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Roles of G protein-coupled estrogen receptor GPER in metabolic regulation

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Abstract

Metabolic homeostasis is differentially regulated in males and females. The lower incidence of obesity and associated diseases in pre-menopausal females points towards the beneficial role of the predominant estrogen, 17β-estradiol (E2). The actions of E2 are elicited by nuclear and extra-nuclear estrogen receptor (ER) α and ERβ, as well as the G protein-coupled estrogen receptor (GPER, previously termed GPR30). The roles of GPER in the regulation of metabolism are only beginning to emerge and much remains unclear. The present review highlights recent advances implicating the importance of GPER in metabolic regulation. Assessment of the specific metabolic roles of GPER employing GPER-deficient mice and highly selective GPER-targeted pharmacological agents, agonist G-1 and antagonists G-15 and G36, is also presented. Evidence from *in vitro* and *in vivo* studies involving either GPER deficiency or selective activation suggests that GPER is involved in body weight regulation, glucose and lipid homeostasis as well as inflammation. The therapeutic potential of activating GPER signaling through selective ligands for the treatment of obesity and diabetes is also discussed.

Keywords

Estrogen; GPER; metabolism; diabetes; inflammation; insulin resistance; obesity

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Competing interests: G.S. and E.R.P. are inventors on a U.S. patent application for the therapeutic use of compounds targeting GPER. E.R.P. is an inventor on U.S. patent Nos. 7,875,721 and 8,487,100 for GPER-selective ligands and imaging agents.

Introduction: Obesity, metabolic syndrome and sexual dimorphism

Obesity is a global health crisis affecting millions of people and represents a serious health and economic burden [1, 2]. It is a heterogeneous disease that leads to insulin resistance and glucose intolerance, elevated lipid levels, hypertension and inflammation, all risk factors contributing to type 2 diabetes and cardiovascular disease [3, 4]. Metabolic syndrome is a term that has been coined to refer to the cluster of metabolic disorders that frequently result from obesity [5]. Current major causes of obesity include calorie (sugar and fat) -rich diets and a sedentary lifestyle, resulting in higher levels of circulating lipids and excessive lipid deposition in metabolically important tissues such as skeletal muscle, liver, adipose and pancreas [6–9]. Increased lipid deposition leads to insulin resistance, which in turn results in further increases in triglyceride and non-esterified fatty acid release from adipose tissue, decreases in insulin-stimulated glucose uptake in skeletal muscle and increased hepatic glucose production [10, 11]. The ensuing lipotoxicity and glucotoxicity in the islets of the pancreas reduces insulin production from pancreatic β-cells, eventually leading to diabetes [12, 13]. Thus, obesity and its associated comorbidities pose severe economic threats to our modern society and it is therefore critical to understand the underlying mechanisms and develop therapeutic strategies to fight obesity.

The prevalence of obesity and its associated risk factors (termed metabolic syndrome) exhibit a sexual dichotomy. Whereas pre-menopausal women are largely protected against weight gain, inflammation and the ensuing metabolic and cardiovascular dysfunction compared to age-matched men, this protection is lost after menopause [14, 15]. Postmenopausal women exhibit a decrease in energy expenditure, increased visceral fat deposition, insulin resistance and impaired glucose and lipid metabolism, with estrogen/hormone therapy normalizing these abnormalities to some extent [16–22]. Furthermore, in addition to increased total fat deposition, differences exist between pre- and post-menopausal women and men in terms of fat distribution [14]. Although premenopausal women exhibit more overall fat compared to age matched men, the fat in premenopausal women is stored to a greater extent in the lower body, exhibiting a gynoid distribution that is more resistant to lipolysis. On the other hand, men and postmenopausal women exhibit an upper body/visceral or android distribution of fat, which is more effective in mobilizing lipids [23]. The expansion of android fat depots is usually associated with a greater risk of developing diseases associated with metabolic syndrome. As increased central/android fat deposition alters the secretion of adipose-derived hormones and cytokines, increases circulating levels of lipids and glucose and induces systemic inflammation, obesity produces multiple negative effects on organs throughout the body [24–26]. A sexual dimorphism is also evident in rodents as male mice exhibit increased weight gain on a high-fat diet compared with females [27] but surprisingly are also responsive to estrogen and estrogen mimetics [28]. Hence, the increase in the incidence of obesity-related metabolic disorders is observed in men and postmenopausal women compared to premenopausal women.

