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The G protein-coupled estrogen receptor GPER in health and disease

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Abstract

Estrogens mediate profound effects throughout the body, and regulate physiological and pathological processes in both women and men. The decreased incidence of many diseases in premenopausal women is attributed to the presence of 17β-estradiol, the predominant and most potent endogenous estrogen. In addition to endogenous estrogens, however, several manmade and plant-derived molecules also exhibit estrogenic activity. Traditionally, the actions of 17β-estradiol are ascribed to two nuclear estrogen receptors (ERs), ERα and ERβ, which function as ligand-activated transcription factors. However, 17β-estradiol also mediates rapid signaling events via pathways that involve transmembrane ERs, such as G-protein-coupled ER 1, (GPER, formerly known as GPR30). In the past 10 years, GPER has been implicated in both rapid signaling and transcriptional regulation. With the discovery of GPER-selective ligands that can selectively modulate GPER function in cell experiments and preclinical studies, and the use of GPER-knockout mice, many more potential roles for GPER are currently being elucidated. This Review highlights the physiological roles of GPER in the reproductive, nervous, endocrine, immune and cardiovascular systems, as well as its pathological roles in a diverse array of disorders including cancer. GPER is emerging as a novel therapeutic target and prognostic indicator for these diseases.

Introduction

17β-Estradiol is commonly recognized as the female sex hormone with a critical role in the development of the female reproductive organs and secondary sex characteristics. However, this hormone is also essential to the development and function of the male reproductive tract.[1] In addition to the reproductive system, 17β-estradiol has important physiological roles in almost every other arena of the body, including the nervous, immune, vascular, muscular, skeletal and endocrine systems. As expected, therefore, 17β-estradiol and its receptors contribute to multiple disorders, including cancer, cardiovascular diseases, hypertension, osteoporosis, cognitive and behavioral alterations, neurodegenerative diseases, metabolic disorders (such as obesity and diabetes) and immune disorders.[2] Our understanding of the widespread physiological effects of 17β-estradiol is complicated by the existence of multiple types of estrogen receptors (ERs) and multiple modes of cellular

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signaling mechanisms that can span time frames from seconds to hours, or even days.[3,4] The pathophysiological mechanisms involving ERs are further complicated by a diverse array of 17β-estradiol-mimicking compounds, both synthetic and plant-derived, to which humans are increasingly exposed.[5]

In this Review, we provide a brief overview of estrogen signaling and describe the discovery and characterization of its receptors, with particular emphasis on G-protein-coupled estrogen receptor 1 (GPER). We will also discuss studies that have elucidated the functions and importance of GPER in health and disease and those that have revealed the therapeutic potential of small-molecule regulators of GPER activity.

Estrogen receptors

ERα and ERβ

The first and best-described 17β-estradiol receptor (now called ERα) was identified in the rat uterus in the 1960s.[6,7] The second, less well-characterized receptor, ERβ, was identified in the rat prostate in 1996.[8] These highly homologous receptors function as ligand-activated nuclear transcription factors that bind *cis*-acting estrogen response elements in the promoter and enhancer regions of hormonally regulated genes.[9] Both ERα and ERβ are soluble receptors that can shuttle between the cytoplasm and the nucleus, but are found predominantly in the nucleus (only ~5% of these receptors are present in the cytoplasm).[4] Highly divergent and sometimes opposing functions for the two receptors have been reported in studies of ERα-knockout and ERβ-knockout mice.10 In addition to their effects on gene expression (that is, their genomic effects), these ERs are also associated with rapid cellular signaling (termed non-genomic effects) that are thought to be mediated primarily by membrane-associated forms of these receptors.[11]

Although multiple modes of action were suggested for these two ERs as early as the 1960s,[1214] not all effects of 17β-estradiol, particularly the rapid and membrane-associated signaling events, could be attributed to ERα and ERβ.[15] In some cases, antagonists of these receptors could not block certain rapid signaling events, which led to the prediction that alternate membrane-bound ERs also existed.[16] Interestingly, most of the 17β-estradiol-mediated rapid signaling events are associated with G protein signaling or growth factor-mediated pathways.

