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Emerging Roles of GPER in Diabetes and Atherosclerosis

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Abstract

G protein-coupled estrogen receptor (GPER) is a 7-transmembrane receptor implicated in rapid estrogen signaling. Originally cloned from vascular endothelial cells, GPER plays a central role in the regulation of vascular tone and cell growth, as well as lipid and glucose homeostasis. This review highlights our knowledge of the physiological and pathophysiological functions of GPER in the pancreas, peripheral and immune tissues, and the arterial vasculature. Recent findings of its roles in obesity, diabetes, and atherosclerosis, including the GPER-dependent regulation of lipid metabolism and inflammation, are presented. The therapeutic potential of targeting GPER-dependent pathways in chronic diseases such as coronary artery disease and diabetes and in the context of menopause is also discussed.

Keywords

atherosclerosis; diabetes; estrogen receptor; rapid signaling; GPER

Estrogen: modulator of metabolic function

The clinical consequences of obesity, insulin resistance, and diabetes account for the majority of morbidity and mortality in industrialized countries, largely caused by atherosclerosis, leading to coronary artery disease and myocardial infarction, stroke, and peripheral vascular disease [1]. Both atherosclerotic vascular disease and obesity-associated metabolic dysfunction, such as in insulin resistance and diabetes, share a strong inflammatory component, contributing to disease propagation and representing a prognostic marker [1]. The same holds true for obesity, where abnormal increases in fat mass and adipocytes cause metabolic dysfunction, which is partly driven by and perpetuated by

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Disclosure

ERP is an inventor on patents for GPER-targeted ligands and imaging agents owned by the University of New Mexico.

inflammation, thereby contributing to organ injury and propelling chronic disease processes such as atherosclerosis and glomerulosclerosis [1-3].

Endogenous estrogens in premenopausal women largely prevent the development of the above pathologies, partly through beneficial effects on blood pressure, lipid metabolism, and glucose homeostasis, and by inhibiting inflammation [2, 4]. However, with the loss of estrogen production after menopause, its beneficial effects prior to menopause are evident as postmenopausal women become prone to the development of obesity, insulin resistance, diabetes, and arterial hypertension, which collectively accelerate the development of atherosclerotic vascular disease [4]. Moreover, the postmenopausal state is characterized by generalized inflammatory activation. Estrogen effects can be divided into chronic (“genomic”) and acute (“non-genomic”) effects that are mediated by specific estrogen receptors [2, 4]. Genomic effects of estrogens such as 17 β -estradiol (E2) are largely mediated by the nuclear receptors estrogen receptor alpha and beta (ER α and ER β) that function as ligand-dependent transcription factors regulating expression of target genes [4]. We [4] and others [5, 6] have recently reviewed the metabolic actions of estrogens in the context of nuclear ER signaling and the related sex differences. Non-genomic effects of estrogens, which include rapid vascular effects as well as signaling in the central nervous system (CNS) [7], are mediated by membrane subpopulations of ER α and ER β , as well as GPER, a recently identified intracellular transmembrane G protein-coupled receptor [8]. GPER was cloned from multiple sources including lymphocytes, breast cancer cells, and shear stress-exposed endothelial cells [9], which early on suggested possible functions for GPER in cancer, immune and vascular function, which were later confirmed in numerous studies [10].

An intracellular G protein-coupled membrane estrogen receptor

GPER was originally identified through cloning approaches and homology analysis as a 7-transmembrane spanning GPCR in the mid-1990's [9] [11]. As no ligand could be identified in early studies, it was termed GPR30, an orphan receptor designation. Only in 2007, after several laboratories had independently demonstrated estrogen binding to and function through GPR30 [12-14] did the International Union of Basic and Clinical Pharmacology (IUPHAR) officially designate GPR30 as GPER [9].

GPER cellular localization

GPCRs are almost exclusively depicted as functioning at the plasma membrane, a model consistent with the majority of GPCR ligands that, unlike E2, are not readily membrane permeable [8]. In contrast to early representations [15, 16], initial studies of GPER suggested that the majority of GPER was localized to intracellular membranes such as the endoplasmic reticulum [13]. Although the localization of GPER remained controversial [12, 17, 18], many subsequent studies also observed intracellular localization [19-21], as well as nuclear localization [22, 23]. Studies demonstrating that only cell-permeable E2 derivatives [24] or intracellularly injected ligands [25] can lead to rapid GPER activation, supported the intracellular localization and functionality of GPER. More recent studies reveal that GPER trafficking is complex, with cell surface receptor undergoing constitutive clathrin-mediated internalization to intracellular membranes [26], likely accounting for lack of detectable

GPER at the cell surface of many cells. However, regulation of GPER trafficking in varied cell types could lead to complex patterns of differential subcellular expression [26].

