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# Metabolic impact of estrogen signalling through ERalpha and ERbeta☆

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ABSTRACT

Estrogens, acting on both estrogen receptors alpha (ERalpha) and beta (ERbeta) are recognized as important regulators of glucose homeostasis and lipid metabolism. ERs belong to the family of nuclear hormone receptors which mainly act as ligand activated transcription factors. Both ERs are expressed in metabolic tissue such as adipose tissue, skeletal muscle, liver and pancreas, as well as in the central nervous system. Expression pattern of both ERs differ between species, sexes, and specific tissues.

The present review will focus on the key effects of ERs on glucose- and lipid metabolism. It appears that ERalpha mainly mediates beneficial metabolic effects of estrogens such as anti-lipogenesis, improvement of insulin sensitivity and glucose tolerance, and reduction of body weight/fat mass. In contrast, ERbeta activation seems to be detrimental for the maintenance of regular glucose and lipid homeostasis. Metabolic actions of both receptors in relevant tissues will be discussed.



**Contents**



## 1. Introduction

The prevalence of metabolic diseases such as obesity, type 2 diabetes (T2DM), dyslipidemia, and obesity-associated hypertension is rising steadily [1–3]. Insulin resistance (IR) is recognised as a common executive metabolic factor associated with those disorders. The pathophysiological penalty of IR are the reduction of insulin-mediated glucose uptake in skeletal muscle and adipose tissue, inhibition of insulin-mediated glucose storage with augmentation of glycogenolysis, and enhanced gluconeogenesis in liver, and reduction of the lipolysis rate in adipose tissue [4]. The exact molecular mechanisms underlying the development of obesity-associated IR are only partially understood (Fig. 1).

Estrogens, acting on both estrogen receptors alpha (ERalpha) and beta (ERbeta), are recognized as important regulators of metabolic homeostasis and lipid metabolism. To provide a few examples, estrogens were demonstrated to regulate lipogenesis, lipolysis and adipogenesis in fat tissue [5–7]. Furthermore, patients lacking aromatase activity, as well as ER-deficient or aromatase-deficient mice (ArKO), in which endogenous production of estrogens is diminished, show distinct and gender-specific metabolic phenotypes [6,8–14]. Estrogen deficiency in postmenopausal women was shown to accelerate the development

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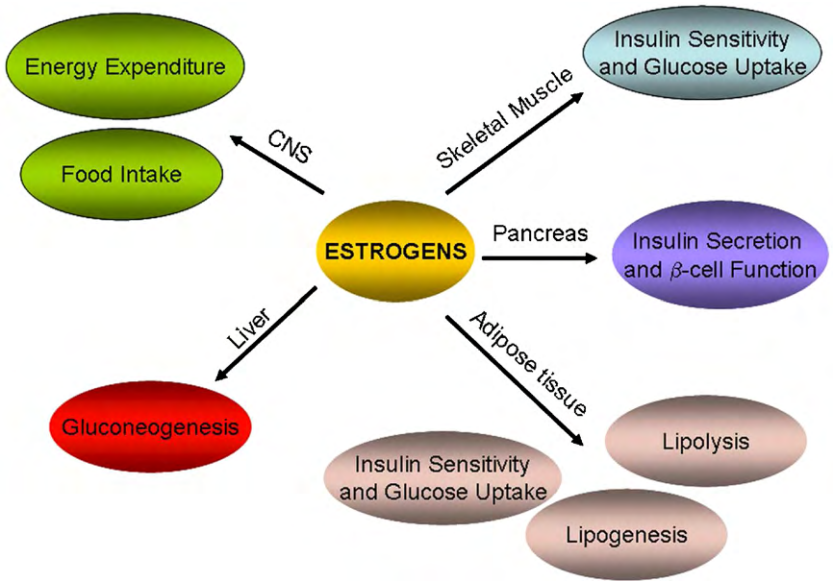


**Fig. 1.** Metabolic function of estrogens. Recapitulates different metabolic actions of estrogens on skeletal muscle, pancreas, adipose tissue and CNS. Precise description and references are discussed in the specific sections of the review.

of visceral obesity, IR and T2DM [15]. Finally, several clinical trials involving postmenopausal women on hormone replacement therapy (HRT) demonstrated a reduced incidence of T2DM, lower glucose plasma levels, and improved systemic insulin sensitivity after HRT [16–18]. This review will outline the major estrogen effects on glucose and lipid metabolism mediated by both nuclear hormone receptors ERalpha and ERbeta (Table 1).

