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REVIEW

Obesity, insulin resistance and diabetes: sex differences and role of oestrogen receptors

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Abstract

Obesity increases the risk of coronary artery disease through insulin resistance, diabetes, arterial hypertension and dyslipidemia. The prevalence of obesity has increased worldwide and is particularly high among middle-aged women and men. After menopause, women are at an increased risk to develop visceral obesity due to the loss of endogenous ovarian hormone production. Effects of oestrogens are classically mediated by the two nuclear oestrogen receptors (ERs) α and β. In addition, more recent research has shown that the intracellular transmembrane G-protein-coupled oestrogen receptor (GPER) originally designated as GPR30 also mediates some of the actions attributed to oestrogens. Oestrogen and its receptors are important regulators of body weight and insulin sensitivity not only in women but also in men as demonstrated by ER mutations in rodents and humans. This article reviews the role of sex hormones and ERs in the context of obesity, insulin sensitivity and diabetes as well as the related clinical issues in women and men.

Keywords adipocyte, aromatase, atherosclerosis, oestradiol, myocardial infarction, visceral fat.

Obesity: a cardiovascular risk factor with a high prevalence

An increase in food intake combined with reduced energy expenditure (as a result of and aggravated by physical inactivity) has led to a dramatic increase in the prevalence of obesity, which is now considered a global epidemic (WHO, 2000, French *et al.* 2001, Barton & Furrer 2003, James 2008). Obesity has been recognized as an independent cardiovascular risk factor (Yusuf *et al.* 2004), mostly because of the hypertension, diabetes and dyslipidemia associated with it (Mokdad *et al.* 2003, Ogden *et al.* 2007) (Fig. 1). Risk is particularly high in individuals with large amounts of abdominal (visceral) fat (Kannel *et al.* 1991), which is a source of bioactive mediators that not only directly contribute to insulin resistance (Xu *et al.* 2003) but also adversely affect lipid profiles, blood pressure and vascular inflammation (Van Gaal *et al.* 2006). As a consequence of increased activity and production of growth factors with pro-inflammatory activity including angiotensin II and endothelin-1 (Barton *et al.* 2003, Barton 2010), obese patients are at an increased risk for atherosclerotic vascular complications such as myocardial infarction and stroke (WHO, 2000, Yusuf *et al.* 2004, Ogden *et al.* 2007). Despite their high prevalence, obesity and associated diseases remain undertreated in primary care (Bramlage *et al.* 2004, Stewart *et al.* 2009).

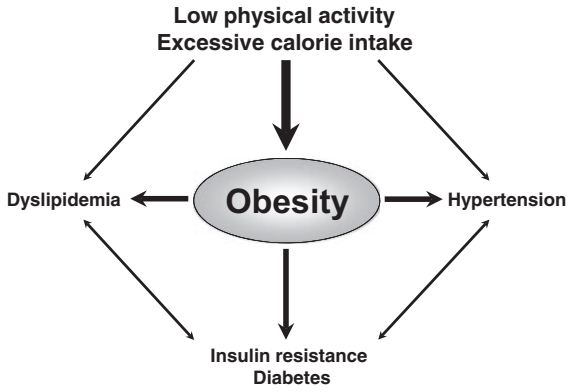

Figure 1 Factors contributing to the development of obesity and its metabolic and cardiovascular consequences. Predominant causes are excessive calorie intake combined with physical inactivity. This has resulted in an alarming, worldwide increase in the prevalence of obesity (adapted from Barton et al. 2003).