GPER

In 2000, it was reported that rapid 17β-estradiol-mediated activation of extracellular signal-regulated kinases (ERKs) was dependent on the expression of an orphan, G protein-coupled receptor with seven transmembrane domains.[17] This receptor, which was then known as GPR30, was cloned by many groups in the late 1990s.[18–23] Following this initial report, other papers described 17β-estradiol-mediated, GPR30-dependent, generation of cyclic AMP (cAMP)[25] and expression of Bcl-2,[26] nerve growth factor[27] and cyclin D2.[28] Furthermore, other researchers described GPR30-mediated expression of c-Fos[29] and an interaction between the effects of progestin and GPR30 expression.[30–32] Two studies published in 2005 described binding of 17β-estradiol to GPR30 in GPR30-transfected COS7 and HEK293 cells as well as various breast cancer cell lines.[33,34] Together, these results suggested that GPR30 was a 17β-estradiol-binding receptor, which led to its designation as G protein-coupled estrogen receptor 1 (GPER) in 2007. GPER is now known to be expressed in numerous tissues,[24] and research into its functions has substantially increased.

Estrogen receptor ligands

Natural endogenous estrogens, predominantly 17β-estradiol, are the primary ligands of ERs. 17β-estradiol is synthesized predominantly in the ovaries, although it is also produced at many sites throughout the body, including the breast, brain, adipose tissue and the arterial wall, where it might have specialized local effects.[35] The 17β-estradiol-based steroids estriol (a GPER antagonist at high concentrations[36]), estrone and estrone sulfate can also modulate biological functions, although their specific actions are less clear than those of 17β-estradiol.[37] Plasma concentrations of 17β-estradiol in premenopausal women are ~0.2–1.0 nmol/l, although it increases by many hundredfold during pregnancy. Local concentrations in specific tissues can be much higher than the plasma values, for example in breast tissue (10–20-fold)[38] or in the placenta at term (~12 μmol/l).[39] The hydrophobic nature of these steroids allows them to diffuse passively through cell membranes and reach their intracellular targets, the ERs.[40]

A large variety of natural and man-made chemicals also have estrogenic activity (Figure 1).[5] Estrogenic compounds synthesized by plants (phytoestrogens) include flavonoids such as coumestans and isoflavones.[41] Synthetic estrogenic compounds (known as xenoestrogens, environmental estrogens, or endocrine disruptors) include many pesticides, herbicides and plastic monomers.[5] Their widespread use results in chronic low-level exposure to these compounds in humans.[42] Although the majority of phytoestrogens and xenoestrogens are believed to exert their physiological effects through modulation of ERα and ERβ,[43] many of these compounds also activate GPER, including the soy isoflavone genistein (for which serum concentrations up to 500 nmol/l have been measured[44]), nonylphenol, the pesticides DDT and DDE (dichlorodiphenyltrichloroethane and dichlorodiphenyldichloroethylene, respectively), bisphenols[45] (such as bisphenol A, which promotes testicular seminoma cell proliferation[46]), the herbicide atrazine[47] and possibly equol—a nonsteroidal equine estrogen found in premarin[48] that is formed by human gut bacteria as a metabolite of the isoflavone, daidzein.[49]

17β-estradiol mimetics are also used extensively in clinical and therapeutic applications. For example, 17α-ethynylestradiol is the predominant estrogen used in female contraceptives. Drugs, such as tamoxifen and raloxifene, which are used in treatments for breast cancer and osteoporosis, act as ER agonists in some tissues and ER antagonists in others, which led to their designation as selective estrogen receptor modulators (SERMs).[50] By contrast, fulvestrant is a ‘pure’ ER antagonist that leads to ER degradation and/or downregulation, which led to its designation as a selective estrogen receptor downregulator (SERD).[51] However, some members of each of these classes of compounds can also act as GPER agonists,[17,34] which complicates the interpretation of their mechanisms of action and the receptors involved under both physiological and disease conditions.[52]

GPER-selective ligands

Research into the specific activities of GPER has been aided by the discovery of GPER-selective agents. Since the identification of the first GPER-selective agonist G-1 in 2006, a number of reports have examined the disease-related or health-promoting effects associated with GPER activation. Importantly, studies using G-1 at concentrations as high as 1–10 μmol/l showed no notable activity of this agent towards ERα in terms of activating or inhibiting rapid signaling events,[34] estrogen response element-mediated transcription,[53] or ERα downregulation.[53] Furthermore, G-1 had no activity on 25 other important G-protein-coupled receptors[54] or in GPER-knockout mice,[55–57] which provided evidence that G-1 is a specific ligand for GPER.