GPER ligand selectivity

GPER contains specific binding sites for natural ligands such as E2 as well as for synthetic ligands [27]. Binding affinities of E2 for GPER have been reported in the 3-6 nM range [12, 13]; this compares to values for ER α / β in the 0.1-0.5 nM range [14], which suggests GPER is perhaps activated under conditions of higher local or systemic E2 concentrations. E2 binding to GPER exhibits high selectivity over other steroids including testosterone, cortisol, and progesterone [12], and despite studies that suggest a role for GPER expression in specific rapid cellular actions of aldosterone [28], binding of aldosterone could not be detected in GPER-containing membranes that displayed E2 binding activity [26]. Rather, it has been found recently that E2 - via ER α - inhibits mineralocorticoid receptor (MR) function [29]. Natural estrogen metabolites formed by catechol-O-methyltransferase, have recently been shown to bind to and signal through GPER, either as an agonist (2-methoxyestradiol, 2-ME2) [30], or antagonist (2-hydroxy estradiol (2-OH-E2) – a hydroxylated metabolite of E2) [31] (Figure 1). Furthermore, a large number of synthetic and natural estrogenic compounds have been shown to interact with GPER (Figure 1), including the therapeutic anti-estrogens ICI182,780 (a selective ER downregulator, SERD) and 4-hydroxytamoxifen and raloxifene (selective ER modulators, SERMs), which surprisingly all act as GPER agonists [13, 32, 33], and synthetic compounds such as MIBE (ethyl 3-[5-(2-ethoxycarbonyl-1-methylvinyl)-1-methyl-1H-indol-3-yl]but-2-enoate) [34]. Numerous synthetic compounds (e.g. pesticides and plastic precursors) that act as endocrine disruptors with metabolic and reproductive effects [35], including atrazine, bisphenol A, daidzein, zearaloxone, nonylphenol, kepone, *p,p'*-DDT, *o,p'*-DDE and 2,2',5',-PCB-4-OH as well as numerous phytoestrogens, including genistein, quercetin, equol, resveratrol, oleuropein and hydroxytyrosol, have also been reported to bind and/or activate GPER (recently reviewed in [9], Figure 1). With this complex pattern of overlapping ligand specificity between GPER and ERs, the identification of highly GPER-selective ligands, both agonists (G-1 [14]) and antagonists (G15 [36] and G36 [37]) (Figure 1) as well as GPER-selective radioimaging agents [38-41], all of which display no significant binding or function towards either ER α or ER β has opened the door to pharmacological studies of GPER in cells, tissues, and animals [10]. Molecular modeling and ligand docking simulations have been employed in an attempt to identify possible binding sites on GPER for E2, selective synthetic GPER ligands and therapeutic ligands such as SERMs and SERDs [27, 42].

GPER signaling

GPER, as other GPCRs, couples to heterotrimeric G proteins that in turn regulate a plethora of downstream cellular effectors [43]. GPER coupling to both G_{i/o} and G_s proteins has been reported [12, 15, 33, 44]. Downstream pathways include the Src-mediated activation of metalloproteinases (MMP), with release of heparin-binding epidermal growth factor (EGF), followed by transactivation of the EGF receptor (EGFR), which in turn leads to activation of extracellular signal-regulated kinases 1/2 (ERK1/2) and phosphoinositide 3-kinase (PI3K) [13, 33, 45]. GPER also activates endothelial nitric oxide synthase (eNOS) to produce nitric