Sex differences and effect of menopause on adiposity and body fat distribution

The prevalence of overweight and obesity continuously increases in both men and women until the age of 80 (Ogden *et al.* 2007). In the United States, it is slightly higher in women than in men although there are marked differences by race-ethnic groups for women but not for men (Ogden *et al.* 2007). In addition, obesity development is accelerated after menopause; factors such as loss of oestrogens, the ageing process and changes in lifestyle may all be contributors (Shi & Clegg 2009, Barton 2010). The effect of menopause is supported by animal models showing that a reduction in circulating oestrogen levels following ovariectomy results in increased body adiposity, which can be reversed by exogenous oestrogen administration (Shi & Clegg 2009, Brown *et al.* 2010). Oestrogens are also known to regulate body fat distribution in animals and humans (Shi & Clegg 2009, Brown *et al.* 2010). In pre-menopausal women, fat tissue is mainly located in subcutaneous depots whereas males tend to accumulate more fat in their visceral depots, independent of age (Enzi *et al.* 1986). After the loss of endogenous oestrogens as a result of menopause, a shift towards visceral adiposity occurs, which is sensitive to oestrogen therapy (Shi & Clegg 2009, Brown *et al.* 2010). In addition, a polymorphism in the oestrogen receptor α (ERα) gene has been associated with increased abdominal fat mass in pre-menopausal women (Okura *et al.* 2003). In view of the adverse metabolic changes associated with increased visceral fat mass (Xu *et al.* 2003, Van Gaal *et al.* 2006), the loss of endogenous oestrogen production following menopause results in an increased cardiovascular risk (Barton & Meyer 2009). Oestrogens may also play a similar role in men as mutations of ERα in young males are associated with insulin resistance and abnormal IGF-1 levels (Smith *et al.* 1994) as well as with premature coronary artery disease (Sudhir *et al.* 1997).

Cellular targets and functions of oestrogens

Human oestrogens comprise a group of structurally related steroid molecules, namely 17*β*-oestradiol, oestrone and oestriol, which are the most important regulators of the female and male reproductive systems. Oestrogens also interact with a number of non-reproductive organs, such as bone tissue, cardiovascular, immune and central nervous systems (Gruber *et al.* 2002). Oestrogens activate nuclear ERs in target cells, acting as transcription factors to regulate the expression of target genes, ultimately controlling cell growth, differentiation and homeostasis (Meyer *et al.* 2009). Two nuclear ERs located on distinct chromosomes have been identified (Walter *et al.* 1985, Green *et al.* 1986, Greene *et al.* 1986, Kuiper *et al.* 1996) and termed ERα and ER*β*. A subpopulation of ERα and ER*β* is localized to the plasma membrane, where their activation induces a variety of intracellular signalling cascades thereby mediating the 'rapid effects' of oestrogen (Hammes & Levin 2007, Meyer *et al.* 2009). Some of these 'rapid effects' are now known to be also mediated by the novel G-protein-coupled oestrogen receptor (GPER), previously termed GPR30, which is predominantly located to the endoplasmic reticulum (Revankar *et al.* 2005). GPER is widely expressed in numerous human organs, including adipose tissue (Hugo *et al.* 2008, Nadal *et al.* 2009, Prossnitz & Barton 2009) and has been implicated in oestrogen-dependent physiology of immune function as well as the central nervous and cardiovascular systems (Meyer *et al.* 2009, Prossnitz & Barton 2009). GPER has been associated with diseases such as obesity, insulin resistance and hormone-sensitive cancers (Martensson *et al.* 2009, Nadal *et al.* 2009, Prossnitz & Barton 2009). There also appears to be complex interplay between ERα and GPER, which has not yet been fully defined (Albanito *et al.* 2007, Prossnitz & Barton 2009, Vivacqua *et al.* 2009).

Production of oestrogens and its role in human obesity

While in pre-menopausal women, 17*β*-oestradiol is primarily and variably synthesized in the ovaries during the menstrual cycle, depletion of ovarian follicles in the perimenopausal period leads to a steady decline in 17*β*-oestradiol production. Thus, oestrone becomes the predominant oestrogen in post-menopausal women (Gruber *et al.* 2002). Therefore, in post-menopausal women, the main source of oestrogens is the conversion

