The effects of E_2 on energy balance are thought to be primarily mediated by ERα, as women or female mice with mutations in the ERα gene become obese (Heine et al., 2000; Ohlsson et al., 2000). Moreover, ERα homozygosity in animals prevents the anti-obesity effects of estrogen replacement (Geary et al., 2001). These gene deletion studies are consistent with pharmacological interventions in ovariectomized (OVX) mice in which the selective ERα agonist PPT was shown to suppress food intake, in contrast to the selective ERβ agonist DPN which failed to influence feeding behavior (Liang et al., 2002; Roesch, 2006; Santollo et al., 2007).

The signaling mechanisms of ER action in hypothalamic neurons are not fully defined, but evidence suggests the involvement of both classical and extranuclear ER actions (Dhillon and Belsham, 2011; Gao et al., 2007). In the arcuate nucleus (ARC), ERα is highly expressed in pro-opiomelanocortin (POMC) neurons shown to modulate food intake, energy expenditure, and reproduction (Fig. 3) (Xu et al., 2011). POMC neurons secrete α melanocyte stimulating hormone (αMSH), which acts in the PVN and lateral hypothalamus on melanocortin 3 and melanocortin 4 (MC3/MC4) receptors to produce catabolism by reducing food intake and increasing energy expenditure (Elias et al., 1999, 2000; Elmquist et al., 1998a, 1999). ARC POMC mRNA levels fluctuate over the course of the estrous cycle, with a marked increase occurring coincident with proestrous when E_2 concentration is the highest (Bohler et al., 1991; Gao et al., 2007; Korner et al., 1999; Slamberova et al., 2004; Wise et al., 1990). Conversely, POMC levels are reduced in ERα knockout mice (Hirosawa et al., 2008). These E_2-induced synaptological rearrangements in POMC neurons are tightly paralleled with the effects of estrogens on food intake, energy expenditure and body weight (Gao et al., 2007), and appear mediated by MC4R (Polidori and Geary, 2002). Indeed, deletion of ERα in POMC neurons of mice leads to hyperphagia without affect to energy expenditure or adipose tissue distribution (Xu et al., 2011).

The ventral medial hypothalamus, VMH, is also thought to be an important neural circuit responsible for the homeostatic regulation of body weight and food intake, as estrogens have been shown to directly alter the electrophysiological properties of VMH neurons (Minami et al., 1990). Small hairpin (sh) RNA-mediated ERα gene silencing and selective ablation of ERα from SF-1 containing neurons of the VMH blunts E_2-induced weight loss, promoting increased visceral fat deposition, and reductions in energy expenditure in the absence of hyperphagia (Fig. 3) (Musatov et al., 2007). These findings support the notion that ERα signaling in VMH neurons plays an important role in regulating physical activity, thermogenesis and fat distribution.

Since leptin was first described in 1994 (Zhang et al., 1994), it has proven to be a powerful catabolic signal in the brain, inhibiting food intake and increasing energy expenditure (Elmquist et al., 1999; Myers et al., 2010; Schwartz et al., 2000). The leptin receptor (Lepr) is localized in several brain areas including the VMH and the ARC, and colocalizes with several neuropeptides known to control food intake and reproduction (Elmquist et al., 1998b, 1998c; van Dijk et al., 1996). ERα crosstalks with Lepr in the ARC (Diano et al., 1998),

which is consistent with estrogens inducing Lepr mRNA (Bennett et al., 1999), possibly by direct genomic action mediated by ERE binding in the promoter of the leptin receptor gene (Lindell et al., 2001). The extensive hypothalamic colocalization of these two receptors suggests a closely coupled interaction between peripheral derived signals in the regulation of energy homeostasis. Indeed, increased E_2 is associated with enhanced central leptin sensitivity in rodents (Ainslie et al., 2001; Clegg et al., 2003b, 2006). Although circulating leptin levels do not change appreciably during the estrous cycle, ARC Lepr expression is highest during estrous and metestrous and is inversely correlated with neuropeptide Y (NPY) mRNA expression (Bennett et al., 1999). Moreover, OVX lowers the sensitivity to central leptin when compared to normally cycling females, and this leptin resistance is prevented by E_2 replacement (Clegg et al., 2006). Analogously in male rodents, exogenous E_2 administration also increases sensitivity to central leptin (Clegg et al., 2006). The differences in central leptin sensitivity caused by the presence or absence of estrogens may occur downstream of Lepr transcription and translation, possibly at the level of STAT3, as E_2 decreases food intake and increases energy expenditure, resulting in a reduction in body weight in leptin-deficient (ob/ob) and leptin resistant (db/db) mice of both sexes (Gao et al., 2007).

NPY is an effective anabolic peptide considering that central administration of NPY potently increases food intake and decreases energy expenditure and fat oxidation (Chavez et al., 1995; Cone et al., 2001; Herzog, 2003; Levin, 1999). ARC neurons co-express NPY mRNA and Lepr protein. Leptin administration decreases, while leptin deficiency or leptin resistance increases NPY (and AgRP) mRNA, demonstrating that leptin is a critical determinant of ARC NPY function (Baskin et al., 1999). NPY neurons in the hypothalamus not only affect feeding, but also influence reproduction; therefore, E_2 can modulate both of these neuroendocrine systems by regulating NPY gene expression, NPY Y1 receptor expression (Hill et al., 2004), and NPY release (Bonavera et al., 1994). Additionally, NPY/AgRP neurons are required to mediate the anorexigenic effects of E_2 and hypothalamic expression of NPY and AgRP is tightly regulated across the estrus cycle, with the lowest levels during estrus concomitant with the E_2 peak and feeding nadir in wild type mice (Olofsson et al., 2009). Importantly, the cyclic changes in food intake and E_2-induced anorexia are blunted in mice with degenerated NPY/AgRP neurons (Olofsson et al., 2009), indicating that neurons co-expressing NPY and AgRP are functionally required for the cyclic changes in feeding across estrous cycle and that NPY/AgRP neurons are essential mediators of the anorexigenic function of E_2. Interestingly, it was shown that ERα is completely excluded from NPY/AgRP neurons in the mouse hypothalamus (Olofsson et al., 2009), suggesting that E_2 may regulate these neurons indirectly via unknown presynaptic neurons expressing ERα.

4. ERα expression in the control of adipose tissue distribution and obesity susceptibility

There is a well-described sexual dimorphism in body fat distribution as men have less total body fat but increased intra-abdominal adipose tissue compared with women who have more total fat but a higher proportion of gluteal/femoral subcutaneous (SC) adipose tissue which

is shown to be less pathogenic (Bjorntorp, 1992a, 1992b, 1992c; Bouchard et al., 1993; Enzi et al., 1986). Following menopause and the decline in circulating E_2, women gain intra-abdominal fat and develop male-pattern adiposity ameliorated by E_2 replacement therapy (Gambacciani et al., 1997; Haarbo et al., 1991a, 1991b). Additionally, adipose tissue redistribution is reported in male–female transsexuals receiving E_2 supplementation in which increased SC fat relative to intra-abdominal adipose tissue is observed (Elbers et al., 1999a). Thus, estrogens are thought to regulate fat distribution (Elbers et al., 1999a, 1999b), and this may contribute to improved metabolic profile in women receiving HRT.