In 2009, a GPER-selective antagonist G15 was identified.[58] G15 has a similar structure to G-1,[58] and is effective in inhibiting all G-1-mediated effects tested to date as well as many 17β-estradiol-mediated effects.58–62 The core structures of G-1 and G15 have been used to generate several radiolabeled agents that can be used for imaging and potentially treatment of GPER-expressing tumors *in viv*.[63,64]

GPER signaling

Although ERα and ERβ are accepted as the predominant nuclear receptors involved in the genomic effects of estrogen, evidence also indicates that rapid modulation of cell-signaling pathways occurs via a subpopulation of ERs located at the plasma membrane (Figure 2),[4] which has led to speculation about the role of GPER.[65] The localization of GPER, however, seems to be predominantly intracellular,[34,203] consistent with reports that describe the constitutive internalization of plasma membrane GPER.[135,204]

Signaling through GPER occurs via transactivation of the epidermal growth factor receptor (EGFR) and involves nonreceptor tyrosine kinases of the Src family.[17] In this mechanism, which is now also accepted for other G-protein-coupled receptors,[66] stimulation of GPER activates metalloproteinases and induces the release of heparin-binding EGF, which binds and activates EGFR[67] leading to downstream activation of signaling molecules, such as ERK1 and ERK2.[68] Moreover, 17β-estradiol-mediated activation of GPER stimulates production of cAMP,[25,33] intracellular calcium mobilization[34,69,70] and PI3K activation.[34] Further research in human breast cancer cells suggested that sphingosine kinase[71] and activation of integrin $\alpha_5\beta_1$[72] were intermediates in 17β-estradiol-mediated EGFR transactivation. The latter suggests a role for GPER in fibronectin assembly.[72]

In addition to the above-mentioned rapid signaling events, GPER also regulates transcriptional activity, albeit indirectly, by activating signaling mechanisms that involve cAMP, ERK and PI3K.{Meyer, 2009 #1462} The genes regulated by GPER include *FOS* that encodes c-Fos,[29] which forms a heterodimer with various other proteins to form the transcription factor AP-1. In turn, these signaling pathways also activate other transcription factors, such as steroidogenic factor 1,[73] which induce expression of additional genes.[74,75]

GPER in Physiology and Disease

Reproductive system

The role of 17β-estradiol is best-defined in the reproductive system, where this hormone regulates uterine and mammary development and function. Although roles for GPER are implicated in almost every system of the body (Figure 3), conflicting observations have been published.[24] No clear developmental or functional defects occur in the reproductive organs of GPER-knockout mice,[76–79] whereas ERα-knockout mice displayed multiple reproductive defects.[80] Furthermore, in wild-type mice treated with G-1, no changes in ductal growth or end bud formation were detected in mammary glands, and no uterine imbibition of water or proliferative response in the mammary gland or endometrium was observed.[78] However, in another study, G-1 treatment of mice stimulated uterine epithelial proliferation by approximately threefold, as compared to the ~15-fold increase in proliferation observed with 17β-estradiol.[58] Importantly, blocking GPER with G15 reduced the 17β-estradiol-mediated proliferative response by ~50%,[58] which suggests that GPER contributes to this response. Surprisingly, high concentrations of G-1 (1,000-fold greater than those needed to observe a proliferative effect) reduce both 17β-estradiol-mediated uterine imbibition of water and proliferation, through inhibition of ERK1 and/or ERK2 in the stroma and phosphorylation of serine 118 in ERα. [81] These data suggest that GPER regulates uterine proliferation, independently of ERα, in a process that may involve crosstalk with the 17β-estradiol–ERα pathway.

In addition to mammalian uterine effects, GPER is also involved in the regulation of meiotic arrest in oocytes of the Atlantic croaker and zebra fish. *In vitro,* 17β-estradiol and G-1 reduced both spontaneous and progestin-induced oocyte maturation, whereas knockdown of GPER or blockade of GPER with G15 prevented the inhibitory effects of 17β-estradiol, which occur via an EGFR-dependent pathway.[61,82] Furthermore, GPER expression in granulosa and theca cells of the hamster ovary is regulated by gonadotropins and the estrous cycle[84] and, in this location, GPER regulates the 17β-estradiol-mediated stimulation of primordial follicle formation.[83] In humans, GPER enhances contractile responses to oxytocin in the myometrium, which suggests a role for GPER in uterine contractility during labor.[85] Moreover, ERα, ERβ and GPER regulate the proliferative and apoptotic pathways involved in spermatogenesis[86–88] during male reproductive development. Overall, the roles of GPER in the reproductive system are complex and require further investigation, particularly with regard to human physiology.