of the adrenal androgens testosterone and androstenedione into 17β-oestradiol and oestrone, respectively, which mainly takes place in adipose tissue (Siiteri 1987). This conversion is catalysed by the enzyme aromatase, the activity of which increases with ageing (Cleland *et al.* 1985). Of note, the conversion rate, measured as the proportion of oestrogens and androgens as a surrogate of aromatization, is also accelerated in obese individuals (Siiteri 1987), likely as a result of increased numbers of adipocytes (where aromatase is highly expressed) rather than increases in aromatase activity (Cleland *et al.* 1985). Indeed, changes in body fat mass are positively correlated with total serum 17β-oestradiol and oestrone concentrations in post-menopausal women (Haffner *et al.* 1991, Kaye *et al.* 1991, Baglietto *et al.* 2009). Interestingly, this association varies with time from the onset of menopause and the changes in hormonal status may take up to 6 years to develop (Baglietto *et al.* 2009). Moreover, physical activity lowers serum oestrone levels (Haffner *et al.* 1991). Thus, oestrogen synthesis in post-menopausal women is determined by age, body weight and physical fitness (Gruber *et al.* 2002). Conversely, plasma concentrations of sex hormone-binding globulin, which is the binding protein of sex steroids in plasma, decreases with increasing body weight and specifically, abdominal adiposity (Haffner *et al.* 1991, Kaye *et al.* 1991, Baglietto *et al.* 2009). This results in an increase of unbound, biologically active oestrogen which has been associated with an increased risk for hormone-sensitive tumours, such as breast cancer in obese women as well as in men (Rinaldi *et al.* 2006, Brinton *et al.* 2010).

Oestrogen serum levels are increased in hypogonadal men, which is caused by increased aromatization of androgens in the adipose tissue (Schneider *et al.* 1979, Cleland *et al.* 1985, Siiteri 1987). As a result, although plasma oestrogen levels in men are low compared to women, local concentrations might be much higher and physiologically relevant at the site of production and/or action, where they may reach micromolar concentrations (Sugioka *et al.* 1987). Moreover, increased oestrogen levels confer a hypogonadal state in men, possibly mediated by inhibition of gonadotropin release via activation of hypothalamic ERs (Zitzmann 2009). Testosterone deficiency may aggravate the development of obesity and hyperinsulinemia, which, in turn, will suppress testicular androgen synthesis even further, resulting in a vicious cycle (Zitzmann 2009). Insulin resistance in a man with a homozygous inactivating mutation of the aromatase gene (Maffei *et al.* 2004, 2007) as well as in a patient with a mutation of ERα (Smith *et al.* 1994) have been reported, indicating that oestrogens and their cellular targets are also important for the maintenance of energy homeostasis in males. Taken together, disturbances and changes in the relationship between oestrogens and androgen metabolism seem to adversely affect fat metabolism and insulin sensitivity independent of sex.

Role of oestrogens in regulation of body weight and insulin sensitivity

Oestrogens are known as a regulator of body composition, energy balance and insulin sensitivity in both women and men, recently reviewed elsewhere (Geer & Shen 2009, Shi & Clegg 2009, Brown & Clegg 2010). Body weight increases in several conditions associated with oestrogen deficiency such as ovariectomy, polycystic ovary syndrome (PCOS), or the lack of a functional aromatase gene and all can be corrected by 17β-oestradiol treatment (Pedersen *et al.* 1992, Asarian & Geary 1999, Jones *et al.* 2000, Gambineri *et al.* 2002, Misso *et al.* 2003, Takeda *et al.* 2003, Maffei *et al.* 2007). Oestrogens not only decrease food intake through 'direct' (central nervous system) effects (Wade 2009) but also through interactions with other hormones that regulate food intake such as insulin, leptin, ghrelin and neuropeptide Y (Brown & Clegg 2010). Moreover, animals and humans lacking endogenous oestrogen synthesis exhibit insulin resistance, which can be treated by oestrogen supplementation (Bailey & Ahmed-Sorour 1980, Morishima *et al.* 1995, Jones *et al.* 2000, Takeda *et al.* 2003). In particular, oestrogens increase hepatic insulin sensitivity by decreasing gluconeogenesis and glycogenolysis (Ahmed-Sorour & Bailey 1981) and increasing insulin release in islets of Langerhans (Alonso-Magdalena *et al.* 2008). Oestrogens also prevent β-cell apoptosis (Le May *et al.* 2006), reduce pro-inflammatory signalling (Evans *et al.* 2001, 2002) and improve insulin action (Brussaard *et al.* 1997). Therefore, the greater amount of visceral adipose tissue in conjunction with lower endogenous oestrogen levels found in men may be related to the higher insulin resistance when compared with pre-menopausal women (Geer & Shen 2009) and could thus contribute to the sex differences seen with cardiovascular disease (Meyer *et al.* 2006).