Accumulation of central intra-abdominal or visceral fat ('android', or male-pattern obesity) is correlated with increased risk and mortality from diabetes and atherosclerosis (Wajchenberg, 2000). Intra-abdominal adipose tissue is thought to be metabolically and functionally different from SC adipose tissue. Indeed, compared with the SC fat, intra-abdominal adipose tissue has more efferent sympathetic axons and capillaries, per unit volume, and these capillaries drain into the hepatic portal system (Wajchenberg, 2000). Surgical removal of intra-abdominal adipose tissue in humans results in decreased insulin and glucose levels (Thorne et al., 2002) and prevents the onset of insulin resistance and glucose intolerance in male rodents (Gabriely et al., 2002). In contrast, surgical removal of SC fat tissue of equal weight has no appreciable impact on the same parameters (Gabriely et al., 2002). Teleologically, males may preferentially deposit adipose tissue in the intra-abdominal depot because of its ability to be rapidly mobilized providing a quick and abundant energy source during times of increased energy demand. In contrast, SC adipose tissue allows for efficient storage of maximal calories per unit volume of tissue. Lipid deposition into SC adipose tissue may provide an evolutionary advantage for females by extending protection during limited caloric supply in order to maintain reproductive function. Importantly, females also mobilize adipose tissue stored in SC depots to meet the caloric demands placed on the body during breast feeding. In contrast to android or male-pattern adiposity, 'gynoid' or female-pattern fat deposition is only weakly correlated with metabolic dysfunction and disease risk (Bjorntorp, 1996; Donahue and Abbott, 1987; Donahue et al., 1987; Lapidus et al., 1984; Ohlson et al., 1985). In fact, transplantation of SC fat from donor mice into visceral regions of recipient mice decreases total fat and improves glucose homeostasis suggesting that adipose-secreted factors may act systemically to improve metabolism (Tran et al., 2008).

In addition to ovarian production, estrogens are also synthesized by adipocytes (via aromatization of androgenic precursors by CYP19), and circulating levels are elevated in proportion to total body adiposity (Schneider et al., 1979; Tchernof et al., 1995). ERα is highly expressed in adipose tissue (Mizutani et al., 1994; Price and O'Brien, 1993), and targeted global deletion of the ERα gene (ERαKO) in mice of both genders promotes increased adiposity, with a near doubling of the visceral depots compared with age-matched wildtype (WT) mice (Fig. 4) (Heine et al., 2000). In contrast, mice with a homozygous deletion of ERβ (βERKO) show a body composition identical to WT mice, suggesting that ERβ may play a limited role in adipose tissue development and metabolism (Ogawa et al., 1999). Reduced ERα expression or impaired ERα function due to genetic alteration has been linked with increased prevalence of specific features of the metabolic syndrome including obesity in both male and female humans and rodents (Casazza et al., 2010; Deng

et al., 2000; Nilsson et al., 2007; Okura et al., 2003a, 2003b, 2003c; Smith et al., 1994; Yamada et al., 2002). The role of ERα in adipocytes and the phenotypic outcomes of adipose-specific ERα deletion in mice are currently under investigation by several laboratories, however initial phenotypic studies indicate that adipose tissue specific deletion of ERα increases adiposity (Drewet al., 2015; Kim et al., 2014). Whether the obesity phenotype observed in whole body ERαKO mice or in women harboring polymorphisms in ESR1 manifests as a consequence of impairment in ERα action in adipose tissue specifically and or as a secondary phenotype of ERα inactivation in other metabolic tissues remains unclear.

5. Estrogen action and insulin sensitivity

Insulin resistance is a central disorder in the pathogenesis of type 2 diabetes and a defining feature of the metabolic syndrome, a clustering of metabolic abnormalities including obesity, hypertension, glucose intolerance and dyslipidemia (DeFronzo et al., 1992; Miranda et al., 2005). Normally cycling women show enhanced insulin sensitivity compared to men when normalized to lean mass, and this is a likely contributor to the reduced incidence of type 2 diabetes in pre-menopausal women (Park et al., 2003; Yki-Jarvinen, 1984). Moreover, although a 40–50% reduction in insulin-mediated glucose disposal is consistently observed in male mice following high fat feeding (Choi et al., 2007; Hevener et al., 2007), E_2-replete females, humans and rodents, are often protected against a high fat diet and acute fatty acid-induced insulin resistance (Djouadi et al., 1998; Frias et al., 2001; Hevener et al., 2002; Hong et al., 2009). Following menopause or OVX, a precipitous decline in insulin sensitivity coincides with increased fat mass, and elevated circulating inflammatory markers, LDL, triglycerides, and fatty acids (Carr, 2003; Pfeilschifter et al., 2002; Sites et al., 2002). OVX mice and rats are insulin resistant, show impaired exercise-stimulated glucose disposal into muscle (Campbell and Febbraio, 2002), and are more susceptible to the deleterious effects of high fat diet or lipid oversupply, and these physiological consequences of OVX are prevented by restoration of circulating E_2 within a physiological concentration (Stubbins et al., 2012).

Although chronic administration of E_2 is shown to improve insulin sensitivity, at least in rodents, the acute action of E_2 to promote insulin-stimulated glucose uptake into muscle remains disputed; this despite consistent observations of E_2-induced activation of Akt and AMP-activated Protein Kinase (AMPK) (Gorres et al., 2011; Rogers et al., 2009b). Furthermore, although administration of intravenous conjugated estrogens and E_2 to postmenopausal women or OVX rats, respectively, is shown to stimulate a significant increase in glucose disposal during hyperinsulinemic–euglycemic clamp studies (Alonso et al., 2010; Van Pelt et al., 2003), ex vivo treatment of skeletal muscle with E_2 failed to recapitulate the same increase in insulin-stimulated glucose disposal (Rogers et al., 2009b). This is also in contrast to short-term E_2 effects on insulin action in myotubes from postmenopausal women and age-matched men (Salehzadeh et al., 2011). Thus, two questions remain: does E_2 enhance insulin sensitivity and what are the critical tissues of E_2 action that confer protection against insulin resistance induced by nutrient oversupply?

Similar to findings for ovarian failure in women and rodents, a reduction in circulating estrogens resulting from rare inactivating mutations or experimental deletion of Cyp19 (aromatase) in mice confers an obesity-insulin resistance phenotype (Guercio et al., 2009; Jones et al., 2000, 2007; Maffei et al., 2004, 2007; Morishima et al., 1995; Rochira et al., 2007; Smith et al., 1994; Takeda et al., 2003). The physiological and genetic evidence argues that E_2 and ERα favor insulin sensitivity in rodents and humans of both sexes when E_2 is maintained within a tight physiological concentration. Indeed, replacement or augmentation of E_2 to supraphysiological levels or over-stimulation of ERs is thought to induce insulin resistance secondary to hyperinsulinemia and or a reduction in total GLUT4 expression in muscle (Barros et al., 2008; Nadal et al., 2009). In fact, two studies have reported that in postmenopausal women, higher plasma levels of E_2 were prospectively associated with increased risk of developing T2D (Ding et al., 2007; Kalyani et al., 2009). Clearly, additional studies in rodents and humans using a dose–response strategy are necessary to better understand the interplay of steroid hormones including E_2, testosterone, and progesterone, on the regulation of metabolism and insulin action in glucoregulatory tissues.