Nervous system and neurohormonal pathways

The effects of 17β-estradiol in the central and peripheral nervous system include maintenance of homeostasis, regulation of synaptic plasticity and cognition, neuroprotection and modulation of pain sensation. Although many of these effects might involve ERα and ERβ, increasing evidence indicates that GPER has multiple roles in 17β-estradiol-mediated neurological functions. GPER mRNA and protein expression have been found throughout the central and peripheral nervous system of male and female rodents, including in the hippocampus, hypothalamus and midbrain, as well as the spinal cord and dorsal root ganglia.[70,89,90] However, conflicting results reporting expression in small arterial surface vessels and pericytes in the brain also exist.[76] Both ERα and GPER activate the ERK1/2 pathway in trigeminal ganglion neurons and increase allodynia, indicating a role for these two ERs in temporomandibular disorder and migraine.[91] Furthermore, in the rat, G-1 depolarizes spinal cord neurons,[89] stimulates mechanical hyperalgesia via protein kinase C ξ[92] and mediates visceral hypersensitivity in the absence of inflammation.[93]

17β-Estradiol has many beneficial effects on the brain, including reducing neuronal loss following stroke, increasing neuronal connectivity and improving cognitive performance.[94] GPER has been implicated in 17β-estradiol-mediated effects on cholinergic neurons in the basal forebrain, which suggests that this ER might be an important regulator of cognitive function, particularly in women following menopause.[95] In studies that used immortalized hippocampal cell lines, GPER (along with ERα) was implicated in the protective effects of 17β-estradiol against glutamate-induced injury,[62] although in cortical neurons G-1 did not have any effect.[96] However, *in vivo* studies showed that G-1 treatment replicates the effects of 17β-estradiol in promoting neuronal survival following global ischemia in the brain.[97,98] Altogether, these results suggest that GPER agonists might represent a new therapeutic approach for stroke and chronic neurodegenerative diseases.[99]

In the brain, G-1 (like 17β-estradiol) attenuates serotonin receptor signaling in the paraventricular nucleus of the hypothalamus and reduces responses to oxytocin and adrenocorticotropic hormone, which suggests that GPER might have a role in mood disorders.[100] Furthermore, G-1 exhibited antidepressant properties in a mouse model of depression, where it reproduced the effects of 17β-estradiol, which were inhibited by the GPER-selective antagonist G15.[58] In primates, GPER contributes to 17β-estradiol-mediated regulation of luteinizing-hormone-releasing hormone neurons, which maintain gonadal function and fertility.[101] This effect probably also involved additional mechanisms.[102] However, whereas GPER activation promoted short latency prolactin secretion, G-1 did not affectthe 17β-estradiol-mediated negative feedback inhibition of either luteinizing hormone secretion or lordosis behavior in rats.[103] Studies with ERα-knockout mice showed that ERα is required for 17β-estradiol regulated positive feedback control of hypothalamic

gonadotropin release,[104] which suggests that the actions of GPER are complex and possibly also require the presence of ERα.

Immune system

17β-estradiol displays multiple effects in the regulation of immune responses, including the development of T cells,[105] autoimmune disease[106,107] and inhibition of inflammation.[106] Studies in ER-knockout and GPER-knockout mice have shown that GPER, along with ERα, contributes to 17β-estradiol-induced thymic atrophy;[79] ERα mediated the early blockage of thymocyte development whereas GPER mediated thymocyte apoptosis. Furthermore, in GPER-knockout mice engineered to express LacZ from the GPER promoter, numbers of L-selectin-expressing T cells decreased, consistent with an altered production of these T cells in the thymus.[76] By contrast, other studies using GPER-knockout mice could not find any difference in either 17β-estradiol-induced thymic atrophy[108] or in 17β-estradiol-induced ameliorative effects on arthritis or bone loss in a model of postmenopausal rheumatoid arthritis.[109] These findings suggest complex roles for 17β-estradiol and GPER in the immune system.

Estrogens are increasingly receiving attention as potential anti-inflammatory agents for the treatment of autoimmune diseases, particularly multiple sclerosis.[107] In a mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), knocking out GPER impaired the protective role of 17β-estradiol.[55] In two other studies, treatment with G-1 reproduced the ability of 17β-estradiol to protect against the clinical and histological manifestations of EAE through enhancing the immunosuppressive activity of $CD4^+Foxp3^+$ T cells, resulting in upregulation of programmed cell death[55] and inhibition of inflammatory cytokine production by macrophages.[54] These findings suggest a protective role of GPER in multiple sclerosis.