Importance of ERα and ERβ for insulin function in obesity and diabetes

Body weight, food intake and obesity

Subcutaneous and intra-abdominal adipose tissues express both ERα and ERβ with a predominance of ERα being expressed in intra-abdominal adipose tissue (Dieudonne *et al.* 2004). The development of knockout animals has provided a powerful tool to examine the role of individual ERs in the function of adipose tissue (Fig. 2). Female and male mice lacking ERα develop

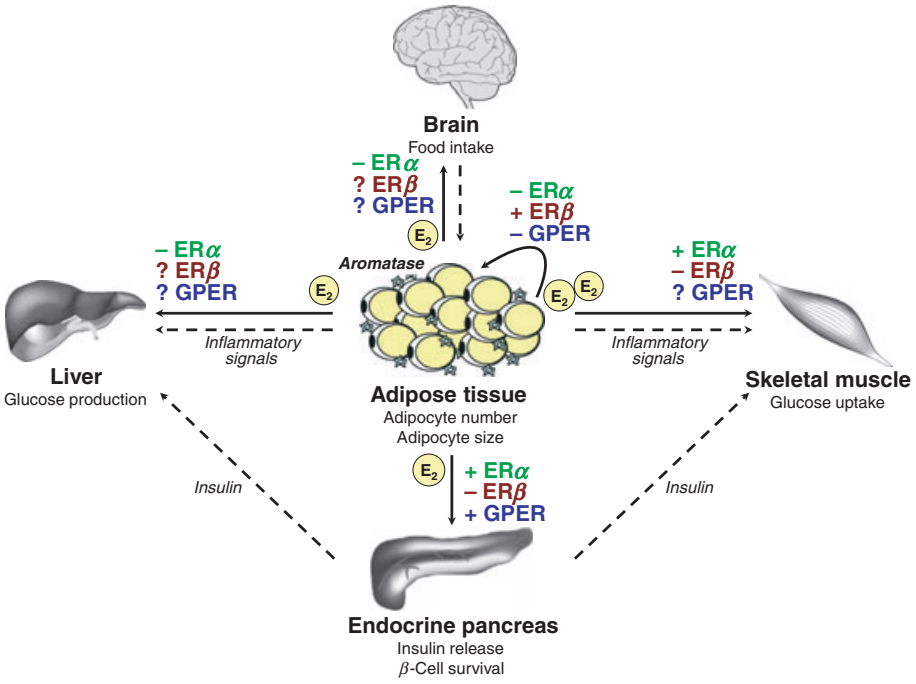

Figure 2 Proposed role of ERα, ERβ and GPER for the regulation of body weight and maintenance of glucose homeostasis. In pre-menopausal women, 17β-oestradiol (E_2) is the predominant oestrogen released by the ovaries. The main source of oestrogen in men and post-menopausal women is adipose tissue, where E_2 is converted from androgen precursors by the aromatase enzyme. E_2 not only has paracrine effects on adipocytes but also acts centrally in the brain as well as peripherally in organs regulating glucose homeostasis such as the endocrine pancreas, liver and skeletal muscle. Note that ERα and ERβ generally mediate opposing effects whereas the role of GPER has only been investigated in part. In addition, insulin released by pancreatic β-cells regulates hepatic glucose production via gluconeogenesis and glucose uptake in skeletal muscle, which is impaired by the action of inflammatory mediators released by adipose tissue. +, stimulatory effect; –, inhibitory effect; ?, effect unknown.

central obesity with increases in white adipose tissue and body weight, which is reflected by increased adipocyte number and size (Heine *et al.* 2000). Despite this increase in tissue and body weight, food consumption and energy intake do not differ between ERα-knockout animals and controls; but energy expenditure is reduced in the absence of ERα (Heine *et al.* 2000). Similarly, silencing of ERα by RNA interference in the hypothalamus reduces energy expenditure and increases food intake in animals (Musatov *et al.* 2007).

Work from Mauvais-Jarvis' group has shown that oestrogens help to sustain insulin production in diabetic male and female mice and that this effect is at least in part ERα dependent (Le May *et al.* 2006). Recent work from the same investigators has extended these findings demonstrating that E2 – independent of ERα – can stimulate islet insulin synthesis through interactions between the extranuclear/membrane ERα and the tyrosine kinase *Src*, which activates ERK1/2 MAPK (Wong *et al.* 2010). An anti-diabetic role of ERα is also suggested by Ribas *et al.* indicating that ERα deficiency increases fasting insulin levels, impairs glucose tolerance and results in skeletal muscle insulin resistance (Ribas *et al.* 2010).