Although, several laboratories have characterized the whole body ERαKO mouse (Fig. 4, phenotype overview), many questions still remain including the tissues responsible for conferring the severe insulin resistance-obesity phenotype. Does obesity arise from loss of ERα within adipocytes specifically or can it be driven as a secondary phenotype resulting from a loss of ERα in brain, skeletal muscle, liver, or even selective immune cells? Furthermore, does a loss of ERα specifically from myocytes drive skeletal muscle insulin resistance, or does this phenotype arise as a secondary consequence of increased adiposity and altered adipokine/cytokine release?

Although two forms of ER are expressed in many of the glucoregulatory tissues, ERα is found in much higher abundance than ERβ, as ERβ transcript is nearly undetectable in human and rodent muscle (Baltgalvis et al., 2010; Salehzadeh et al., 2011; Wiik et al., 2005). Consistent with these observations, homozygous deletion of ERβ failed to produce insulin resistance (Ohlsson et al., 2000) in contrast to the marked skeletal muscle insulin resistance observed in ERαKO animals (Fig. 4) (Riant et al., 2009; Ribas et al., 2010a). The underlying mechanism contributing to impaired insulin action in ERαKO animals remains disputed as findings reported by Bryzgalova et al. (2006), suggesting reduced total GLUT4 levels in muscle as an underlying cause for the ERαKO insulin resistance phenotype was not supported by Ribas et al. (2010a). Furthermore, despite maintenance of GLUT4 mRNA and protein, Ribas et al. reported more dramatic skeletal muscle insulin resistance in ERαKO mice than Bryzgalova et al. Work by Hevener and colleagues suggests that the skeletal muscle insulin resistance observed in ERαKO mice is predominantly due to direct effects of ERα deletion on mitochondrial function, pro-inflammatory signaling, and proximal insulin signal transduction.

Indeed, emerging findings in muscle from muscle-specific ERα knockout mice and myotubes with ERα knockdown show no alteration in GLUT4 mRNA or protein despite a marked impairment in insulin-stimulated glucose disposal. These observations in the muscle-specific ERα mouse are entirely consistent with those of whole body ERα KO mice (Figs. 4 and 5) (Ribas et al., 2010a, 2010b). Furthermore, additional studies by Barros et al.

(2006, 2008) investigating alteration in GLUT4 expression in response to ovariectomy and E_2 supplementation are in conflict with other published studies of similar design (Alonso et al., 2009; Baltgalvis et al., 2010; Campbell et al., 2003; Hansen et al., 1996; Salehzadeh et al., 2011). Given the lack of consensus ERE in the GLUT4 promoter (Barros and Gustafsson, 2011) and absence of confirmatory findings in cellular reporter and chromatin immunoprecipitation assays, the regulation of GLUT4 expression by ERα requires further investigation. GLUT4 expression is regulated by several redundant transcriptional pathways (Murgia et al., 2009; Zorzano et al., 2005). Redundancy in regulation is likely responsible for the maintenance of total GLUT4 transcript and protein levels in the absence of ERα. Maintenance of GLUT4 total protein is often observed even in the context of obesity and type 2 diabetes (Fu et al., 2009; Garvey et al., 1992, 1998; Hoeg et al., 2009). Considering the concomitant increase in ERα and GLUT4 expression observed in muscle of exercise-trained humans and mice, it is conceivable that while ERα deletion fails to impact GLUT4 expression, increased ERα action may mediate in part the training-induced increase in total GLUT4 content (Banks et al., 1992; Brozinick et al., 1993, 1994; Dela et al., 1994; Fu et al., 2009; Lemoine et al., 2002a; Rodnick et al., 1990).

Myocyte enhancer factor 2 (MEF2) expression and a functional MEF2 element in the GLUT4 promoter are critical for GLUT4 gene expression (Mora and Pessin, 2000). Furthermore, reciprocal positive regulation between ERα and MEF2 can be observed in cardiomyocytes via ERα interaction with class II HDAC (van Rooij et al., 2010). Despite complex transcriptional signal integration in the regulation of GLUT4 expression (Gan et al., 2011; Moreno et al., 2003; Murgia et al., 2009; Oshel et al., 2000; Smith et al., 2008; Zorzano et al., 2005), it is reasonable to speculate that elevated ERα action could promote increased GLUT4 transcription via heightened protein tethering with MEF2 on the GLUT4 promoter or by indirect action via AMPK (Gong et al., 2011; Rogers et al., 2009b). It is important to note that transcriptional activity of the GLUT4 promoter is quite low under basal conditions and other ovarian hormones, e.g. progesterone, are shown to play an antagonistic role in the regulation of GLUT4 expression (Campbell and Febbraio, 2002). These issues as well as the dose of E_2 administration during interventional studies (presumably off-target effects of supraphysiological doses of E_2 are deleterious to metabolism), the age and hormone status of the human subjects and rodents used are important considerations when interpreting the literature. Given the varying roles that muscle and adipose tissue play in controlling whole body metabolic homeostasis, it is likely that the interplay of transcriptional regulators of GLUT4 vary markedly between tissues. Taken together, these data suggest a potential role for ERα in enhancing GLUT4 transcription in muscle under certain conditions such as exercise, but not necessarily obligatory in the direct regulation of GLUT4 expression under basal conditions.

Collectively, work by Ribas et al. suggests that the skeletal muscle insulin resistance observed in whole body ERαKO mice and animals with a muscle-specific deletion of ERα is predominantly the result of impaired insulin signal transduction (Ribas et al., 2010b). A role for ERα in the regulation of proximal insulin signal transduction has been suggested previously as E_2 administration to insulin resistant rodents increases insulin receptor substrate (IRS)-1 abundance and insulin-stimulated tyrosine phosphorylation and as well as the phosphotylation of Akt at Ser473 (Ordonez et al., 2008; Riant et al., 2009). Akt serves

many functions in myocytes including ERα-induced regulation of myogenic differentiation (Galluzzo et al., 2009), suppression of muscle-atrophy associated ubiquitin ligases via FOXO1 inhibition (Stitt et al., 2004), and induction of genes associated with myocellular proliferation (Enns and Tiidus, 2008; Enns et al., 2008; Galluzzo et al., 2009; Kamanga-Sollo et al., 2010; Thomas et al., 2010). In breast cancer cell lines, endothelial cells and cortical neurons, ERα-specific binding and activation of PI3kinase as well as suppression of the tumor suppressor and PI3kinase inhibitory protein, PTEN, are well-established (Lee et al., 2005; Mannella and Brinton, 2006; Noh et al., 2011; Simoncini et al., 2000, 2002); however, studies on these direct interactions in skeletal muscle are limited. Additionally, E_2 acting via ERα is also shown to promote phosphorylation of p38 MAPK (Ronda et al., 2010a, 2010b), a signaling cascade shown to enhance GLUT4 intrinsic activity and glucose uptake (Furtado et al., 2002; Niu et al., 2003; Sweeney et al., 1999). Furthermore, it is possible that ERα activation of Akt and MAPK pathways may underlie in large part the E_2-mediated protection of muscle against age-induced sarcopenia (Chen et al., 2005; Leger et al., 2008; Messier et al., 2011; Sipila et al., 2001; Sorensen et al., 2001; Teixeira et al., 2003; Tiidus, 2000), exercise-induced muscle damage (Dieli-Conwright et al., 2009; Sotiriadou et al., 2006; Thomas et al., 2010; Tiidus, 2000), and myocyte apoptosis in the face of a variety of cellular perturbations (Boland et al., 2008; McLoughlin et al., 2009; Vasconsuelo et al., 2008; Wang et al., 2010). Thus, ERα stimulation of muscle growth and insulin sensitivity via direct and indirect interaction with these pathways requires further exploration.