## 2. Molecular function of estrogen receptors ERalpha and ERbeta

The estrogen receptors (ERs) belong to the family of nuclear hormone receptors (NHR), which comprises 48 different transcription factors and transcriptional regulators, such as peroxisome proliferator-activated receptors (PPARs), thyroid receptors (TRs), androgen receptors (AR), retinoid acid receptors (RXRs) and others [19,20]. ERs are ligand activated nuclear receptors with a wide range of biological effects. ERs are involved in the regulation of embryogenesis, development and reproduction due to their impact on proliferation and cell differentiation [21]. In addition to their role in metabolism, ERs mediate physiological effects of estrogens on the cardiovascular system, bone tissue, hematopoesis and CNS [22].

Two major ERs: ERalpha and ERbeta transmit the physiological signalling in response to 17beta-estradiol (E2) [21]. Both ERs show overlapping – but distinct expression pattern in gonadal tract, breast, testis, bone, skeletal muscle, liver, adipose tissue, CNS, vascular endothelium and bone marrow [23,24]. Some of the recent studies in mice indicated that in some areas of prostate or CNS ERbeta show clear predominance, whereas murine ERalpha was demonstrated to be predominately expressed in uterus, mammary glands, liver and skeletal muscle [25]. Both isoforms were reported to exhibit gender-dependent expression pattern in several tissues [26–28], whereby in females expression differs between pre-/postmenopausal state [29,30]. In pre-menopausal myometrium ERalpha is the predominant receptor which changes after menopause when the abundance of ERalpha expression is decreasing. Interestingly, reduction of the ERalpha expression in response to aging was linked recently with a methylation status of the CpG island of its promoter [31]. Furthermore, expression varies among different species. Focussing on metabolic tissues, in human adipose tissue ERalpha and ERbeta expression appears to be comparable, whereas in mice ERalpha expression is more pronounced. Correspondingly, prominent murine expression of ERalpha was also demonstrated in liver, skeletal muscle and pancreas (biopps.gnf.org) [32]. In contrast, expression pattern of both ERs measured in those metabolic organs in humans seems to be mainly similar (biopps.gnf.org). Furthermore, there are several distinct ERalpha and ERbeta splicing isoforms, identified in rodents, as well as in humans [33].

In addition to endogenous estrogen-ligands, ERs are activated by a range of synthetic selective estrogen receptor modulators (SERMs) such as the ERalpha-modulators raloxifen and tamoxifen, ERalpha specific ligand propyl-pyrazole-triol (PPT) or ERbeta-specific agonist diarylpropionitrile (DPN), and many others [34]. The ERs share a common molecular structure with other NHRs including a N-terminal transactivation domain (AF-1), DNA-binding domain (DBD) and C-terminal ligand binding domain (LBD) with a second activation domain (AF2) [35,36]. The AF1-domain is responsible for ligand independent transactivation and shows low homology between both ERalpha and ERbeta receptors (approximately 24%). In contrast, DBD- and LBD- domain show an increased similarity in amino acid sequence (97% and 56%, respectively),