Gustafsson and co-workers showed that after sexual maturation, body fat increases in male mice lacking either ERα or both ERα and ERβ, an effect, which was not observed in ERβ-knockout animals (Ohlsson *et al.* 2000). Obese ERα-knockout animals also display increased serum cholesterol levels (Ohlsson *et al.* 2000). These findings support a substantial physiological role for ERα in mediating the effects of oestrogens in the control of body weight. Consistent with these results, insulin resistance developed in a 28-year-old man with a mutation in the ERα gene; this individual also had increased height as a result of insufficient epiphysial plate fusion (Smith *et al.* 1994). ERα gene expression in subcutaneous adipose tissue and isolated adipocytes is reduced in obese pre-menopausal women, but increases after weight reduction (Nilsson *et al.* 2007). Moreover, several ERα single nucleotide polymorphisms have been associated with obesity phenotypes in women and men (Deng *et al.* 2000, Okura *et al.* 2003, Fox *et al.* 2005).

The effect of oestrogens on adipose tissue development has also been investigated in ovariectomized ERα-knockout mice. Loss of oestrogen following ovariectomy in these animals resulted in decreased body

weight, fat-pad weight and adipocyte size, an effect that was reversed by 17β-oestradiol treatment (Naaz *et al.* 2002), suggesting that increases in body weight were mediated by an ER other than ERα, possibly by ERβ. In addition, only small effects on retroperitoneal fat-pad weight were observed in ERβ-knockout mice whereas animals lacking ERα demonstrated a markedly increased amount of total body fat, suggesting an adipogenic role of ERβ (Ohlsson *et al.* 2000). In contrast, mice lacking both ERα and ERβ also develop obesity questioning a role for ERβ (Ohlsson *et al.* 2000). In addition, Ouchi and co-workers suggested that in rats, ERβ inhibits food intake and reduces body weight through effects in the central nervous system (Liang *et al.* 2002). In humans, polymorphisms in the ERβ gene have been associated with lower BMI although other investigators found no correlations (Goulart *et al.* 2009, Saltiki *et al.* 2009). In conclusion, the metabolic effects of oestrogens appear to be largely mediated by ERα whereas the role of ERβ and possible cross-talk with other ERs is currently unclear. Indeed, ERβ inhibits ERα-mediated gene expression in certain cell types and often opposes the action of ERα (Matthews & Gustafsson 2003), an interaction that might be also important for the regulation of body weight. Finally, it should be noted that compensatory developmental changes in both animal models and humans may alter hormone responsiveness in ways that are different from the inherent biology in healthy individuals or 'wild type' animals respectively.

Insulin sensitivity and inflammation

Impaired insulin sensitivity/glucose intolerance and hyperinsulinemia were noted in a man lacking functional ERα (Smith *et al.* 1994). A metabolic function of ERα is also supported by animal studies, which suggest oestrogen-dependent effects on glucose homeostasis through both ERα and ERβ (Fig. 2), whereas glucose tolerance is normal in ERβ-knockout mice (Heine *et al.* 2000, Naaz *et al.* 2002, Bryzgalova *et al.* 2006, Ribas *et al.*, 2010). Impaired insulin sensitivity as determined by the hyperinsulinemic clamp technique in ERα-deficient animals was attributed to either inadequate suppression of hepatic glucose production by insulin or impaired insulin action in skeletal muscle (Bryzgalova *et al.* 2006, Ribas *et al.*, 2010). In addition, adiponectin, an adipokine associated with suppression of insulin resistance and inflammation is decreased in the absence of ERα whereas PAI-1, a surrogate marker of systemic inflammation (Ridker *et al.* 2004) is increased (Ribas *et al.*, 2009). Increased inflammation-associated changes following streptozotocin-induced injury of pancreatic islets have been described in ERα-deficient mice (Le May *et al.* 2006); moreover, enhanced inflammatory signalling and impaired fatty acid oxidation were also found in the skeletal muscle of ERα-knockout mice (Ribas *et al.*, 2010), further indicating an ERα-dependent insulin sensitivity phenotype (Bandyopadhyay *et al.* 2006). Indeed, insulin-stimulated glucose uptake in skeletal muscle, mediated by the glucose transporter isoform GLUT4 (Ryder *et al.* 2001), is suppressed in the absence of ERα (Bryzgalova *et al.* 2006). GLUT4 expression was not affected in mice lacking ERβ arguing in favour of an oestrogen-dependent regulation of GLUT4 expression by ERα (Barros *et al.* 2006). In addition, insulin sensitivity is preserved in mice lacking ERβ although these animals, like wild-type C57BL/6J mice (Barton *et al.* 2000, Mundy *et al.* 2007), become obese following a high-fat diet (Foryst-Ludwig *et al.* 2008). In addition, ERβ acts as an inhibitor of peroxisome proliferators-activated receptor gamma activity, a major inhibitory regulator of glucose and lipid metabolism (Foryst-Ludwig *et al.* 2008).