In contrast to the protective effects of ERα, it is suggested that ERβ may promote insulin resistance in skeletal muscle when the ERβ:ERα ratio is elevated. In OVX mice, while ERα-specific activation by PPT improved muscle insulin action (Gorres et al., 2011), conversely, ligand-specific activation of ERβ by DPN failed to ameliorate insulin resistance (Gorres et al., 2011). Moreover, ovariectomy of hyperestrogenic female ERα-deficient mice was shown to improve glucose tolerance and insulin sensitivity presumably through elimination of ERβ activation by endogenous E_2 (Naaz et al., 2002). Similarly, administration of an ERβ-selective agonist to male E_2-deficient androgen receptor knockout (ArKO) mice decreased glucose uptake (Barros et al., 2006). Finally, evidence indicates that ERβ-deficiency protects against diet-induced insulin resistance in male mice by increasing PPARγ signaling in adipocytes, which indirectly improves skeletal muscle insulin action by promoting lipid accumulation in adipose tissue and diminishing ectopic lipid deposition in muscle (Barros et al., 2009; Foryst-Ludwig et al., 2008). A role for ERβ in the pathogenesis of human insulin resistance remains unknown and there is still much work to do in determining the tissue-specific interactions of these transcription factors under more physiological conditions.

6. ERα and skeletal muscle fatty acid metabolism and inflammation

Normally cycling women are protected against acute lipid-induced insulin resistance compared with estrogen-deficient women and men (Frias et al., 2001; Hoeg et al., 2011). Furthermore, muscle from premenopausal women shows enhanced insulin sensitivity despite 47% higher triglyceride content compared with age-matched men (Hoeg et al., 2009). These observations are consistent with a reduced respiratory quotient and greater reliance on the oxidation of fatty acids as a fuel source in women (Cortright and Koves, 2000). Interesting

similarities between E_2 replete women and exercise trained subjects including elevated muscle ERα expression (Lemoine et al., 2002a, 2002b; Wiik et al., 2005), heightened insulin sensitivity (Torgan et al., 1993), elevated muscle lipid tolerance (Amati et al., 2011), and enhanced oxidative capacity (Maher et al., 2010a; Turcotte et al., 1992) are consistently observed. Estrogen supplementation is shown to enhance lipid oxidation in men during acute endurance exercise (Hamadeh et al., 2005) as well as palmitate oxidation inmyotubes from male subjects ex vivo (Salehzadeh et al., 2011). The effect of E_2 to increase the expression of fatty acid transport protein FAT/CD36 and FABP as well as transcription factors and key enzymes that regulate oxidative metabolism (Campbell et al., 2003; Fu et al., 2009; Maher et al., 2010b) likely underlie these observations in male subjects. In addition, exercise and E_2 are shown to rapidly stimulate AMPK phosphorylation in both muscle and myotubes (D'Eon et al., 2008; Rogers et al., 2009b). AMPK is considered a central regulator of many cellular processes including growth, mitochondrial biogenesis, and oxidative metabolism (Hardie, 2011; Mihaylova and Shaw, 2011). Similar to the effects of E_2, the ERα-selective agonist PPT stimulates AMPK phosphorylation in muscle of female rats (Gorres et al., 2011) while OVX or whole body ERα deletion is associated with reduced skeletal muscle levels of phosphorylated AMPK (Kim et al., 2010; Ribas et al., 2010a). Muscle PPARα, PPARδ, and UCP2 expression are also reduced in whole body ERαKO mice suggesting that ERα is essential in the regulation of a coordinated program regulating oxidative metabolism. Importantly, although the impairment in muscle fatty oxidation was recapitulated in the muscle-specific ERαKO mice (MERKO), no alteration in basal p-AMPK, PPARα, PPARδ, or UCP2 was observed (Ribas et al., 2010b), thus suggesting that these specific alterations in muscle gene expression in ERαKO mice are secondary to the loss of ERα in other metabolic tissues, likely the CNS, adipose or liver. Despite these model differences, the skeletal muscle insulin resistance and bioactive lipid accumulation (triacylglycerol, diacylglycerol and ceramides) was surprisingly similar between ERαKO and MERKO. Consistent with these observations, oxygen consumption rates in C2C12 myotubes with ERα knockdown were reduced significantly. In addition, mitochondria from muscle cells depleted of ERα produced high levels of reactive oxygen species thus precipitating increased cellular oxidative stress. Collectively, these data support the notion that ERα is critical for maintaining fatty acid oxidation in skeletal muscle by mechanisms including the regulation of: (1) fatty acid transport into the cell, (2) activation of intermediary signaling critical for shifting substrate metabolism, (3) transcriptional regulators of fatty acid metabolism and mitochondrial function. Thus, ERα expression in skeletal muscle may be a central regulator of adiposity by indirect action as MERKO mice reproduced the obesity phenotype observed in the whole body ERαKO (Fig. 5).

Moreover, E_2 treatment reduces HFD-induced insulin resistance in skeletal muscle by 50% (assessed by hyperinsulinemic–euglycemic clamp) in an ERα-dependent manner (Riant et al., 2009). The mechanistic link between the accumulation of lipid intermediates, activation of inflammatory signaling cascades, and impaired insulin action is shown inmyocytes and rodent muscle, and indeed these factors are observed concurrently in obese, type 2 diabetic subjects (Adams et al., 2004; Itani et al., 2002; Wellen and Hotamisligil, 2005; Yang et al., 2009a), as well as muscle from whole body and muscle-specific ERαKO mice (Ribas et al., 2010a). Bioactive lipid intermediates including diacylglycerol and ceramides are believed to

activate stress kinases including IKKβ, c-Jun-N-terminal kinase (JNK), and certain nPKCs (Holland et al., 2007a, 2007b; Itani et al., 2002; Summers, 2006). Indeed, muscle from normal chow fed whole body ERαKO mice showed heightened inflammatory signaling as reflected by markedly increased JNK phosphorylation and TNFα transcript (Ribas et al., 2010a). In addition to the increase in bioactive lipid intermediates found in ERαKO muscle, the production of reactive oxygen species as well as the possible ERα de-repression of selective inflammatory targets within the nucleus are likely mediators of heightened muscle inflammation.

Markers of inflammation and oxidative stress are elevated in rodent models of obesity and in patients with type 2 diabetes (Donath and Shoelson, 2011; Hotamisligil, 2008). Myotubes and skeletal muscle with ERα deletion showed a marked reduction in Gpx3 expression, an antioxidant enzyme reported to scavenge hydrogen peroxide and diminish oxidative stress (Baltgalvis et al., 2010; Ribas et al., 2010a). E_2 replacement in OVX animals also increased Gpx3 expression in skeletal muscle (Baltgalvis et al., 2010). Given that Gpx3 expression levels in skeletal muscle are elevated in females compared to male (Borras et al., 2003), reduced in T2DM patients (Chung et al., 2009), are associated with insulin action and metabolic function (Chung et al., 2009), and the gene is now identified as a causal candidate for obesity (Yang et al., 2009b), additional work studying the direct role of estrogen action in the regulation of anti-oxidant enzymes appears warranted.