Although the protective effects of G-1 against EAE were absent in GPER-knockout mice, 17β-estradiol-mediated effects were partially retained, showing that ERα and GPER could activate independent, yet overlapping, mechanisms. Further research showed that the therapeutic effect of ethynyl estradiol in established EAE was mediated via GPER, but not via ERα, and possibly involved production of the anti-inflammatory cytokine IL-10.[110] Recent studies showed that G-1 treatment elicits *de novo* production of IL-10 in T helper type 17 polarized cells, *in vitro* as well as *in vivo*, via an ERK1/2-dependent pathway.[111] Thus, the immunomodulatory effects of G-1 mediated by activation of GPER indicate that GPER agonists might have novel clinical applications in chronic inflammatory diseases.

Cardiovascular system

Endogenous 17β-estradiol is implicated in sex-specific differences observed in arterial hypertension and cardiovascular disease,[112,114] as the loss of 17β-estradiol production following menopause accelerates these conditions.[112,149] However, the cellular mechanisms and signaling pathways conferring this protective effect of 17β-estradiol are only partially understood.[115] Although ERα and ERβ are implicated in the cardiovascular protective effects of 17β-estradiol, a protective effect of 17β-estradiol is also seen in the absence of both ERα and ERβ.[116–118] These observations provided the initial evidence for the existence of alternative receptors, such as GPER, and signaling pathways involved in 17β-estradiol-mediated regulation of cardiovascular function.

GPER is expressed in mouse[77] and human[137] myocardium, as well as in cultured cardiomyocytes.[138] 17β-Estradiol-mediated inhibition of calcium influx and contraction in mouse cardiomyocytes is independent of ERα and ERβ,[116] and deletion of GPER from these cells leads to left ventricular dilatation and elevation of end-diastolic pressure in male,

but not female, mice.[139] In patients with myocardial infarction, ischemia–reperfusion injury after reopening of the occluded coronary artery is a critical determinant of outcome and complications, such as arrythmia and heart failure.[140,141] Myocardial hypoxia owing to infarction[142] is an important stimulus that upregulates GPER expression in cardiomyocytes.[138] Several groups have independently demonstrated that G-1 treatment after myocardial infarction led to reduced reperfusion-related injury and infarct size, and improved contractile function in structurally normal hearts from rodents and humans of both sexes.[137,140,143–145] Similar benefits were also obtained for G-1 treatment in cerebrovascular occlusion-related reperfusion injury, in animal models of stroke.[97,146] Under these conditions, activation of GPER by G-1 resulted in reduced myocardial expression of proinflammatory cytokines (IL-1β, IL-6 and tumor necrosis factor),[145] increased activation of Akt,[132] ERK1/2,[132,143] increased phosphorylation of eNOS[132] and decreased mitochondrial permeability .[144] These cardioprotective effects were blocked by an inhibitor of PI3 kinase.[132]

GPER is expressed in human endothelial[23,119] and smooth muscle cells,[57,120] as well as in intact arteries (Table 1).[120] Expression of GPER in macrophages,[128] which contribute to atherogenesis, also suggests a functional role for GPER in atherosclerosis and the associated inflammation (Table 1). In human endothelial cells, activation of GPER (but not of ERα) [121] inhibits cell proliferation,[119] indicating an antiangiogenic role for this ER. In human and rat vascular smooth muscle cells, activation of GPER by either G-1[57,122] or raloxifene[123] stimulates the ERK1/2 pathway and inhibits growth, similar to the effect of ERα activation in these cells.[124] These findings are in keeping with the antiproliferative effects of 17β-estradiol on vascular smooth muscle cells in ERα and ERβ double-knockout mice.[117] Moreover, the GPER agonists G-1,[57,60,125,126] genistein[127] and fulvestrant[125] cause vasodilatation in human, porcine and rodent arteries, whereas this effect is blocked by the GPER antagonist G15[60] and is absent in GPER-deficient mice.[57]