**Table 1**
Metabolic role of ERalpha and ERbeta.

| Metabolic action | ERalpha | ERbeta |
|---|---|---|
| Insulin sensitivity and glucose tolerance in WAT and skeletal muscle (Glut-4 expression) | ↑ | ↓ |
| Lipogenesis (Lpl expression) | ↓ | ↓ |
| Lipolysis (HSL activity, Epinephrme-induces lipolysis) | ↑ | ? |
| Insulin secretion and pancreatic beta-cell function | ↑ | ? |
| Food Intake | ↓ | ↔ |
| Respiratory quotient (RQ) | ↑ | ↓ |
| Gluconeogenesis | ↓ | ? |
| Hepatic insulin sensitivity | ↑ | ? |

Summarizes action of both ERs on insulin sensitivity, lipogenesis and lipolysis, insulin secretion, gluconeogenesis, and energy homeostasis. References are integrated into the specific sections of the review. (↑) increased activity; (↓) reduced activity; (↔) no influence on metabolic outcome; (?) metabolic impact is currently not known.

which may explain the similar binding pattern of both ERs to the target promoters upon activation [36].

Activation of ERs by specific ligands can either lead to the manifestation of so-called non-genomic effects, which are mediated by membrane-associated or cytoplasm-localised ERs, or can result in the manifestation of classical genomic effects, mediated mostly by nuclear-associated ERs.

Non-genomic effects mediated by ERs are defined as rapid cellular responses (usually seconds or minutes), leading to nitric oxide (NO) release, calcium flux, and/or involving subsequent activation of the Ras/Raf/Mek/Erk [37–42]. Activation of MEK/ERK pathway consequently influence also gene expression profiles through the activation of other transcription factors such as CREB or NFAT [43]. Apart from ERalpha and ERbeta, several new estrogen receptors were already identified in plasma membrane, cytosol, endoplasmic reticulum and mitochondria, such as G-protein-coupled estrogen receptor (GPR30), reviewed by Prossnitz et al. [44], non-classical membrane estrogen receptor (ncmER), identified on beta and alpha pancreatic cells [45–47], or other putative estrogen receptors. The metabolic actions of those receptors are mostly unknown.

Classical genomic effects of ERs are reflecting the binding of the specific ligand/agonist within the LBD, followed by homo- or hetero-dimerization of those receptors. In general, unliganded ERs are bound to so called nuclear corepressors, such as SMRT (silencing mediator for retinoic acid receptor any thyroid hormone receptor), N-COR (nuclear receptor repressor) or RIP140 (Nuclear receptor interacting protein). Dimerization of ERs is followed by dissociation of corepressors, and binding of ER-dimers within specific target promoters. Importantly, binding of the ERs within target promoters could also occur in the presence of bound corepressors such as RIP140 and SHP, as discussed by Nilsson et al. [48]. These target promoters were shown to possess one or more of a palindromic consensus sequences (GGTCAxxxTGACC), so called estrogen response elements (EREs), although the sequence of the EREs can vary. Binding of ERs within target promoters depends on the recruitment of coactivatory proteins to the dimerized ERs instead of corepressors, as coactivators enhance and corepressors repress transcription. Most of NHR share a common set of coactivators including p160/SRC (steroid receptor coactivator) family such as SRC1, transcriptional intermediary factor 2 (TIF2), SRC3, vitamin D receptor (VDR)-interacting protein 205 (DRIP205) and many others. Importantly, binding of coactivators or corepressor to the ERs was shown to depend on several factors such as ligands, expression level of corepressors or coactivators in the given tissue, or chromatin remodelling influencing accessibility of the target promoters [49–52]. For example, tamoxifen was shown to recruit coactivator complexes to ER-dependent promoters in endometrium, and in parallel corepressors to the same promoters in breast cancer cells [49]. In addition, ERs were shown to regulate gene transcription by binding to other DNA-bound transcription factors, such as AP1 or NF-kappaB, or to GC-reach SP-1 binding sites. ERs were also reported to regulate gene expression in ligand independent manner, for instance by interacting with other nuclear hormone receptors, such as PPARs [11,53]. This can explain the redundancy of the ERs response observed among different cell types and different tissues. Both non-genomic and genomic responses of ERs induce or modulate gene expression, respectively. This review will summarize recently published data on metabolic function of ERs on glucose and fat metabolism.