Estrogen and metabolism

In premenopausal females, the protective effects on metabolism are largely attributed to estrogens, an important class of female sex hormones. The most potent of estrogens is 17β-

estradiol (E2), which modulates food intake and energy expenditure through the central nervous system [29] and also exerts direct effects on the physiology of important metabolism-regulating tissues such as adipose, skeletal muscle, liver, pancreas as well as immune cells [30–32]. Besides regulating amount of fat, E2 also regulates the site of fat deposition as well as inflammation and glucose and lipid homeostasis [30, 33–35]. E2 specifically promotes accumulation of subcutaneous fat and inhibits visceral fat deposition and suppresses lipogenesis in adipose tissue, skeletal muscle, liver and pancreas [36–39]. In addition, E2 maintains glucose homeostasis by enhancing glucose-induced insulin secretion from pancreatic β-cells [19, 40]. Ovariectomized mice, where surgical removal of the ovaries eliminates the endogenous production of E2, is a frequently used model to study the metabolic effects of E2 deprivation [41]. Ovariectomized mice and postmenopausal women share similar metabolic traits resulting from E2 reduction, such as increased adiposity, changes in body fat distribution (specifically central fat), lower energy expenditure, glucose intolerance and reduced insulin sensitivity [16, 41]. Administration of E2 or conjugated equine estrogens (CE) to postmenopausal women or ovariectomized female rodents alleviates multiple aspects of metabolic syndrome. Specifically, treatment with estrogens reduces fat mass, decreases fasting glucose and insulin levels, improves dyslipidemia, and ameliorates insulin resistance and glucose intolerance [32, 42–44]. Ovariectomized mice, supplemented with E2 or CE, exhibit increased lipid oxidation with a concomitant decrease in lipogenesis in metabolically active peripheral tissues such as adipose, liver and skeletal muscle, thereby preventing lipid accumulation and improving metabolic output of these tissues [30, 44]. Weight gain in ovariectomized mice is associated with increases in adipocyte size and visceral fat pads resulting in the altered production of hormones and other bio-active substances such as leptin, resistin, pro-inflammatory cytokines and reactive oxygen species, which further mediate many pathological consequences of obesity on metabolism [45, 46]. Treatment of ovariectomized mice with E2 or CE reduces the size of adipocytes and visceral fat pads [41, 44, 47]. Furthermore, E2 and CE confer protection against oxidative stress and inflammation both in postmenopausal women as well as ovariectomized rodent models [44, 48, 49]. Another important mouse model that reinforces the importance of E2 in regulation of metabolism is the aromatase knockout (ArKO) mice. Aromatase is the key enzyme involved in the final step of E2 biosynthesis from testosterone. Male and female ArKO mice with E2 insufficiency develop adiposity due to an accumulation of intra-abdominal fat and displayed increases in adipocyte volume, circulating levels of leptin, insulin and cholesterol as well as a decrease in lean mass and physical activity [50]. Thus, E2 supplementation exerts pleiotropic effects via multiple pathways in metabolic tissues to mitigate the effects of adiposity and associated metabolic dysfunction arising from E2 insufficiency.