Elevated vascular resistance is a key feature of arterial hypertension.[114] Although GPER-deficient mice exhibit a normal mean arterial blood pressure that does not change with age,[77] infusion of the GPER agonist G-1 markedly lowers blood pressure in normotensive[57] and hypertensive rats.[60,129,130] In rats with hypertensive cardiomyopathy, G-1 treatment ameliorates diastolic dysfunction, reduces cardiac hypertrophy and decreases the size of myocytes.[129] This effect is probably mediated through direct vasodilatory actions of G-1[57,126,131] or 17β-estradiol, as this hormone also has vasodilatory effects (which are derived at least in part from GPER, as they are blocked by the GPER antagonist G15).[60] Vasodilatory actions of G-1 involve both nitric-oxide-dependent and nitric-oxide-independent pathways and have been observed in human, pig and rat arteries.[57,60,126,130] Phosphorylation of eNOS as a result of GPER activation might contribute to this response.[49,132] At least some of the vasoprotective effects mediated by GPER are probably the result of interference with endothelial cell dysfunction—a vascular abnormality common to hypertension and coronary artery disease.[113,133]

Altogether, these data indicate a central regulatory role for GPER in cardiovascular function and suggest that GPER agonists have potential roles in the treatment of vascular and myocardial disease in both men and women.

Renal system

Endogenous 17β-estradiol is also implicated in the sex-specific differences in renal disease,[113] and GPER is implicated as it is expressed at high levels in renal tubules,[90] as well as in renal epithelial cells.[135] In humans, the *GPER* locus is associated with low-renin hypertension,[134] which leads to kidney injury and vascular dysfunction (the latter abnormality is ameliorated by G-1 treatment).[130] Endothelial cell dysfunction is also present

in animals with glomerulosclerosis, which leads to proteinuria due to loss of the glomerular filter function. In hypertensive rats, GPER activation reduces proteinuria and improves creatinine clearance despite continued hypertension.[136] These findings suggest renoprotective potential for GPER agonists in hypertensive nephropathy.

Pancreatic function and glucose metabolism

The increased prevalence of obesity, insulin resistance and diabetes after menopause indicates a protective role for endogenous 17β-estradiol in premenopausal women.[147,148] These protective effects are largely attributed to signaling via nuclear ERα, [150,151] as its deletion results in obesity and insulin resistance.[147,148] However, other forms of ERα signaling are also involved in metabolic diseases;[151,152] for example, insulin secretion mediated by 17β-estradiol occurs through rapid signaling via membrane-bound ERs.[160–162] Although ERα and ERb individually affect insulin action,[147,148] mice deficient in GPER develop insulin resistance and obesity in a sex-dependent manner.[57,77,153] GPER activation also has anti-inflammatory properties in pancreatic islets through attenuating the effects of proinflammatory cytokines[154] that are important for maintenance of metabolic function.[155] The protective, antidiabetic effects of 17β-estradiol in islet cells seem to involve activation of both membrane-bound ERα and GPER,[56,156] and might also be induced by GPER agonists, such as genistein.[158]

GPER is expressed in whole adipose tissue in humans and rodents,[57,159] as well as in the human liver,[18–20,22,23] key target organs of insulin resistance.[155] However, the role of GPER in 17β-estradiol-mediated metabolic protection is not clearly defined. GPER is expressed in the pancreatic islets of mice[56,77,154,156,157] and humans,[156] and in female mice it maintains normal metabolic function.[77] GPER deficiency results in a reduction in insulin secretion (stimulated by 17β-estradiol, G-1 and glucose) from the pancreas, but does not affect the morphology of pancreatic β-cells, which suggests that GPER has a key role in maintaining the metabolic functions of insulin in mice[77,163] and humans.[164] Furthermore, the protective effect of 17β-estradiol on survival of pancreatic β-cells in a mouse model of type 1 diabetes mellitus is absent in GPER-deficient animals.[56] Whether GPER contributes to peripheral insulin resistance is currently not known. However, expression of GPER has been reported in human skeletal muscle,[56,77,154,156] and is unaffected by menopause.[165]

Bone growth and chondrocyte metabolism [heading level 2]