## 3. Estrogens regulate systemic insulin sensitivity and glucose tolerance

Estrogens have been clearly shown to regulate glucose and lipid metabolism using either models of estrogen-/ER-depletion or estrogen application/replacement [54]. For example, studies using ovariectomized (OVX) animals indicate, that depletion of E2 results in an increase of daily energy consumption, body weight and fat mass [55]. OVX-rats were reported also to show dyslipidemia, impaired glucose tolerance and impaired insulin-mediated glucose uptake in skeletal muscle [56]. In consonance, E2 replacement therapy improved systemic insulin resistance in those animals mainly due to elevated expression of glucose transporter 4 (Glut-4) measured in skeletal muscle. Along this line, long-term treatment with E2 also improves glucose tolerance, insulin sensitivity and reduces lipid accumulation in liver of leptin-deficient, diabetic ob/ob mice, although experiments done by Gao et al. were performed with relative high (non-physiological) levels of E2 [57]. Similar results were observed in ob/ob mice treated with the ERalpha specific agonist PPT [58]. Moreover, chronic E2 administration to OVX- and high fat diet (HFD)-fed mice was recently shown to protect against glucose intolerance and insulin resistance, and to improve insulin signalling in skeletal muscle, when compared with vehicle-treated control animals [59]. Looking at other ER-ligands, also phytoestrogens have been demonstrated to reduce body weight and adipose tissue mass by increasing energy expenditure [39]. In the subsequent study [38] the authors could link the improved metabolic phenotype of those mice with increased activity of AMP-activated protein kinase (AMPK) followed by elevated mitochondrial biogenesis and increased peroxisomal fatty acid oxidation rate. Finally the importance of endogenous estrogens is supported by the fact that aromatase-deficient mice, who carry a genetic impairment in endogenous estrogen synthesis, exhibit decreased glucose tolerance accompanied by increased adiposity and pronounced IR [60–62].

In summary, previous studies point towards a crucial role of estrogens and ER-signalling in glucose- and lipid metabolism, which is likely to be beneficial after activation of the system. The molecular mechanism underlying this protective role of estrogens remains largely elusive.

Taken into account a beneficial role of E2/estrogens in glucose- and lipid metabolism it is not surprising that both nuclear ERs are involved in this regulation. The metabolic role of ERalpha was elucidated in several studies. Both female and male ERalpha-deficient mice exhibit profound IR and impaired glucose tolerance, as well as adipocyte hyperplasia and hypertrophy [6,8–10]. Expression level of Glut-4 transporter was strongly reduced in skeletal muscle of ERalpha-deficient mice [63]. Furthermore, study using ERalpha-selective agonists indicated that activation of these NHR showed beneficial metabolic effects in several obesity models in mice [58]. These studies indicate that ERalpha plays a protective role in metabolic disorders by improving metabolic outcome and increasing systemic insulin sensitivity. The role of ERbeta in de regulation of metabolism and obesity is less clear. Studies on ERalpha-deficient and OVX mice demonstrated an improvement in systemic IR and glucose intolerance associated with reduction of adipocyte size when compared with sham operated animals [9]. However, ERbeta-deficient mice have a similar body weight and equal fat distribution, as well as lipid and insulin levels, when compared to control littermates [64]. Moreover, fed with chow diet both female and male mice showed normal insulin response and glucose tolerance, and are metabolically healthy. However, we could recently demonstrate, that when challenged with HFD female ERbeta-deficient mice showed averted accumulation of triglycerides and preserved regular insulin signalling in liver and skeletal muscle, improved whole body insulin sensitivity and glucose tolerance [11]. Importantly, loss of ERbeta resulted in enhanced body weight gain and fat accumulation in HFD-fed mice. Female ERbeta-deficient mice fed with HFD showed augmented food efficiency and increased respiratory quotient (RQ), which is indicative for attenuated fatty acid oxidation. This metabolic phenotype was