oxide (NO) in endothelial cells [44, 46] and regulates calcium mobilization [13, 47, 48] and potassium channels [49]. Finally, as a result of these and other rapid signaling events, GPER modulates gene expression (distinct from that of ER α and ER β) [50, 51]. Just how the actions of classical ERs and GPER interact to bring about cellular effects remains to be fully explored, as the multiple receptors may act independently, synergize with each other, or alternatively antagonize the other receptor's activity [52, 53]. Importantly, functional cross-talk between GPER and nuclear receptors has not only been described for ER α , but also for other nuclear steroid receptors such as the vitamin D receptor (VDR), the glucocorticoid receptor (GR) and the MR [52], whereas no binding of aldosterone [26] or other steroids [12] to GPER has been demonstrated. Under these complex conditions, with the ultimate cellular output being dependent upon the integration of multiple pathways, the specific role(s) of individual receptors is a challenge to ascertain. Not surprisingly, these diverse GPER-regulated pathways impinge upon numerous varied cellular responses ranging from growth to migration to secretion to metabolism, which in turn suggest roles for GPER in multiple aspects of normal physiology and disease. The complexity and open questions regarding GPER function have been discussed in detail elsewhere [52, 54].

Models and phenotypes of GPER deficiency

Given the expansive functions of E2 in both sexes discussed above, ascertaining the distinct contributions of individual ERs requires either their specific genetic or pharmacological manipulation. The use of transgenic mice has been highly informative in the dissection of the roles of ER α and ER β [55]. As GPER expression has been detected in most organs and tissues throughout the body [52, 56], yet with cell type specificity [26], GPER likely plays important roles in mediating many estrogen-associated aspects of physiology and disease. A phenotype of GPER⁰ mice was first reported in 2008 [57], with the initial identification of GPER playing a role in E2-induced thymic atrophy; GPER⁰ mice also develop visceral obesity [47, 58-61]. Genetic ablation of GPER reduces anxiety and alters stress in a sex-dependent manner [62], decreases mammary tumor size and metastasis [63], and modulates immune responses consistent with an anti-inflammatory role for GPER [60, 64]. Unlike mice lacking ER α [55], GPER⁰ mice are fertile [56], consistent with studies showing GPER exhibits limited activity in uterine and other reproductive functions [36, 65]. This has led to questions regarding the role of GPER as an estrogen receptor [66, 67]. Three additional GPER⁰ mouse models have also been reported [65, 68, 69] and their genetic and initial basic phenotypic properties have been reviewed [56, 67]. Although discrepancies exist between reports of the phenotypes of these different knockout mice, a number of themes (particularly in the areas of endocrine, metabolic and cardiovascular functions) have emerged in recent years, with apparent discrepancies potentially explained in part by complex age- and sex-dependent effects, or differences in genetic backgrounds in the various studies [52]. Finally, statements questioning the role of GPER as an estrogen receptor based largely on the lack of similarities between GPER and ER α knockout mouse phenotypes would seem imprudent, given the breadth of E2 effects throughout the body.

GPER and obesity

Both male and female GPER⁰ mice are obese with substantial increases in visceral, subcutaneous, and perivascular fat [47, 58-61]. Following ovariectomy, GPER⁰ mice also exhibited a reduced response to E2 in terms of reductions in weight and adipocyte size, and no improvement in glucose tolerance with E2 supplementation [58]. While GPER⁰ mice show a decrease in energy expenditure, suggesting alterations in energy metabolism [58, 60], recent data also indicate that hypothalamic signaling through GPER is involved in the anorectic response mediated by estrogen [70]. There is also evidence supporting a role for GPER in adipogenesis [71]. Consistent with the obesity phenotype observed in mice lacking GPER [47, 60, 61], Zhu et al. recently reported that the known E2-mediated inhibitory effects on adipogenesis *in vitro* involve GPER-dependent mechanisms, as effects were mimicked by the selective GPER agonist, G-1, and blocked by GPER gene silencing [71]. Furthermore, the GPER-selective agonist G-1 attenuates fatty acid synthesis and triglyceride accumulation in human and rodent pancreatic islets and β -cells [72].