Estrogen receptors

Estrogen, via its receptors, regulates a myriad of physiological effects in multiple metabolic tissues. Effects of E2 are mediated by nuclear and extranuclear estrogen receptors (ERs), ERα and ERβ, which mediate genomic responses through transcriptional activation and rapid actions [51–53]. In the last decade evidence has emerged towards the role of the G protein-coupled estrogen receptor (GPER) in metabolic regulation [54, 55], as well as

cardiovascular physiology [56–59], immune regulation [60–62], the nervous system [63, 64], reproduction [65, 66] and cancer [67–73]. GPER is known to exert its effects through non-genomic rapid signaling as well as transcriptional activation [74]. The receptors and mechanisms involved in the actions of E2 are dependent on the type of tissue, the abundance of receptor types present and cross talk between different receptor types. Non-genomic rapid signaling in response to E2 via GPER can activate multiple signaling pathways including MAPK, PI3K, PKC, Ca^{2+} mobilization and adenylyl cyclase (to produce cAMP) [54, 75]. As described above, loss of E2 leads to metabolic imbalance in humans as well as mice. Similarly, mice lacking either ERα or GPER recapitulate multiple aspects of metabolic syndrome, such as obesity, dyslipidemia, insulin resistance, glucose intolerance as well as inflammation [76–78]. With advances in the medical sciences and an increase in life expectancy, women live a large part (up to half) of their life after menopause with an elevated risk of obesity, diabetes and cardiovascular disease. Although menopausal hormone therapy (containing estrogens) in postmenopausal women has shown promise in alleviating these metabolic disturbances, this benefit is not without side effects such as an increased risk of some cancers. Thus, it is imperative to identify new targets for therapeutic intervention of obesity and diabetes to improve the quality of life in post-menopausal women. Numerous studies have elucidated the importance of ERα in energy homeostasis, either through ERα KO mice or by activating ERα through semi-selective ligands (Reviewed in [32, 70, 79, 80]). In the present review, we focus on the recent advances in understanding the effects of GPER deletion or selective activation in the regulation of obesity and metabolic function.

GPER expression and selectivity

GPER is a 7-transmembrane G protein-coupled receptor (GPCR), first described as an orphan GPCR in late 1990s [81]. It has since been shown to bind E2 and activate multiple signaling pathways [82–84]. Antibodies raised against GPER have demonstrated its expression and distribution in a wide variety of cells and tissues. Although GPER, as a 7-transmembrane GPCR, is presumed to be located on the plasma membrane as most GPCRs are, many reports observed that in diverse cells and tissues, GPER is predominantly, though not exclusively, localized to intracellular membranes, particularly those of the endoplasmic reticulum and Golgi apparatus [82, 85, 86]. GPER is widely expressed in reproductive tissues, heart, intestines, ovary, CNS, pancreatic islets, adipose tissue, skeletal muscle, liver, neurons and inflammatory cells [87]. In some tissues, GPER expression is developmentally regulated, such as in developing female reproductive tissues and during the estrous cycle in females [87]. GPER expression in certain tissues also exhibits sexual differences such as in brain [88] and pancreatic islets, where females express higher levels than males [89]. Because GPER is expressed in numerous tissues, it has been implicated in diverse (patho)physiologies such as cancer, immune regulation, and cardiovascular, reproductive and metabolic/endocrine function [87].

When performing experiments with E2, whether *in vitro*, *in vivo* or *ex vivo*, it is difficult to ascertain the effect to a particular receptor, since E2 binds to all the three estrogen receptors (ERα, ERβ and GPER). Certain pharmacological agents, such as tamoxifen and raloxifene, defined as selective estrogen receptor modulators (i.e. inhibitors in some tissues but activators in others), nevertheless activate GPER, further complicating interpretation of their

physiological profiles, particularly in cancer [70]. In order to delineate the effect(s) of distinct E2 receptors more precisely, receptor-selective pharmacological tools [75] and genetically modified animals [78] have been developed and employed. In 2006, the first (and to this day only) highly selective GPER agonist G-1 was identified [90]. This was followed in 2009 and 2011 by the identification and characterization of the GPER-selective antagonists G15 and G36 [91, 92]. Since their discoveries, G-1, G15 and G36 have been used in over 300 studies to assess GPER function in a wide variety of cellular and *in vivo* studies. Pharmacological findings have largely been supported by studies with genetically engineered GPER KO mice [78], which not only lack the stimulatory effects of G-1, demonstrating the lack of off-target effects of this compound, but also lack many effects of E2, demonstrating its essential role in E2 function in many systems. In particular, recent studies employing GPER KO mice and GPER-selective pharmacological agents reveal multiple roles for GPER in obesity and metabolism [77, 78, 93].