associated with strong activation of PPARgamma in adipose tissue from female ERbeta-deficient mice. PPARgamma target genes and PPARgamma–DNA binding were markedly induced in gonadal fat of mice lacking ERbeta. In accordance, we showed that blockade of adipose PPARgamma signalling by antisense oligonucleotides strategy reversed that metabolic phenotype [11]. This pro-diabetogenic function on ERbeta seems to be ligand independent, since no difference in expression of PPARgamma target genes could be detected in soy-free-fed, OVX mice, treated with ERbeta-specific agonist DPN. Recently Barros and colleagues [63] demonstrated that ERbeta played a suppressive role on Glut-4 expression in skeletal muscle in mice, which also suggests a pro-diabetogenic function of this NHR.

Taken together it appears that ER isoforms have opposing actions on glucose- and lipid metabolism with ERalpha mediating beneficial actions whereas activation of ERbeta might be detrimental.

## 4. The metabolic function of adipose tissue is modulated by estrogens

Adipose tissue plays a major role in the regulation of glucose homeostasis and insulin sensitivity. There are well-documented sex differences in the pathophysiology of obesity and metabolic disorders [65,66]. Women tend to accumulate more subcutaneous fat whereas men accumulate more visceral fat [17,18,67]. The prevalence of early insulin resistance and glucose intolerance seems to be higher in men than in women [68,69]. Furthermore, increased abdominal obesity observed in postmenopausal women associated with insulin resistance can be improved by HRT [17]. Together, these data implicate a central role of estrogens, as well as androgens, in adipose tissue biology.

### 4.1. Regulation of adipose tissue lipogenesis/lipolysis by estrogen

A recently published study from Macotela and colleagues [70] focused on sex- and depot-specific differences in adipose tissue in mice. The authors analyzed sex differences in adipose glucose and lipid metabolism on the cellular level regarding insulin-dependent glucose uptake, activation of insulin signalling pathways, expression level of Glut-4, Glut-1 and fatty acid synthase (FAS). They demonstrated an enhanced lipogenic capacity of adipocytes isolated from female mice in comparison to male mice which resulted from enhanced female insulin sensitivity. However, these data do not allow the conclusion that female sex steroids directly stimulate lipogenesis since sexual dimorphic regulation of lipid metabolism was more likely a result from differences in insulin responsiveness. Sex dimorphisms in insulin sensitivity may result from different reasons including lower body weight in females, differences in food intake, etc. A more definite answer about direct actions of estrogens on adipose lipid metabolism provides the model of OVX mice. Since estrogens have a profound effect on food intake, and castration of female mice results in increased food intake and body weight it is important to apply a pair-feeding protocol in this model in order to avoid the confounder of varied energy intake. This has exactly been performed by D'Eon and colleagues showing that E2 in pair-fed OVX mice directly inhibits lipogenesis and reduces adipose tissue mass.

These findings are further supported by previous publications [71,72] demonstrating that E2 inhibits lipogenic gene expression, promotes catecholamine-stimulated lipolysis in adipocytes and induces lipid-oxidation in muscle. Estrogens were shown to affect adipose tissue by induction of lipolysis (e.g. due to activation of hormone-sensitive lipase, HSL) [73] and reduction of lipogenesis, mostly by decreasing activity of lipoprotein lipase (LPL) [74–76]. These results are in accordance with other studies showing that adipose tissue undergoes profound sex-specific molecular changes during exercise, such as increased lipolysis in females most likely resulting from an augmented expression of HSL and/or adipose tissue triglyceride lipase (ATGL) by E2 [77–79]. This is in line with human data which showed that women exhibit higher adipose tissue lipolysis than men [80].

In summary, it seems that the majority of previous reports point towards a direct anti-lipogenic and pro-lipolytic action of estrogens in adipose tissue.