Although reductions in mitochondrial number and function have been implicated in the pathobiology of insulin resistance (Befroy et al., 2007; Morino et al., 2005; Patti et al., 2003; Petersen et al., 2004), and indeed gender dimorphisms in mitochondrial biology have been described (Gomez-Perez et al., 2008), whether E_2/ERα preserves insulin action by maintenance of mitochondrial integrity remains unknown. Emerging unpublished findings from the Hevener laboratory indicate that skeletal muscle ERα is critical for the maintenance of mitochondrial function and the turnover of damaged organelles. However, the mechanisms underlying these observations remain incompletely understood at the present time.

7. ERs and hepatic insulin sensitivity

Hepatic insulin resistance contributes to impaired glucose tolerance and fasting hyperglycemia of type 2 diabetes by unrestrained hepatic glucose production. Although a direct role of the liver in the insulin resistance phenotype induced by E_2 deficiency or tissue-selective ablation of ERα remains unclear. Bryzgalova et al. showed that the global insulin resistance of female mice with a homozygous ERα null mutation was due almost exclusively to impaired suppression of hepatic glucose production (HGP) during euglycemic–hyperinsulinemic clamp studies in anesthetized mice (Bryzgalova et al., 2006). In contrast, Ribas et al. reported in the same ERα-deficient female mice only modest reduction in liver insulin sensitivity during euglycemic–hyperinsulinemic clamp studies in conscious animals (Ribas et al., 2009). Thus, the possibility exists that anesthesia artificially contributed to the severe hepatic insulin resistance phenotype observed by Bryzgalova et al. in ERα-deficient mice (Bryzgalova et al., 2006). Studies in liver-specific ERα-deficient mice should provide the definitive findings required to determine the role of liver ERα in

controlling hepatic insulin action and glucose tolerance. Still, E_2 and PPT treatments ameliorate insulin resistance in genetically obese leptin resistant and high fat diet-fed mice (Bryzgalova et al., 2008; Riant et al., 2009). Numerous studies are in agreement that E_2 suppresses lipogenic gene expression, triglyceride accumulation, and steatosis in liver of HFD-fed (Bryzgalova et al., 2008; Hewitt et al., 2004) and leptin-resistant female mice (Fig. 6) (Gao et al., 2006). Interestingly, this effect is not always reproduced by the ERα, selective agonists PPT (Lundholm et al., 2008). A significant limitation of studies inducing chronic E_2 elevation is the inability to ascribe specific actions of estradiol or ERα activation to a select tissue or cell type as circulating E_2 impacts all metabolic tissues producing numerous secondary phenotypes due to extensive tissue crosstalk. Moreover, E_2, and possibly ERα, cyclicity appears critical in the regulation of gene expression and cellular function, and this cyclicity is eliminated during chronic E_2 or ERα agonist administration (Villa et al., 2012). Together, these data suggest that ERα activation protects from hepatic insulin resistance by preventing ectopic lipid accumulation in liver (lipotoxicity), but the direct involvement of ERα and the molecular mechanisms of action in hepatocytes require further investigation.

8. Estrogen action, immunity and the metabolic syndrome

Estrogens affect many immune and inflammatory conditions including auto-immune diseases (Atwater et al., 2002; Dulos et al., 2010; Gold et al., 2009; Spence and Voskuhl, 2012; Tiwari-Woodruff and Voskuhl, 2009; Yang et al., 2010) as well as immuno-modulatory responses to parasitic and bacterial infection (Calippe et al., 2010; Douin-Echinard et al., 2011; Hepworth et al., 2010; Klein et al., 2008; Lezama-Davila et al., 2008; Vegeto et al., 2010). Following OVX, immune cell infiltration and increased tissue inflammation (TNFa, iNOS and CD11c) coincided with an ~ 4-fold increase in perigonadal and inguinal fat. The T-cell marker CD3 and the Th1 cytokine interferon γ were also elevated in perigonadal fat from ovariectomized female mice (Rogers et al., 2009a) suggesting that the absence of E_2 promotes immune cell inflammation. Indeed, similar to findings in rodents, circulating levels of pro-inflammatory cytokines, are elevated in women following natural or surgical menopause (Pfeilschifter et al., 2002). In line with these studies, work by the laboratory of Pierre Gourdy showed that E_2 heightens the inflammatory response to intraperitoneal injection of thioglycollate or lipopolysaccharide, and that ERα is critical in mediating these actions as well as reducing bacterial burden through phagocytosis (Calippe et al., 2010). Taken together, these data suggest that ERα expression in immune cells is critical for mediating a variety of cellular responses necessary for normal innate and adaptive immunity.

ERα is expressed in macrophages and other immune cells known to exert dramatic effects on glucose homeostasis. Macrophages are central effector cells of innate and adaptive immunity, and over the past decade their role in modulating whole body metabolism and insulin sensitivity has taken on increasing interest (Chawla et al., 2011; Olefsky and Glass, 2010). Recently Ribas et al. investigated the impact of ERα expression on macrophage function to determine whether hematopoietic or myeloid-specific ERα deletion manifests an obesity-induced insulin resistance phenotype in mice (Ribas et al., 2011). This group sought to determine the contribution of myeloid cells to the whole body ERαKO phenotype. Indeed, altered plasma adipokine and cytokine levels, glucose intolerance, insulin resistance,

and increased adipose tissue mass were observed in animals harboring a hematopoietic or myeloid-specific deletion of ERα (Fig. 7) (Ribas et al., 2011). A similar obese phenotype with increased atherosclerotic lesions was produced in LDLR-KO mice transplanted with ERαKO bone marrow. In isolated macrophages, Ribas et al. found that ERα is necessary for repression of inflammation, maintenance of oxidative metabolism, IL4-mediated induction of alternative activation, full phagocytic capacity in response to LPS, and oxidized LDL-induced expression of ApoE and Abca1 (Fig. 7) (Ribas et al., 2011). Moreover, bone marrow-derived macrophages lacking ERα secrete factors that induce skeletal muscle and adipocyte insulin resistance in culture (Ribas et al., 2011). A major limitation in the field is the failed identification of these pro-inflammatory insulin-resistance producing substance secreted from immune cells. Thus, metabolomic and proteomic analyses will be necessary to move the field forward in this regard. It is likely that these macrophage-secreted factors include a combination of cytokines, fatty acids, and reactive oxygen/nitrogen species that act to alter metabolic function of adjacent cells in contact with or in close proximity to tissue resident macrophages.

Taken together, these data suggest that ERα expression in immune cells is critical for mediating a variety of cellular responses necessary for normal innate and adaptive immunity. When E_2 levels are low or ERα action is impaired, disease susceptibility increases as the functionality and responsiveness of critical immune cell types become compromised. Although a few direct ERα targets in myeloid cells have been identified, considering the intricate and diverse signaling by ERα as well as the complex nature and crosstalk between cell types, the impact of sex steroids on immunometabolism requires further and more sophisticated dissection.