GPER, adiposity and energy balance

Multiple groups have examined the role(s) of GPER in regulating body weight and abdominal fat through the use of GPER KO mice. In early 2009, although Haas *et al.* observed an increase in the body weights and visceral adiposity in both male and female GPER KO mice [56], Mårtensson *et al.* reported a slightly lower body weight in female GPER KO mice compared to WT mice and did not observe any differences in the body weights of male GPER KO mice compared to WT mice [94]. The differences in the two studies might be attributed to the different methods used to generate GPER KO mice. Whereas Haas *et al.* used mice created by homologous recombination of embryonic stem cells, Mårtensson *et al.* generated GPER KO mice using cre/lox approach that could generate some cryptic or pseudo loxP sites resulting in chromosomal translocations. Alternatively, differences in chow, bedding or environmental factors could have contributed to the differences reported. In 2013, we reported a detailed analysis of body weight of male GPER KO mice between 6 months and 2 years of age [77]. GPER KO mice exhibited higher body weights at all time points. GPER KO mice exhibited an increase in both subcutaneous fat as well as perirenal and epididymal fat pads, suggesting a role of GPER in controlling adiposity. We as well as others did not observe any changes in food consumption or locomotor activity between various WT and GPER KO mice [77, 95].

Consistent with our observations [77], a recent study by Davis *et al.* also reported increased body weights in male and female GPER KO mice due to increased fat mass with enlarged adipocytes [95]. Expression of GPER in both male and female WT mice was predominantly located in the adipocyte fraction as opposed to the stromal vascular fraction, suggesting a direct role of GPER in adipocyte physiology. Furthermore, knockout mice of both sexes exhibited lower energy expenditure in the dark period compared to their WT counterparts. Expression of certain metabolically important genes in brown adipose tissue, such UCP1 and β_3-adrenergic receptor, were lower in GPER KO males, with only β_3-adrenergic receptor expression (and not UCP1) down-regulated in female GPER KO mice [95]. We have observed that male GPER KO mice exhibited dyslipidemia with higher levels of circulating cholesterol and triglycerides [77]. As a result of excess ectopic lipid accumulation, female and male GPER KO mice also exhibited hepatic steatosis [95]. As

numerous groups have reported that GPER KO mice exhibit increased body weight, it would be tempting to speculate that GPER activity and thus activation by selective ligands may have therapeutic implications for counteracting obesity. Surprisingly, a single recent study has reported that female GPER KO mice were protected from diet-induced obesity due to a reduction in fat mass with increased energy expenditure during the dark phase [96]. At this time, it is unclear what the confounding factors may be regarding this unique report.

E2 is known to regulate food intake through enhancing the anorexigenic effects of leptin and cholecystokinin (CCK). Female GPER KO mice have been reported to be less sensitive than WT mice to the feeding-inhibitory effects of leptin and CCK. Whereas WT female mice exhibited reduced food intake in response to leptin (for up to 24 hours) or CCK, female GPER KO mice did not (even as early as 4 hours following leptin administration) [95]. In contrast, both male WT and GPER KO mice exhibited similar reductions in food intake in response to both leptin and CCK. Thus, GPER deficiency impacts leptin- and CCK-mediated decreases in food intake in females but not males.