Whether these actions are mediated through ERalpha or ERbeta is currently unknown. ERalpha-deficient mice exhibit increased adipose tissue mass in the absence of differences in energy intake suggesting a role of ERalpha in adipose tissue biology [8]. This notion is corroborated by data in 3T3-L1 pre-/adipocytes in which cells stably transfected with ERalpha showed attenuated triglyceride accumulation and reduced LPL expression [75]. We could recently show that ERbeta-deficient female mice have a higher body weight under high fat diet feeding than their wild type littermates. Higher body weight in ERbeta−/− mice resulted from enhanced adipogenesis and subsequent increased adipose tissue mass. Lipogenesis was not investigated in this study. However, we could demonstrate that PPARgamma, a key adipogenic and lipogenic factor, is negatively regulated by ERbeta suggesting also anti-lipogenic actions of this isoform.

Together, it appears that both ER isoforms participate in the anti-lipogenic actions of estrogens.

### 4.2. Regulation of adipose tissue inflammation by estrogens

Several recently published studies support the thesis, that the first step towards the development of insulin resistance in adipose tissue is inflammation [81–83]. Pharmacological attenuation of the inflammatory response in fat tissue resulted in improved insulin sensitivity and glucose tolerance in the diet-induced obesity (DIO) mouse model [82]. Additionally, HFD-fed mice with IkappaB kinase (IKKbeta)-deletion in myeloid cells (lymphocytes, macrophages and neutrophils) were protected against diet-induced insulin resistance and glucose intolerance when compared to control littermates [84]. Furthermore, depletion of c-Jun N-terminal kinases (JNK1) resulted in reduced adiposity and improved insulin sensitivity [85]. Inhibition or loss of function of IKKbeta, a kinase responsible for the proinflammatory signalling of the NF kappaB pathway, and proinflammatory kinase JNK led to the improvement of systemic insulin sensitivity in mouse models [82,85]. It is still elusive how the development of inflammatory response in adipose tissue (mostly due to the recruitment of proinflammatory macrophages and T lymphocytes) causes systemic insulin resistance [86,87], but reduction of the proinflammatory response was clearly shown to improve insulin sensitivity and glucose tolerance in several mouse models as well as humans [81,88,89]. Interestingly, obesity and IR observed in OVX mice was shown to correlate with an augmented inflammation in adipose tissue, increased infiltration of immune cells, and elevated expression of TNFalpha, monocyte chemoatractant protein-1 (MCP-1), interleukin 6 (IL-6) and macrophage-specific markers, such as CD11c or F4/80 in abdominal fat when compared to non-OVX littermates [72]. In contrast, Riant and colleagues [59] demonstrated that administration of E2 in DIO mice model led to an augmentation of adipose tissue inflammation in an ERalpha-dependent manner. However, this proinflammatory action did not result in a deterioration of insulin- and glucose metabolism which makes the results difficult to interpret.

In summary, a putative anti-inflammatory action of E2 in adipose tissue is intriguing and may, at least in part, explain the anti-diabetogenic properties of E2, however, additional studies seem to be required.

## 5. Estrogens regulate glucose homeostasis by acting on skeletal muscle and liver

Intensive glucose clearance in response to postprandial insulin secretion is mainly mediated by skeletal muscle. The insulin signalling pathways inducing sufficient glucose uptake in skeletal muscle, as well as in white adipose tissue are well studied and involve insulin receptor, insulin receptor substrate (IRS), phosphatidylinositol-3 kinase (PI3-K) and AKT kinase leading to subsequent translocation of Glut-4 to the cell membrane. Both ERalpha and ERbeta receptors seem to have opposing effects on the expression of Glut-4 transporters. ERalpha was shown to induce – whereas ERbeta seems to inhibit-Glut-4 expression in this tissue [63,90]. Recently published data from Barros et al. [90] indicated that tamoxifen-treated ERalpha-deficient mice showed increased Glut-4 expression in skeletal muscle, which also indicate pro-diabetogenic effects of ERbeta. The "beneficial" actions of ERalpha activation have recently been supported in a study in which phytoalexin resveratrol (RSV), previously described as an ERalpha ligand, regulates glucose uptake in skeletal muscle in vivo and in vitro [91,92]. RSV-treatment increased insulin-stimulated glucose uptake in high-cholesterol-fructose (HCF)-fed rats, as well as steady-state glucose uptake measured in soleus muscle [92]. Inhibition of ERalpha activity by ICI 182780 led to the complete abrogation of RSV-dependent Glut-4 translocation, which indicates a key role of ERalpha in the regulation of glucose balance in this model. Up to now it appears that both ER isoforms determine metabolic estrogen actions in skeletal muscle where, in accordance with other tissues, ERalpha mediates protective actions and ERbeta deleterious.