GPER and glucose homeostasis

Estrogen and its receptors play critical roles in glucose homeostasis, the result of glucose-induced insulin production by the pancreas and peripheral insulin responsiveness, including metabolism and storage in multiple peripheral tissues (particularly skeletal muscle, adipose and liver) [73-75]. In the pancreas, E2 exhibits several important effects, including promoting insulin secretion [76, 77] and synthesis [74, 78], enhancing β -cell survival [5, 6], increasing islet oxygenation during transplantation and preventing lipotoxicity [72]. The roles of ER α and to a lesser extent ER β have been extensively investigated and reviewed elsewhere with respect to metabolic and specifically glucose regulation [5, 73, 75], including functions in the CNS [79]. Studies in GPER-deficient mice revealed that ovary-intact female GPER⁰ mice become glucose intolerant at six months of age, whereas male mice initially appeared unaffected [69]. However, subsequent studies revealed that male GPER⁰ mice are in fact insulin resistant at six months of age and only become glucose intolerant with increased age [60]. Estrogen receptor-linked, age-dependent phenotypes have also been reported in male ER β -deficient mice [80]. Pancreatic islets from GPER⁰ mice are also unresponsive to E2 in terms of insulin secretion [69, 81], and are more sensitive to apoptotic stimuli [82]. Female GPER⁰ mice also appear to be less sensitive to modulators of food intake such as cholecystokinin (CCK) and leptin, possibly due to impaired hypothalamic E2-dependent ERK phosphorylation [58]. A very recent study has identified GPER as mediating hypothalamic signaling involved in the anorectic eating behavior mediated by estrogen [70].

Under conditions of peripheral insulin resistance (prediabetes), the pancreas is called upon to secrete ever increasing amounts of insulin in an attempt to mitigate the effects of hyperglycemic toxicity. This ultimately leads to β -cell “exhaustion” and apoptosis, leading to a decrease in β -cell mass. To examine whether the observed elevated plasma glucose levels and glucose intolerance in female [69] and older male GPER⁰ mice [60] could be a result of diminished insulin secretion in GPER⁰ mice, isolated pancreatic islets were studied *in vitro*. Whereas high glucose-stimulated insulin secretion was minimally reduced in male GPER⁰ mice [60, 69], effects in female mice were greater, with moderately reduced insulin

mRNA and protein levels in islets also observed in females [69]. Similar results were observed for the decrease in high glucose-stimulated glucagon secretion, although islet glucagon mRNA was unaltered in GPER⁰ mouse islets [69]. Furthermore, following ovariectomy, E2 treatment failed to increase serum insulin levels in GPER⁰ mice as it did in wild type mice [69]. To evaluate possible direct effects of GPER on hormone secretion by islets, the effects of E2 stimulation were determined in wild type and GPER⁰ mouse islets. Whereas E2 stimulated insulin and inhibited glucagon secretion in islets from both male and female wild type mice, these effects were completely absent in islets from GPER⁰ mice [60, 69, 81]. Furthermore, the GPER-selective agonist G-1 stimulated insulin secretion from islets, similar to that of E2, whereas the GPER-selective antagonist G15 inhibited insulin secretion by both E2 and G-1 [81]. Together, these results demonstrate that GPER plays a critical role in glucose-mediated insulin secretion in female mice and in estrogen-mediated islet secretory function in both female and male mice.

Maintaining functional β -cell mass is a major goal in patients with type 2 diabetes. The lower incidence of diabetes in premenopausal women is consistent with the anti-diabetic functions of estrogen in both humans and rodents [4, 83]. A comparison of mice deficient in ER α , ER β , or GPER in a streptozotocin-induced type 1 diabetes model revealed that both ER α and GPER mediate protective roles, with that of ER β being through non-genomic actions [82]. Importantly, in the absence of both ER α and ER β , E2 partially restored protection in ovariectomized streptozotocin-treated mice, suggesting an alternative mechanism for the actions of E2. Along these lines, female type 1 diabetic mice lacking GPER lost the protective effects of endogenous E2. Furthermore, the GPER-selective agonist G-1 protected from ROS-induced apoptosis in both murine and human islets as effectively as E2 [82]. Although the protective effect of G-1 was absent in islets isolated from GPER⁰ mice, the effects of E2 remained, suggesting the ER α can compensate for the absence of GPER, unlike the requirement for GPER in insulin secretion [82].

Together, data available to date reveal a complex interplay between estrogen receptors in the E2-mediated protection of β -cells from apoptosis [6]. Consistent with these described survival effects, G-1 as well as ER α - and ER β -selective estrogenic ligands improved human islet-graft survival in a murine insulin-deficient xenotransplantation model; however, whereas all three ligands improved islet survival, only the ER α - and ER β -selective ligands improved islet revascularization [84]. Recent results also demonstrate the regulation of GPER expression by insulin [85] and insulin-like growth factor-I [86], as well as the GPER-mediated down regulation of miR-338-3p microRNA during pregnancy, enhancing both proliferation and survival under pro-apoptotic conditions [87], providing additional possible links between GPER, β -cell survival and glucose metabolism.