9. Estrogen action and pancreatic β-cell function

The role of estrogens and ERs in β-cell function and the protection of β-cell mass has been previously reviewed (Tiano and Mauvais-Jarvis, 2012a), so we will focus only on the more recent developments. In rodent models, treatment with E_2 protects pancreatic β-cells against various injuries encountered in both type 1 diabetes mellitus (T1DM) and T2DM, including oxidative stress, amyloid polypeptide toxicity, lipotoxicity and apoptosis (Tiano and Mauvais-Jarvis, 2012a). Three receptors: ERα, ERβ and GPER – have been identified in rodent and human β cells. Unlike the classical nuclear ERs acting as ligand-activated transcription factors in breast or uterine cells, β-cell ERs reside mainly in extranuclear locations. They promote their effect via cytosolic interactions with kinases such as Src, ERK, and AMPK or transcription factors of the STAT family (Tiano and Mauvais-Jarvis, 2012, 2012a, 2012b; Tiano et al., 2011; Wong et al., 2010). Activation of ERα enhances glucose-stimulated insulin biosynthesis (Alonso-Magdalena et al., 2008; Wong et al., 2010) through a pathway involving Src, ERK and the stimulation of the nuclear translocation and binding to the insulin promoter of the insulintropic transcription factor NeuroD1 (Fig. 8) (Wong et al., 2010). Activation of ERα reduces de novo synthesis of fatty acids and restrains lipogenesis and accumulation of toxic lipid intermediates in islets (Fig. 8) (Tiano and Mauvais-Jarvis, 2012, 2012b; Tiano et al., 2011). This anti-lipogenic action involves extranuclear ERα activation and promotes the nuclear translocation of STAT3 leading to inhibition in the expression of the master regulator of lipogenesis, the liver X receptor

(LXR)β, and hence the expression of its transcriptional targets, sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate response element binding protein (ChREBP). The suppression of LXRβ and SREBP1c mRNA may be mediated via a membrane associated ERα working through Src and STAT3 (Tiano and Mauvais-Jarvis, 2012b). In βcells, chronic LXRβ activation promotes lipogenesis associated with lipotoxicity and apoptosis (Choe et al., 2007). Thus, ERα suppression of LXRβ expression in β-cells may account for the inhibition of lipogenesis and prevention of islet lipotoxicity (Fig. 8) (Tiano and Mauvais-Jarvis, 2012b). Moreover, ERα can also activate AMP-kinase to suppress SREBP-1c gene and protein expression (Tiano and Mauvais-Jarvis, 2012b). Thus, taken together, ERα acts via STAT3 and AMPK pathways to decrease expression and activity of the master effector of lipogenesis under conditions of glucose surplus (Tiano et al., 2011).

Additionally, ERα promotes β-cell survival from most proapoptotic stimuli encountered in the diabetic condition (Le May et al., 2006; Liu and Mauvais-Jarvis, 2009; Liu et al., 2009). Anti-apoptotic mechanisms involve a combination of rapid ERα actions mediated by protein phosphorylation (Liu and Mauvais-Jarvis, 2009; Liu et al., 2009), and a more classical genomic mechanism inducing an anti-inflammatory cascade via liver receptor homolog-1 (LRH-1) (Baquie et al., 2011). Activation of ERβ seems to predominantly enhance glucose-stimulated insulin secretion (Soriano et al., 2009, 2012) via a membrane pathway and activation of the ANF receptor promoting closure of KATP channels (Soriano et al., 2009). GPER activation, however, protects β-cells from lipid accumulation (Tiano and Mauvais-Jarvis, 2012) and promotes cell survival (Balhuizen et al., 2010; Kumar et al., 2011; Liu et al., 2009). GPER activation also enhances glucose-stimulated insulin secretion (Balhuizen et al., 2010; Sharma and Prossnitz, 2011) via activation of the epidermal growth factor receptor (EGFR) and ERK (Sharma and Prossnitz, 2011), but has no effect on insulin biosynthesis (Wong et al., 2010). However, it has been proposed that GPER induces the expression of ERα36, a splice variant of the classical long isoform of ERα66 (Kang et al., 2010), as both ERα66 and ERα36 are expressed in β-cells (Tiano et al., 2011). Thus, it is unclear whether GPER effects on β-cells are due to intrinsic GPER action or indirect effects of GPER collaborating with ERα36 at the membrane. Importantly, the beneficial effects of ER ligands on β-cell survival, function, and nutrient homeostasis described earlier in rodents, are all observed in human β-cells (Contreras et al., 2002; Kumar et al., 2011; Liu et al., 2009; Tiano and Mauvais-Jarvis, 2012a; Tiano et al., 2011).

Perhaps the translational potential of E_2 therapy in β-cell protection would be best achieved in the context of pancreatic islet transplantation (PIT). Fertile women with T1DM show E_2 deficiency compared to non-diabetic women (Salonia et al., 2006), suggesting that islet survival in T1DM women undergoing islet transplantation could be enhanced by short-term augmentation of circulating E_2. To explore this hypothesis, Mauvais-Jarvis and colleagues used a T1DM model with xenotransplantation of human islets in nude mice rendered insulin-deficient by streptozotocin. In this model a 4 week E_2 treatment protected β-cell mass and enhanced islet revascularization and engraftment (Liu et al., 2010). Thus, transient E_2 treatment provided an immediate therapeutic impact to improve PIT and achieve insulin independence with fewer islets. Studies in human subjects are warranted and considering the

short-term duration of E_2 administration, the risk of secondary complications arising in reproductive tissues is likely minimal.

10. Conclusions and perspectives

Over the past decade, a vast literature of molecular targets has emerged promising the prospect of pharmacological intervention for the restoration of metabolic homeostasis and insulin action in humans with type 2 diabetes. The inherent simplicity and elegance of using E_2 or ER agonists as therapeutic agents, at least in women, is underscored by decades of research and in depth knowledge related to biological/clinical efficacy and toxicity profiles obtained by in vivo studies of preclinical animal models and humans. Estradiol and ERα-specific agonists promote energy homeostasis, improve body fat distribution, and ameliorate insulin resistance, βcell dysfunction and inflammation. The challenge with estrogen supplementation, however, is the relatively narrow therapeutic index that is required when administered chronically. Thus, although successful in rodents, the translation of basic science advances showing amelioration of complications associated with metabolic dysfunction by E_2 described in this review becomes problematic when extending to clinical practice. However, 10 years after the WHI concluded that the risks of hormone therapy outweighed benefit, reevaluation of the WHI findings determined that the risks of breast cancer, coronary heart disease, stroke, and pulmonary embolism with estrogen-progestin treatment were overstated, and a revised position statement was issued by the North American Menopause Society (2012). The revised position statement indicating that HRT has a role in short-term treatment of menopausal symptoms led to the renewed interest in investigating the therapeutic benefits of HRT. Thus, moving forward, it will be important to determine whether short-term HRT during early menopause offers protection against metabolic dysfunction.