The maintenance of glucose homeostasis is depending on whole body glucose uptake, discussed above, and glucose production by glycogenolysis and gluconeogenesis in liver. Estrogens were shown to regulate liver glucose homeostasis and hepatic cholesterol output, mostly due to ERalpha activity. A study published by Bryzgalova et al. on both ERalpha- and ERbeta-deficient mice indicate, that ERalpha likely plays the predominant role in the regulation of hepatic glucose homeostasis [10]. The endogenous glucose production assessed by euglycaemic-hyperinsulinaemic clamp analysis revealed that ERalpha deficiency was associated with a pronounced hepatic IR. Furthermore, microarray analysis of the hepatic tissue isolated from ERalpha-deficient and control mice revealed ERalpha-dependent upregulation of the key genes involved in hepatic lipid biosynthesis, and successive downregulation of the genes regulating lipid transport. ERbeta-deficient mice exhibited normal glucose tolerance and insulin release, as reported previously [93]. Those findings are in consonance with studies in diabetic ob/ob mice showing that a major anti-diabetic effect of long E2-treatment is associated with decreased expression of lipogenic genes in the liver [57].

Thus, ERalpha is the main mediator of hepatic estrogen effects involving inhibition of hepatic lipogenesis and glucose production.

## 6. Insulin production and pancreatic beta-cell function is modulated by estrogens

Estrogens are known regulators of pancreatic beta cell function. A recently published study in mice [94] suggested that long-term exposure to E2 increased pancreatic beta-cell insulin content, insulin gene expression, and insulin release without changing beta-cell mass. ERalpha has been identified as the functional predominant receptor isoform in the murine pancreas. E2-dependent insulin release in cultured pancreatic islets was reduced in ERalpha-deficient mice, when compared to islets derived from either ERbeta-deficient or wt mice [94]. ERalpha was also reported to mediate pancreatic beta-cell survival after oxidative stress, induced by single doses of streptozotocin applied to wt and ArKO mice [95]. In this study, E2-treatment inhibited streptozotocin-induced beta-cell apoptosis, increased insulin production, and improved insulin resistance and glucose intolerance. The protective actions of E2 were abrogated in ERalpha-deficient mice. Also work done by Barros et al. demonstrated that ERbeta-deficient mice show mild islet hyperplasia and delayed first phase insulin resistance [90].

Together these studies demonstrate that estrogens mediate protective actions in the pancreas involving beta-cell preservation and maintenance of insulin secretion, effects which are mainly induced by ERalpha activation.

## 7. Central regulation of energy balance by estrogens

Central regulation of energy balance is mediated via a complex signaling network within the central nervous system (CNS) integrating multiple endocrine signals from the periphery. The major neuronal circuits involved in the maintenance of energy homeostasis have been extensively reviewed elsewhere [96]. The present paragraph will only focus on central signalling pathways relevant for estrogen receptor action.