GPER in lipid metabolism, atherosclerosis, and inflammation

Inflammation has been identified as a unifying theme of obesity, diabetes, dyslipidemia, and atherosclerosis, and inhibition of inflammation is currently pursued as a means to induce plaque stabilization [1, 2]. Dyslipidemia, i.e. high levels of LDL cholesterol and triglycerides, is a major risk factor for the development of coronary atherosclerosis and is typically found in patients with obesity, insulin resistance, or diabetes, translating into an

increased cardiovascular risk [1, 2]. Decreased HDL cholesterol and increased triglyceride levels [60] are observed in female GPER⁰ mice (GPER-*lacZ* reporter with a partial deletion of the GPER coding sequence) in association with hepatic steatosis [88, 89]. In female mice under atherogenic conditions, deletion of GPER increases total and LDL cholesterol levels [46]. Moreover, aged (but not young) male GPER⁰ mice exhibit elevated LDL and triglyceride levels [60].

Activation of GPER inhibits proliferation of human vascular smooth muscle cells *in vitro* [47, 90], one of the key events in early atherogenesis [2]. While part of the estrogen-mediated protection from atherosclerosis in females is mediated by ER α [91], subsequent studies by Villablanca and coworkers demonstrated estrogen-mediated inhibition of atherosclerosis in mice deficient in ER α [92]. This indicated the involvement of additional estrogen signaling pathways. Using a model of diet-induced atherosclerosis, it was recently reported that ablation of GPER increases atherosclerotic plaque formation, both in ovary-intact and surgically postmenopausal mice, and that GPER deficiency is associated with increased levels of plasma LDL cholesterol [46]. These data are the first *in vivo* indication that GPER plays an essential role in vascular disease, the most prevalent health condition in postmenopausal women. Regulation of LDL cholesterol through GPER has also been demonstrated by a recent report where carriers of a GPER polymorphism showed higher circulating levels of plasma LDL cholesterol [93]; furthermore, experiments performed in hepatocytes *in vitro* demonstrated an inhibitory role for GPER in the regulation of LDL receptor expression [93]. In mice with overt atherosclerosis, it was also observed that the aggravating effect of GPER deficiency on disease progression was associated with pronounced vascular inflammation, involving macrophage and T-cell-dependent mechanisms [46]. Treatment with the highly selective, orally active small molecule agonist of GPER, G-1, was effective in reducing atherosclerosis in postmenopausal mice, and was associated with a pronounced reduction of vascular inflammation [46].

The anti-inflammatory effect of GPER activation in the vasculature *in vivo* is also supported by studies in endothelial cells and macrophages *in vitro*, demonstrating potent anti-inflammatory effects of drugs acting as GPER agonists [94, 95]. As GPER was also cloned from a human B cell lymphoblast cell line cDNA library [9], and is expressed and functional in white blood cells [96] and macrophages [11, 97], immunomodulating functions of this receptor may be expected. Indeed, studies in models of multiple sclerosis showed that GPER deficiency exacerbated inflammation, and that treatment with the GPER agonist, G-1, was effective in reducing inflammation [64, 98]. Investigation of the molecular mechanisms underlying the immunomodulating effect of GPER activation identified a prominent role for the forkhead box P3 (FOXOp3) protein pathway in promoting regulatory T cell differentiation and IL-10 secretion [99, 100]. In agreement with these observations indicating inhibitory function of GPER on immune responses, genetic ablation of GPER in aged male mice is associated with a pro-inflammatory state [60].

Enhanced vasoconstriction, just as inflammation, is a hallmark of metabolic diseases such as diabetes or insulin resistance and can also be observed in obese humans [1]. The enhanced vasoconstriction is due to breakdown / inactivation of the vasodilator NO and /or enhanced activity of vasoconstrictor prostanoids and vasoconstrictors such as endothelin-1. [1] The

fact that GPER was also cloned from shear-stress exposed endothelial cells [9] suggested a possible vascular role for this receptor. Indeed, its vascular functions are among the best described with numerous mechanisms through which GPER contributes to vascular homeostasis having been identified [101]. The acute estrogen-dependent vasodilator effects mediated by ER α , ER β and GPER vary markedly between vascular beds [102].