Glucose- and arginine-stimulated insulin release in pancreatic islets is similar in mice lacking either ERα or ERβ when compared with control animals (Bryzgalova *et al.* 2006). ERα-knockout mice have an obese phenotype and develop insulin resistance (Heine *et al.* 2000), yet 17β-oestradiol is without effect in increasing insulin levels in isolated islets from ERα-knockout animals compared to controls or to ERβ-knockout mice (Alonso-Magdalena *et al.* 2008). Moreover, in the absence of ERα, 17β-oestradiol only partially protects pancreatic β-cells from apoptosis (Le May *et al.* 2006). A recent study investigated the role of ERs in vascular inflammation associated with diabetes. In both healthy and diabetic mice lacking ERβ, 17β-oestradiol reduced inflammatory nitric oxide synthase expression in the aorta. This inhibitory effect was absent in ERα-knockout animals (Cignarella *et al.* 2009) indicating that the protective effects of oestrogens on inflammatory responses in the vessel wall are mediated by ERα (Cignarella *et al.* 2009). In summary, these studies not only indicate an important role of ERα in the regulation of insulin sensitivity but also point to an inhibitory effect of ERβ on ERα-dependent actions (Matthews & Gustafsson 2003).

Novel metabolic functions of G-protein-coupled oestrogen receptor

Body weight, food intake and obesity

G-protein-coupled oestrogen receptor or GPER (originally cloned and designated as GPR30) is a transmembrane G-protein-coupled receptor located predominantly in the endoplasmic reticulum (Prossnitz *et al.* 2007, 2008). GPER binds 17β-oestradiol, an agonist activating three major ERs, with subsequent

cellular signalling via multiple pathways (Filardo *et al.* 2000, Revankar *et al.* 2005, Thomas *et al.* 2005, Prossnitz *et al.* 2007, 2008). GPER can also be activated by selective oestrogen receptor modulators (SERMs) or selective oestrogen receptor downregulators (SERDs) (Lin *et al.* 2009, Chow *et al.* 2010, Meyer *et al.* 2010), traditionally thought only to modulate the function of ERα and ERβ (Filardo *et al.* 2000, Revankar *et al.* 2005, Meyer *et al.* 2010). A GPER-selective agonist (G-1) and an antagonist (G15) have recently been described and are being widely employed to examine GPER function and physiology (Bologa *et al.* 2006, Dennis *et al.* 2009). GPER is highly expressed in the reproductive and cardiovascular systems (Prossnitz *et al.* 2008, Prossnitz & Barton 2009) as well as in pancreatic islets, adipocytes, neurons and inflammatory cells (Hugo *et al.* 2008, Haas *et al.* 2009, Liu & Mauvais-Jarvis 2009, Liu *et al.* 2009, Martensson *et al.* 2009, Nadal *et al.* 2009, Balhuizen *et al.* 2010, Kanda & Watanabe 2003, Blasko *et al.* 2009, Noel *et al.* 2009, Terasawa *et al.* 2009, Rettew *et al.* 2010). Interestingly, sexual dimorphisms for GPER expression and/or function have been described not only in the brain (Canonaco *et al.* 2008) but also in the pancreatic islets, where it is expressed at a much higher level in women than in men (Balhuizen *et al.* 2010). Accordingly, a role for GPER, in addition to ERα and ERβ, in the regulation of obesity-associated metabolic functions has recently been proposed. Deficiency of GPER was found to be associated with increased visceral adiposity (Ford *et al.* 2010, Haas *et al.* 2009) whereas Martensson *et al.* (2009), using a different GPER knockout strategy, found changes in body weight that were limited to female GPER-deficient animals. The same investigators found no effect of GPER deficiency on the anti-obesity effects of 17β-oestradiol (Windahl *et al.* 2009). By contrast, Isensee *et al.* found no effect of GPER deficiency on body weight in animals on either a normal or high-fat diet in another model, LacZ-GPER reporter mice from Deltagen®, which represent a partial GPR30 deletion (Isensee *et al.* 2009, Olde & Leeb-Lundberg 2009, Langer *et al.* 2010). Experimental evidence from studies with tamoxifen and raloxifene – SERMs and SERDs that are also GPER agonists (Revankar *et al.* 2005, Lin *et al.* 2009, Chow *et al.* 2010, Meyer *et al.* 2010 and E.R. Prossnitz unpublished observation 2010) – supports the concept that GPER activation has inhibitory effects on food intake, body weight and fat mass (Baptista *et al.* 1997, Meli *et al.* 2004).