Hypothalamic neurocircuits are essential for the regulation of energy balance involving different neuronal subsets such as the arcuate nucleus (ARC), the ventromedial nucleus (VMN), the dorsomedial nucleus (DMN), the paraventricular nucleus (PVN), and the lateral hypothalamic (LHA) region [96]. The ARC contains NPY (neuropeptide Y) and AgRP (agouti-related protein) neurones that stimulate food intake (orexigenic), next to POMC (pro-opiomelanocortin) neurones whose activation results in a decrease of food intake (anorexigenic) via secretion of alpha-MSH (alpha-melanocyte-stimulating hormone) [96]. Both neuronal subsets project to adjacent hypothalamic areas including the PVN that mediates anorexigenic signals and the LHA where neurons that stimulate food intake are concentrated [96]. Lesions in the VMN region has been shown to be associated with weight gain, enhanced accumulation of visceral fat, impaired glucose homeostasis and decreased energy expenditure [97].

ERalpha and ERbeta are both expressed in all hypothalamic nuclei [98]. Among the isoforms, ERalpha seems to be the major player in the central control of body weight by estrogens. Whether ERalpha mediates these effects via the regulation of food intake or actions on energy expenditure has been discussed controversially. Targeted deletion of ERalpha in mice resulted in an obese phenotype with increased fat accumulation but absence of marked differences in food intake between wild-type and knockout mice [8,64]. This is in accordance with data from ERbeta mice in which food consumption is similar with wild-type mice when fed a high fat diet [11]. In contrast, ovariectomy of mice or rats leads to a weight gain of 10–25% which has been shown to be associated with an increase in food intake [99,100]. These data suggest that estrogens reduce food intake which has been attributed to augment cholecystokinin-signalling and reduction in meal size [100]. It can be speculated that differences between genetic disruption of estrogen signalling during embryogenesis and ligand deficiency after birth account for this discrepancies. This controversy might be resolved by a recent study in which ERalpha was directly silenced in the VMN of adult mice by adeno-associated viral vector based injection of small hairpin (sh) RNA [101]. ERalpha silencing in the VMN resulted in an increase of food consumption as well as reduced energy expenditure caused by diminished physical activity and impaired thermogenic responses to feeding [101]. Importantly recently work published by Thammacharoen et al. [102] done on OVX-rats and -mice treated with E2 and PPT indicated a strong ERalpha-dependent inhibitory effect on eating behaviour observed

in those animals, when compared to vehicle-treated littermates and ERalpha-deficient mice.

Other hypothalamic regions might also be involved in the anorexigenic actions of estrogens. In this regard, treatment of ovariectomized mice with estradiol results in upregulation of POMC mRNA and decrease of NPY mRNA in the ARC [103].

In summary, among the ER isoforms ERalpha is the major regulator of central energy homeostasis and its activation results in a reduction of food intake and increased energy expenditure contributing to the overall reduction of body weight by estrogens. These actions are mainly mediated in hypothalamic nuclei, in particular in the VMN and ARC.

## 8. Summary and future perspectives

In the present overview we underlined molecular and physiological mechanisms that explain, at least in part, estrogen actions on glucose and lipid metabolism. We focused on metabolic effects of both ERalpha and ERbeta. However, several newly described receptors such as estrogen related receptor alpha (ERRalpha) or membrane estrogen receptor GPR30 were shown to exhibit putative metabolic actions. Future studies investigating these non-genomic actions, and the role of non-ER-estrogen binding receptors will provide an improved understanding of the metabolic actions of estrogens.

Most of the discussed studies are based on experiments performed in global ERalpha- or ERbeta-deficient mice. In this regard, generation of mice with tissue specific ER deletion in metabolically important organs would help to create a more complete molecular picture in this field.

Taken under consideration the limitations outlined above, studies on ERalpha indicate its protective function on insulin- and glucose metabolism in most organs including white adipose tissue, skeletal muscle, liver, and pancreatic beta cells. Moreover, ERalpha was demonstrated to regulate food intake and energy expenditure. In contrast, ERbeta seems to negatively regulate insulin signalling and glucose metabolism due to an impairment of regular adipose tissue function and downregulation of Glut-4 expression in skeletal muscle.

Estrogen signalling plays a major role in the maintenance of regular metabolic functions whereby the balance between the “good” ERalpha and the “bad” ERbeta seem to be crucial in most organs.

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