While GPER has been implicated in acute vasodilation and release of nitric oxide [101], its absence or inhibition is associated with enhanced vasoconstriction [61, 103]. Increased vasoconstriction in mice lacking GPER or in arteries treated with a GPER antagonist is brought about in part by enhanced release of endothelium-derived contracting factor (EDCF), mediated by cyclooxygenase-derived prostanoids [103].

Moreover, GPER⁰ mice show increased activities of the vasoconstrictor endothelin-1 [48] and the recently identified adipose-derived contracting factor (ADCF) [61], and male and female GPER⁰ mice exhibit excessive formation of perivascular adipose [61]. ADCF released from perivascular adipose contributes to enhanced vasoconstriction in GPER⁰ mice, an effect that can be prevented by expressing GPER, by ablation of perivascular adipose, or by inhibiting cyclooxygenase enzymes [61]. Thus, GPER is an important endogenous inhibitor of vasoconstriction in the setting of visceral obesity and atherosclerosis, the development of which has been recently linked to the presence of perivascular fat [104].

Given that its activation improves the lipid profile, inhibits inflammation and atherosclerosis, and improves vasodilation, GPER represents a promising therapeutic target for the treatment of coronary artery disease and its risk factors. Furthermore, postmenopausal women may also be eligible for GPER-targeting therapy to provide vascular protection given that selective GPER agonists (unlike natural or equine estrogens [2, 105]) are devoid of uterotrophic effects [10, 36].

Concluding remarks and future perspectives

Since the discovery of GPER, research has helped to identify multiple physiological functions and roles in many organs, and we are now beginning to understand its role in disease. There is now good evidence that GPER plays an essential role in metabolic regulation (including lipid and glucose homeostasis, as well as insulin production and action), arterial tone, blood pressure, and immune functions (Figure 2), factors that are all linked to the risk of developing coronary artery disease due to atherosclerosis [1]. Interestingly, widely used drugs such as SERMs and niacin may exert their lipid-lowering effects in part through activation of GPER [8, 52, 106, 107]. There is also data to support a vasoprotective role of GPER in the brain [108-110]. The precise mechanisms of how GPER is involved in this regulation have only been identified in part, and some of the findings are particularly intriguing [52, 54]. For example, although data clearly show that GPER mediates multiple activities of estrogen *in vivo* (i.e. many physiological effects of estrogen are lost in GPER⁰ mice), there is accumulating evidence that GPER also has effects in males, in some instances independently of sex steroids (reviewed in [8-10, 52]), and that certain GPER-dependent phenotypes only become apparent with age [60]. Similar observations have been made with regard to physiological functions of ER β in aged male

mice [80]. In addition to its anti-diabetic effects, the vasculotropic expression profile and the numerous vasoprotective functions of GPER (Figure 2) suggest therapeutic potential in the treatment of atherosclerotic vascular disease, the main cause of myocardial infarction and stroke. The currently available data suggest a strong anti-inflammatory component contributes to the activity of GPER in the vascular wall, in endothelial cells, in the pancreas, as well as potentially in adipose tissue, all of which can contribute to the vasoprotective effects of GPER [8, 10]. Continuing research efforts should be directed towards further identifying the precise mechanisms underlying the vasoprotective and metabolic effects of GPER. Development of GPER-selective drugs, such as G-1, which unlike natural estrogen or conjugated equine estrogens, lacks uterotrophic activity [46], may lead to therapeutic applications in other non-communicable chronic diseases driven by chronic inflammation. Finally, targeting GPER may also allow its theranostic use [38-41] and thus offers new approaches for personalized medicine.

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HIGHLIGHTS

- The 7-transmembrane G protein-coupled estrogen receptor (GPER) contributes to vascular tone and blood pressure.
- GPER deletion augments endothelium-dependent vasoconstriction and the activity of vasoactive peptides.
- Mice lacking GPER develop visceral obesity, increased LDL cholesterol levels, a prodiabetic metabolic profile and generalized inflammation.
- GPER regulates pancreatic hormone secretion (including insulin) and modulates insulin responsiveness of peripheral tissues.
- Loss of GPER accelerates atherogenesis and vascular inflammation in an estrogen-dependent fashion. Both pathologies can be alleviated using GPER-targeting drugs.