Additionally, it is imperative that we determine mechanistically how best to modulate specific ERα-regulated pathways involved in energy balance and glucose homeostasis and develop targeted estrogen mimetics yielding metabolic benefit without unwanted side effects. This could be achieved possibly by fusion peptides (Finan et al., 2011, 2012) or through novel SERMs that retain the beneficial metabolic effects of E_2 in desired tissues, while exerting minimal or antagonistic effects on ERs in breast and uterus. With regard to whole body metabolism and obesity, future studies should focus on identifying the critical brain sites where ERs regulate body weight homeostasis and delineate the intracellular signaling pathways that are required for estrogen action. Additionally, determining the functional role and molecular mechanism(s) of ER action in islets, immune cells, skeletal muscle, liver and adipose tissue as well as the metabolic crosstalk between these tissues may reveal additional pharmacological targets for therapeutic intervention. A major limitation in our understanding and interpretation of E_2 action is the lack of information regarding the contribution of extranuclear vs. nuclear ER actions, as well as ligand vs. non-ligand-mediated functions of estrogen receptors in metabolic tissues. Delineation of these pathways and the tissue specificity with which these signaling pathways are engaged will be critical in moving the field forward and advancing therapeutic strategies to improve women's health.

Acknowledgments

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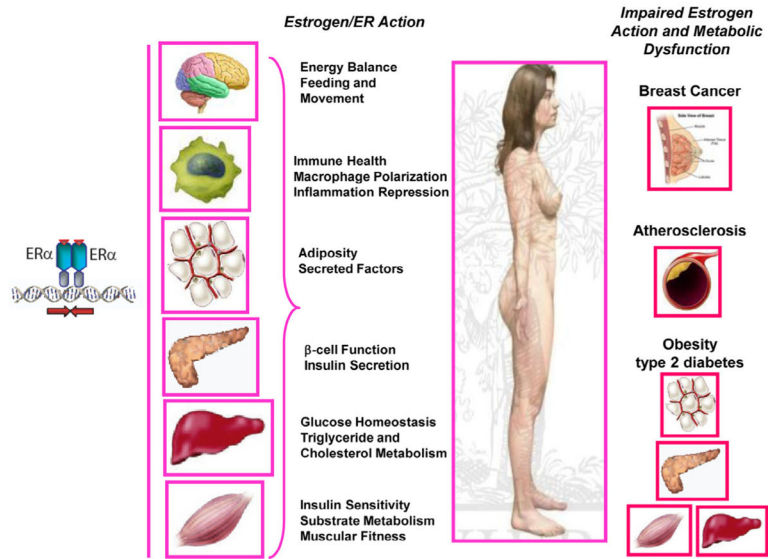
Fig. 1.

Schematic overview. The role of estrogen receptor (ER) α action in the maintenance of glucose homeostasis and insulin action for the protection against obesity and chronic diseases associated with metabolic dysfunction including atherosclerosis, type 2 diabetes and certain forms of cancer.
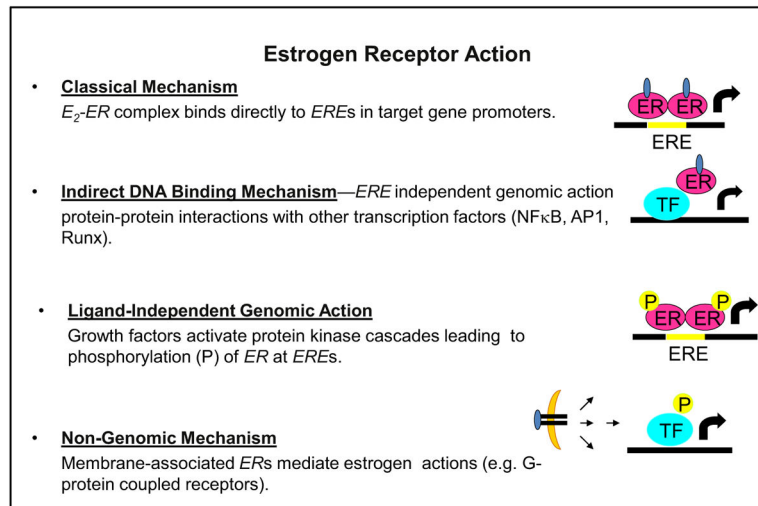
Fig. 2.
Molecular actions of ERα to activate or repress target genes by classical, DNA binding, or non-genomic actions. ERE, estrogen response element in target gene promoters; P, phosphorylation; TF, transcription factor.
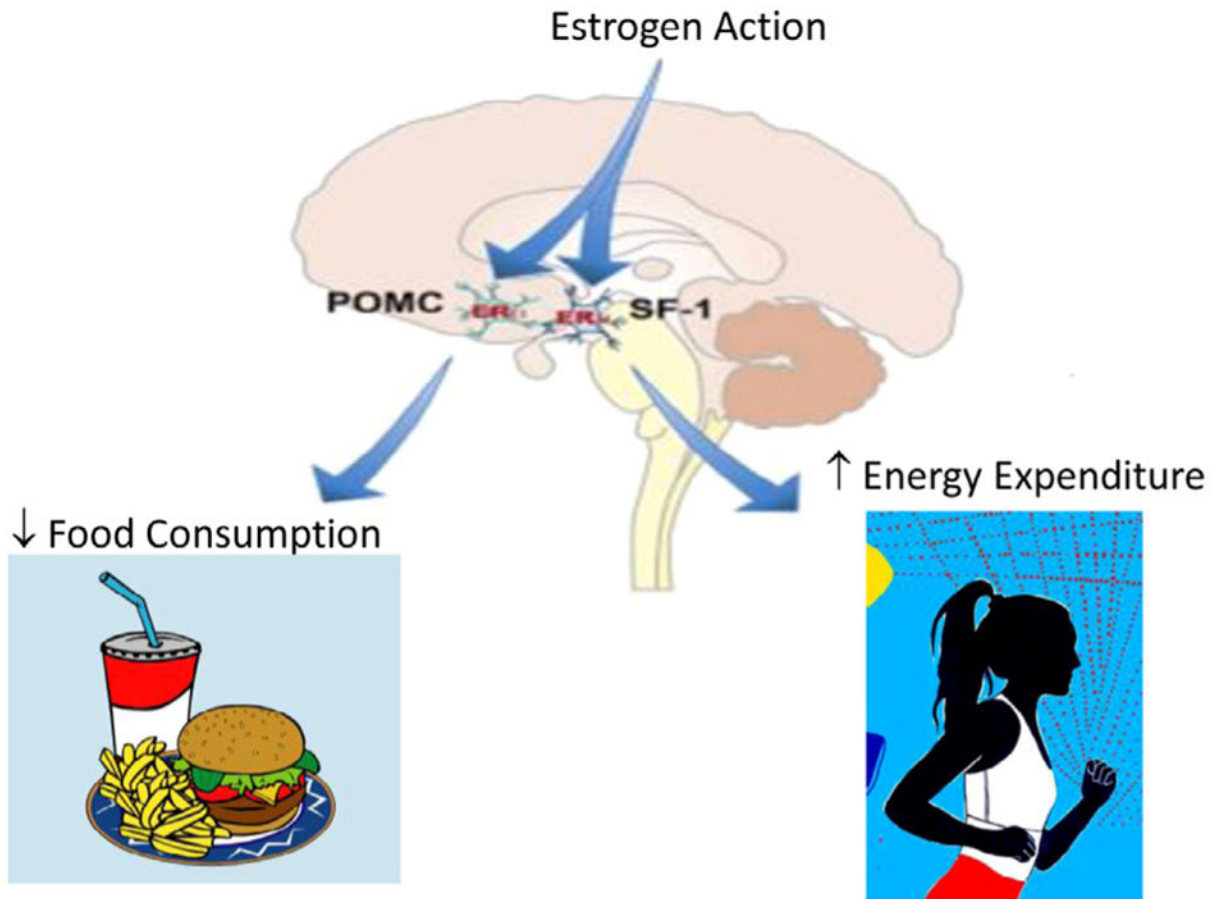
Fig. 3.
The effects of ERα action in POMC and SF-1 neurons to control feeding and energy expenditure. Findings from Xu et al. (2011).
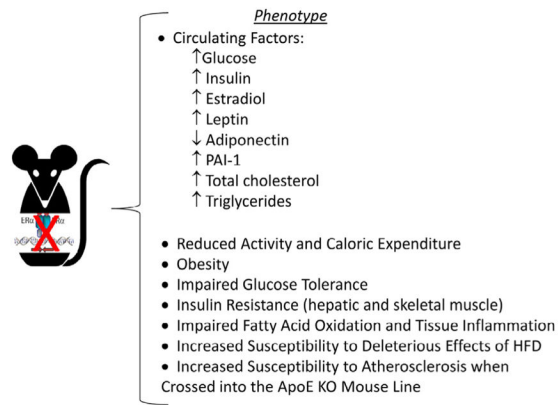
Phenotype
- Circulating Factors:
  - ↑Glucose
  - ↑ Insulin
  - ↑ Estradiol
  - ↑ Leptin
  - ↓ Adiponectin
  - ↑ PAI-1
  - ↑ Total cholesterol
  - ↑ Triglycerides