GPER, insulin sensitivity and glucose tolerance

The role of GPER in glucose homeostasis has been assessed in GPER KO mice. Six month-old female GPER KO mice displayed increased blood glucose levels and impaired glucose tolerance, which correlated with decreased insulin release *in vitro* [94]. On the contrary, male mice lacking GPER exhibited normal glucose tolerance at the same age [94]. Since male GPER KO mice exhibited normal glucose tolerance at 6 months of age but are dyslipidemic, we determined the effect of aging on glucose tolerance and insulin sensitivity in male mice [77]. Although male GPER KO mice displayed normal glucose tolerance at 6 months of age, they did exhibit insulin resistance, which eventually progressed to glucose intolerance with increasing age, reaching significance by 18 months of age. Male GPER KO mice also displayed a pro-inflammatory state with higher levels of circulating pro-inflammatory cytokines such as TNFα, MCP1, IL-1β with a concomitant decrease in adiponectin [77]. A possible explanation for GPER KO mice becoming glucose intolerant only with age could be the cumulative effects of prolonged elevations in circulating lipids and insulin resistance. Our observations were subsequently confirmed in a study demonstrating an increase in circulating levels of serum amyloid A3, a marker of inflammation as well as a decrease in adiponectin levels both in male and female GPER KO mice compared to their WT controls [95]. Further, whereas supplementation with E2 improved glucose tolerance in ovariectomized WT mice, E2 failed to do so in ovariectomized GPER KO mice [95].

GPER and islet function and survival

GPER is expressed in most islet cells and is highly sexually dimorphic with greater expression in females [89]. The first evidence of a role for GPER in insulin release was reported in 2009 in a study employing isolated islets from female and male GPER KO mice. In response to a pharmacological dose of E2 (5μM), islets from GPER KO mice showed impaired insulin release at low and high glucose levels as well as in the presence of the insulin secretagogue tolbutamine [94]. These authors further reported that ovariectomized

(ovx) female GPER KO mice, treated with E2, exhibited decreased glucose-stimulated insulin secretion (GSIS) compared to ovx/E2-supplemented WT controls. In cultured islets from female WT mice, G-1 increased GSIS and inhibited glucagon and somatostatin secretion to an extent similar to E2 [89]. Furthermore, activation of GPER by E2 and G-1 similarly increased islet cAMP content. These multiple effects on islets in response to E2 or G-1 could not be blocked by ERα and ERβ antagonists (ICI-182,780 and EM-652, respectively), suggesting that G-1 and E2 activate similar non-genomic signaling events in islet hormone secretion [89].

Studies using cultured human islets have revealed that GPER expression in female islets was markedly higher than in males [97]. As in the mouse, E2 and G-1 stimulation enhanced GSIS and suppression of glucagon and somatostatin secretion from isolated islets of female donors. The insulinotropic potential of G-1 (and E2) was further demonstrated by the improvement of GSIS from islets of type 2 diabetic patients [97]. Experiments in the mouse insulinoma MIN6 cell line revealed that the mechanism(s) of GPER-stimulated insulin secretion involve intracellular calcium release and activation of ERK1/2 and PI3K [93]. Similar to GPER signaling in many cancer cell lines, insulin secretion from islets in response to GPER activation required transactivation of EGFR and ERK and was further modulated by PI3K [93]. In MIN6 cells and murine islets, E2- or G-1-induced insulin secretion was abolished with pharmacologic GPER-selective antagonism with G15 [93]. Furthermore, knockdown of GPER by either siRNA in MIN6 cells or using GPER KO islets resulted in a blunted insulin secretory response to stimulation with either E2 or G-1. Together, these results reveal multiple important roles for GPER in islet function.

Activation of GPER by G-1 also protects cultured islets from bioactive lipid accumulation [38, 39]. Indeed G-1 activation of GPER inhibits β-cell lipid synthesis by suppressing the expression (and activity) of fatty acid synthase. The mechanism seems to involve activation of STAT3 leading to suppression of the gene transcription of the two lipogenic transcription factors ChREBP and SREBP1c. In the case of SREBP1c, treatment with G-1 also prevented SREBP1c cleavage into the active mature form to an extent similar to E2 [38]. G-1 also promotes mouse and human islet survival from pro-apoptotic diabetic injuries like oxidative stress and proinflammatory cytokines [89, 97, 98]. In the absence of GPER, mouse islets lose protection from oxidative stress when stimulated by G-1 but retain protection by E2 (still acting via ERα) [98]. Importantly, in mice of both sexes and their cultured islets, E2 was able to protect from streptozotocin-induced islet apoptosis and insulin-deficient diabetes via GPER and in absence of ERα and ERβ [98]. The beneficial effects of G-1 activation of GPER on β-cell survival, function and lipid accumulation that are described above, are all observed in human β-cells [39, 40, 97–99]. Investigation of the mechanisms involved in GPER-mediated cell survival in islets subjected to a cytokine cocktail revealed suppression of the activation of stress proteins such as, pSAPK/JNK and p38 and phosphorylation of pro-survival genes such as CREB, Akt and ERK1/2 [81].