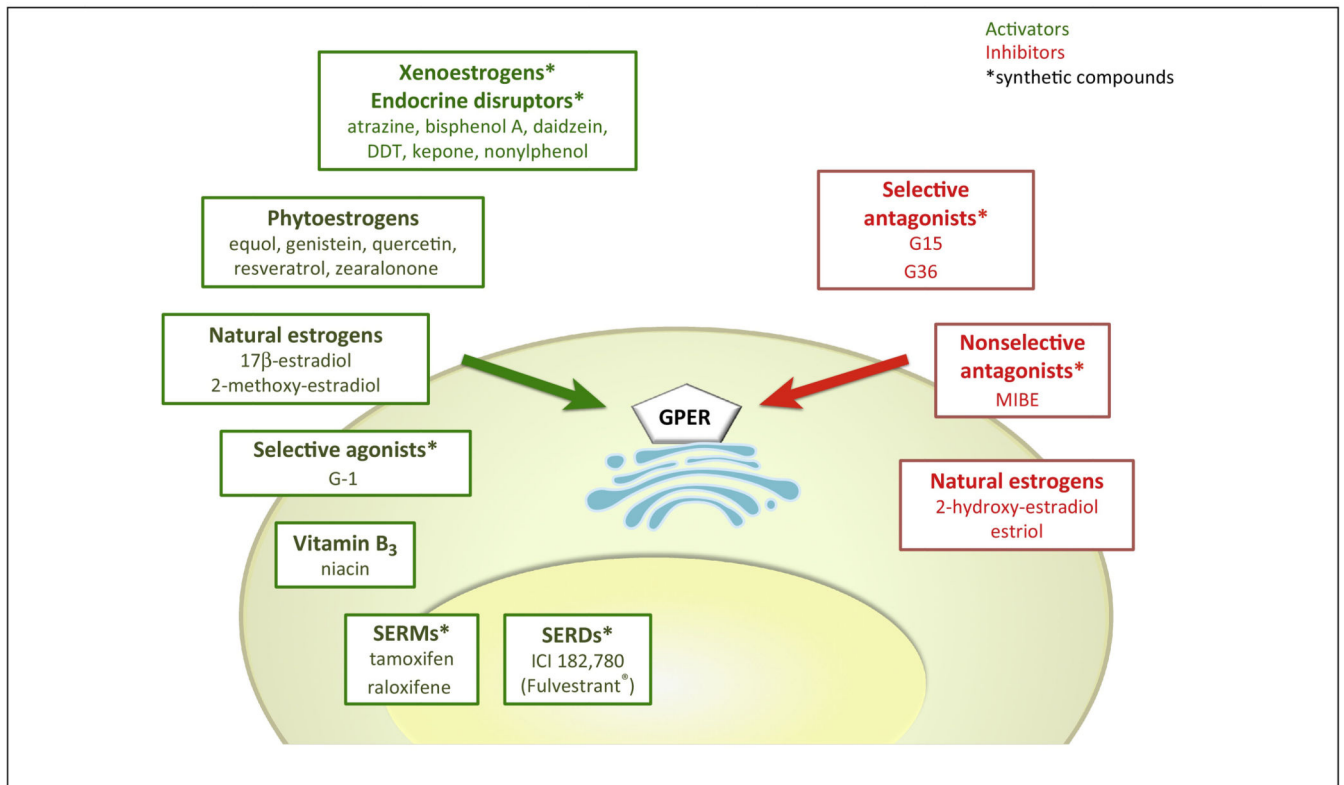


Figure 1. Agonists and antagonists with intrinsic activity mediating or inhibiting GPER signaling
 Agonists and antagonists of GPER with intrinsic activity mediating or inhibiting GPER-mediated signaling. Green arrows: activation; red arrows: inhibition; Receptors are activated by natural (endogenous estrogen such as 17 β -estradiol, 2-methoxyestradiol) as well as by phytoestrogens (such as equol, quercetin, genistein, zearalonone, resveratrol), highly stable environmental pollutants, also known as xenoestrogens (including atrazine, zearalonone, bisphenol A, nonylphenol, or DDT), SERMs, SERDs, or GPER-selective synthetic drugs. The synthetic GPER-selective compounds G15 and G36, the non-selective MIBE, and the estrogen metabolites 2-hydroxyestradiol (2 OH-E2) and estriol act as GPER antagonists. See text for explanation. * denotes synthetic compounds as opposed to natural substances; DDT, dichlorodiphenyltrichloroethane; SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor downregulator. MIBE, ethyl 3-[5-(2-ethoxycarbonyl-1-methylvinyl)-1-methyl-1H-indol-3-yl]but-2-enoate).