Insulin sensitivity

In normal animals and healthy humans, the expression of GPER is high in the pancreatic islets and in the liver, two important organs controlling insulin function (Liu *et al.* 2009, Samuel *et al.* 2010). Recent work from Mauvais-Jarvis' group found that GPER has a critical role in islet survival (Liu & Mauvais-Jarvis 2009, Liu *et al.* 2009) although glucose tolerance of the normal-diet fed GPER-deficient mice was normal despite increased central obesity (Liu *et al.* 2009, Haas *et al.* 2009, Ford *et al.* 2010). In contrast, Martensson *et al.* (2009) reported that glucose tolerance is impaired only in female mice lacking GPER. The subsequent hyperglycemia in these animals is caused by a loss of oestrogen-stimulated pancreatic insulin secretion (Martensson *et al.* 2009). In addition, deficiency of GPER predisposes to a loss of β-cells and a decrease in pancreatic insulin production after acute exposure to oxidative stress in females (Liu *et al.* 2009). Selective GPER activation, in turn, prevents apoptosis in islets as efficiently as non-selective ER activation by 17β-oestradiol (Liu *et al.* 2009). Together, these studies imply that GPER is a novel and important oestrogen-dependent regulator of glucose metabolism and body weight (Fig. 2), although to date, little is known about the individual anti-adipogenic actions of ERα, ERβ and GPER.

Conclusions

Oestrogens are important, sex-independent regulators of body weight, body fat distribution and insulin resistance. Although conventional oestrogen therapy might beneficially affect adiposity and diabetes risk, its previous use in women was associated with adverse effects including an increased risk for breast cancer and thromboembolism. This increased risk may partly result from non-selective activation of ERs, which are ubiquitously expressed in the human body. Future basic science investigations should therefore lead to a better understanding of the molecular mechanisms whereby different ERs regulate body weight and insulin sensitivity in both females and males. In particular, potential interactions and cross-talk between ERα and GPER, which seem to mediate most beneficial effects and ERβ that often opposes these functions, might be identified. This identification may help to define novel pharmacological targets selectively associated with fat metabolism and glucose homeostasis. Of note, such an approach would also imply a therapeutic potential in men bypassing the unwanted effects of oestrogens.

From a clinical perspective, it should be noted that obesity is associated with increased cardiovascular risk regardless of the accompanying metabolic status (Arnlov *et al.* 2010). In addition, prevention of weight gain or loss and maintenance of body weight may also reduce the risk of several other obesity-associated diseases such as breast cancer in women (Harvie *et al.*

2005). In view of the number of obese children increasingly diagnosed with type 2 diabetes (Sorof & Daniels 2002, Ludwig 2007), arterial hypertension (Andrade *et al.* 2010), fatty liver disease (Denzer *et al.* 2009, Alisi *et al.* 2010), often in combination with a lack of exercise (Belcher *et al.* 2010, Chen *et al.* 2005), appropriate steps need to be taken to avoid the projected decline in life expectancy related to the long-term clinical complications of obesity (Olshansky *et al.* 2005, Stewart *et al.* 2009).

Conflict of interest

None

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