GPER has also been implicated in the expansion of β-cell mass observed during pregnancy. In female rodents, GPER expression is markedly increased during pregnancy (when E2 levels are high) and is correlated with β-cell mass expansion [100]. Pregnancy-induced increases in islet GPER expression are associated with decreased expression of the islet

microRNA miR-338-3p. Interestingly, in INS832/13 insulin-secreting cells and dissociated rat islet cells, downregulation of miR-338-3p using anti-miR molecules promoted β-cell proliferation and protected from pro-inflammatory cytokines-induced apoptosis. Further, in isolated rat islets, exposure to E2 or the GPER agonist G-1 also decreased miR-338-3p to levels observed during gestation. In contrast, prolactin and progesterone, two maternal hormones elevated during pregnancy, did not affect miR-338-3p levels in INS832/13 cells [100]. Together, these observations suggest that E2 may participate in the increased β-cell proliferation and mass expansion of pregnancy in rodents, via GPER-mediated suppression of miR-338-3p. In fact, transcriptomic analysis of INS832/13 cells with downregulated miR-338-3p exhibited enrichment in the expression of genes involved in cell cycle and growth. Consistent with the fact that GPER couples to $G\alpha_s$, triggering a rise in cAMP and activation of protein kinase A (PKA) [101], the effect of GPER in suppressing miR-338-3p in β-cells was dependent upon cAMP production and PKA activation [100]. Although E2 exposure also reduced the level of miR-338-3p in cultured human islet cells, which also enhanced survival, neither E2 nor silencing of miR-338-3p elicited proliferation of human β-cells in culture [100]. Likewise, neither E2 nor G-1 treatment yielded proliferation of human β-cells transplanted in male mice [102], although they do stimulate proliferation of dispersed rat islet cells (that include other cell types in addition to β-cells, which, however, represent ~80% of the cell population) [100]. This result is not surprising since proliferation of human β-cells is an extremely rare event [103]. Further effects of E2 on β-cell division independent of GPER are discussed elsewhere [104].

Conclusions and future directions

There is increasing evidence that GPER is a key player in body weight regulation and metabolism. However, E2 exerts metabolic effects through distinct receptors via multiple pathways, both transcriptional and rapid. These effects are likely complex and may be direct or indirect. Furthermore, deletion of GPER in mice yields phenotypes [78] that are to some extent similar to ERα deletion [105], such as increased adiposity, insulin resistance, inflammation and altered glucose and lipid homeostasis, suggesting that estrogen action through GPER is important to maintain a normal metabolic homeostasis. In mice lacking both ERα and ERβ, E2 still exerts anti-diabetic actions, suggesting a contribution by GPER [98].

Future studies should aim to understand the role of GPER on peripheral tissues important in glucose and fat metabolism, such as adipose, muscle, and liver. As there is an urgent need to identify novel molecular targets and therapeutic agents capable of preventing or limiting the development and consequences of metabolic abnormalities arising from obesity, GPER-selective agonists, which exert little estrogenic effect on the uterus in terms of imbibition and epithelial proliferation (i.e. non-feminizing), may represent very promising candidates to treat obesity and its comorbidities.

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Highlights

- Estrogens are important regulators of body weight and glucose and lipid homeostasis.
- GPER-deficient mice are obese, dyslipidemic, insulin resistant and exhibit hepatic steatosis.
- GPER regulates leptin- and CCK-mediated food intake.
- GPER-selective agonist enhances insulin secretion and islet survival
- GPER activation reduces lipid synthesis and inflammation.