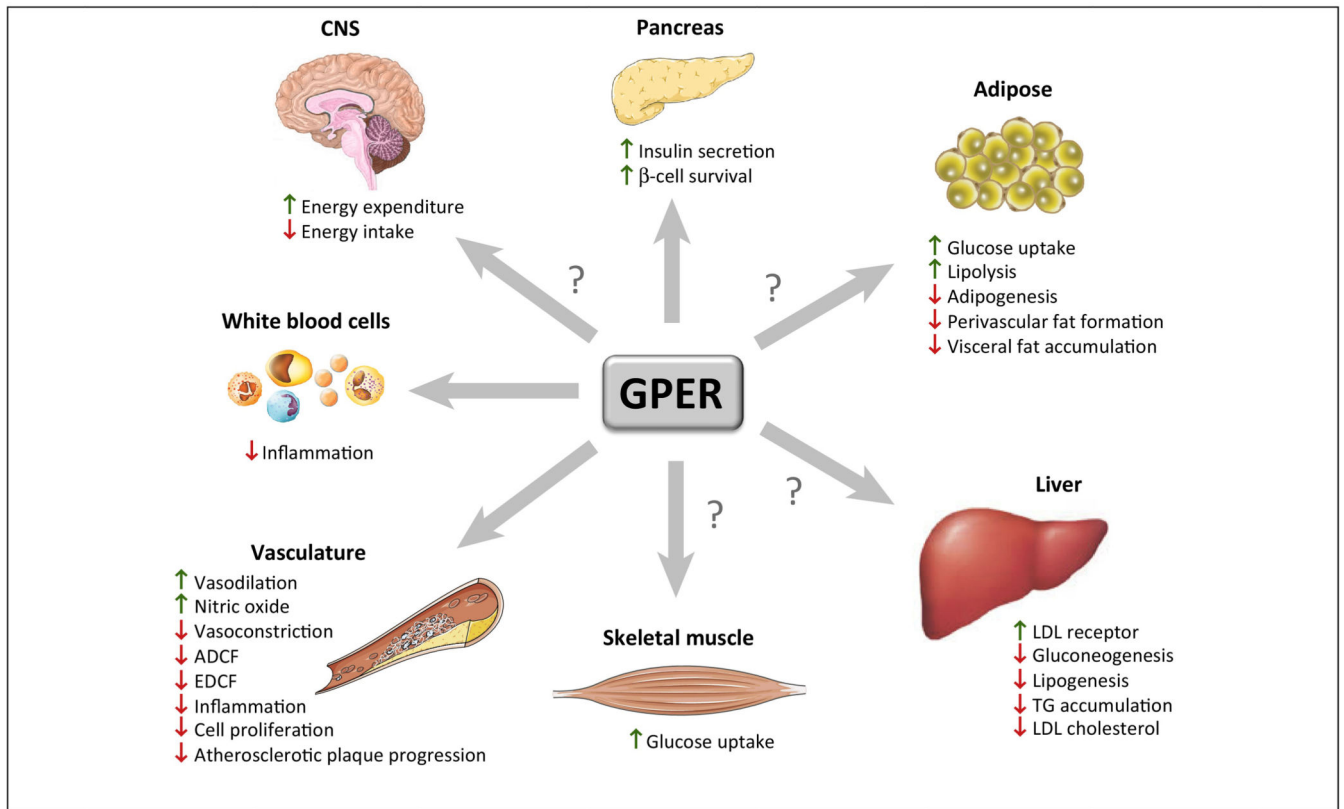


Figure 2. Roles of GPER in physiology and disease

Metabolic, vascular, immunological, physiological, and pathophysiological functions of GPER in the brain, pancreas, adipose tissue, arterial vasculature, skeletal muscle, liver, and white blood cells. ? indicates functions attributed to estrogen activity, where the precise role or contribution of GPER is unknown or requires further study. Abbreviations used: ADCF, adipose-derived contracting factor; CNS, central nervous system; EDCF, endothelium-derived contracting factor; LDL, low-density lipoprotein; TG, triglycerides; VSMC, vascular smooth muscle cells.