- Reduced Activity and Caloric Expenditure
- Obesity
- Impaired Glucose Tolerance
- Insulin Resistance (hepatic and skeletal muscle)
- Impaired Fatty Acid Oxidation and Tissue Inflammation
- Increased Susceptibility to Deleterious Effects of HFD
- Increased Susceptibility to Atherosclerosis when Crossed into the ApoE KO Mouse Line

Fig. 4.

ERαKO metabolic phenotype. Animals with a homozygous deletion of ERα develop insulin resistance, impaired glucose tolerance and obesity as early as 3–6 months of age and are more susceptible to the deleterious effects of HFD on metabolism and insulin action than age-matched WT mice (Heine et al., 2000; Ribas et al., 2010a).

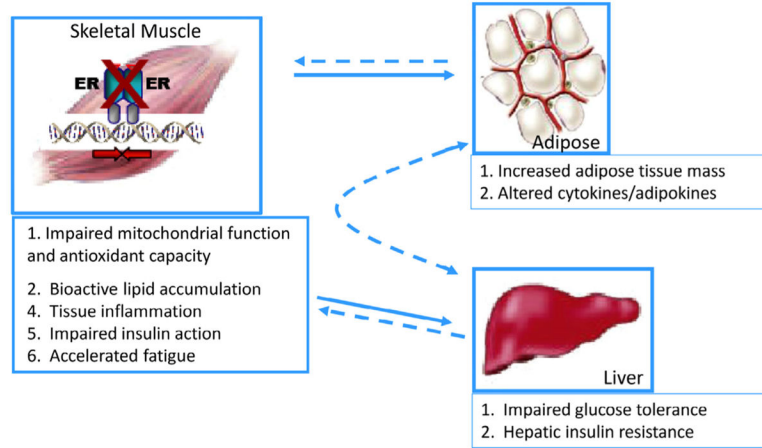Muscle specific-ERα Deletion Promotes Insulin Resistance and Obesity

Fig. 5.
The impact of skeletal muscle-specific ERα deletion on insulin sensitivity and adiposity in female mice (Ribas et al., 2010b).
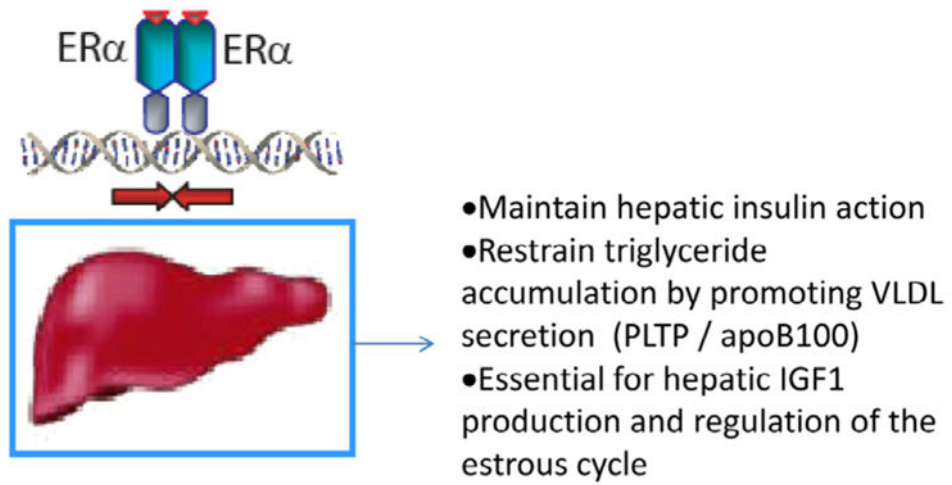
Fig. 6.
Proposed actions of E_2 and ERα in the protection against hepatic triglyceride accumulation and insulin resistance (Della Torre et al., 2011; Villa et al., 2012; Zhu et al., 2014).
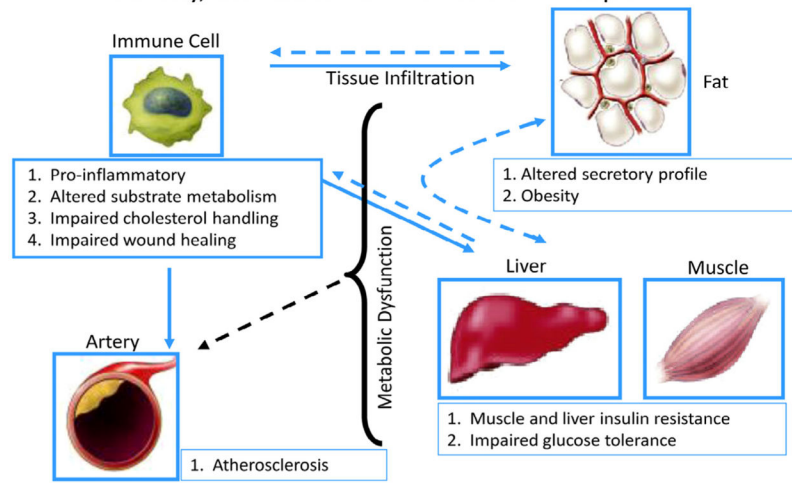
Fig. 7.
Myeloid-specific ERα deletion promotes obesity, insulin resistance, and atherosclerosis susceptibility in female mice.

•Increased susceptibility to apoptosis during exposure to oxidative stress, amyloid polypeptide and lipotoxicity
•Impaired glucose-stimulated insulin biosynthesis
•Increased LXR expression and elevated *de novo* fatty acid synthesis in islets

Fig. 8.
The effects of islet-specific ERα deletion on pancreatic function and glucose homeostasis (Tiano and Mauvais-Jarvis, 2012a).