Bone and articular cartilage are hormone-sensitive tissues,[166] and serum 17β-estradiol levels inversely correlate with the risk of hip fracture in both women and men.[167] Perhaps the best evidence of a role for endogenous 17β-estradiol in overall bone health and formation of trabecular bone in particular is the postmenopausal onset of osteoporosis. The bone-preserving effects of estrogen therapy, especially with SERMs and SERDs,[168] which act as GPER agonists, indirectly suggest a role for GPER in bone metabolism. Endogenous 17β-estradiol also has an important role in bone metabolism in men, since lack of 17β-estradiol owing to aromatase deficiency[169] or mutations in *ESR1* (which encodes ERα)[170] in men leads to osteopenia, enhanced bone remodeling through increased bone resorption and osteoclast activity and suppression of bone growth-plate closure.[171] Although part of this effect is mediated through ERα and ERβ,[168] several avenues of research now suggest a role for GPER in bone and cartilage metabolism. In bone, GPER is expressed in osteocytes, osteoclasts and osteoblasts,[172,173] and is also detected in chondrocytes,[172,174] differentiation of which is regulated by GPER.[174] In addition, GPER expression also regulates bone growth, as illustrated by several models of GPER-deficiency, albeit in a sex-dependent manner. GPER deficieny inhibits bone growth in female mice;[77] similar results were reported in ovariectomized, estrogen-treated animals,[108] suggesting a role for GPER in estrogen-induced bone growth and development. By contrast, GPER-deficient male mice

had increased femur size, bone mineral density, trabecularization and cortical bone thickness.[153] Tamoxifen, a GPER agonist, decreases tibia length independently from ERα or ERβ.[52] Although *in vitro* studies and clinical trials with SERMs show beneficial effects on bone structure in postmenopausal women,[168] the role of GPER in bone and chondrocyte metabolism in humans is still not clear and warrants further study.

GPER in cancer growth and metastasis

17β-Estradiol is a critical mediator of breast carcinogenesis and is involved in a number of other hormone-sensitive cancers. Normal breast tissue is highly sensitive to 17β-estradiol, which stimulates proliferation of this tissue during puberty and pregnancy; thus, the majority of breast cancers are highly responsive to 17β-estradiol and utilize 17β-estradiol signaling pathways in cancer initiation, progression and metastasis.[175] This understanding has led to development of various cancer therapies that target 17β-estradiol signaling, the most widely used of which is tamoxifen.[176] Antiestrogen therapy has been extended to include SERDs (such as fulvestrant), aromatase inhibitors (for postmenopausal women) and other SERMs (such as raloxifene).[50] Many of these agents, particularly tamoxifen and fulvestrant, are also GPER agonists and have complex physiological and therapeutic actions. For example, long-term 17β-estradiol deprivation in the weakly metastatic human breast cancer cell line MCF-7 increased expression of GPER,[197] whereas tamoxifen treatment of these cells stimulated proliferation via GPER-mediated transactivation of EGFR.[198]

GPER is expressed in ~50% of all breast cancers, regardless of their ER status,[186] although conflicting results have been reported regarding coexpression of GPER and human epidermal growth factor receptor 2 (Her2).[184,186,188] Nevertheless, in general, GPER expression in breast cancers correlates with clinical and pathological biomarkers of poor outcome. High levels of GPER protein expression in samples of human breast cancers also correlate with increased tumor size and metastasis.[186] Importantly, in patients treated only with tamoxifen, GPER protein expression increased and survival was significantly lower in patients with initial GPER-positive tumors, suggesting breast cancer patients with high GPER expression should not be treated with tamoxifen alone.{Ignatov, 2011 #2254} In addition, GPER is widely expressed in cancer cell lines and primary tumors of the breast,[17,18,34,177,184–188] endometrium,[178–180,189,190] ovaries,[47,53,181,191,192] thyroid,[180] lung,[182] prostate,[183] testicular germ cells[193] and the brain (unpublished work). In cell lines of thyroid, ovarian, endometrial and breast cancers, stimulation of GPER with 17β-estradiol[53,180,194] or other estrogenic compounds, such as atrazine,[47] genistein,[180] bisphenol A[46,195] or tamoxifen[194] activates a signaling mechanism that typically promotes proliferation, although inhibition of proliferation has also been reported.[69] In particular, genistein can stimulate MCF-7 cell growth via induction of acid ceramidase, which occurs through a GPER-dependent mechanism.[196] In endometrial cancer[190] and ovarian cancer,[191] high levels of GPER expression also predicted poor survival, whereas among post-pubertal testicular germ cell tumors, GPER was highly expressed in intratubular germ cell tumors, seminomas and embryonal carcinomas, with little expression in teratomas.[193]

Importantly, treatment of the ERα-negative human breast cancer cell line SKBr3 with 17β-estradiol or tamoxifen increased the expression of several transcription regulators (including c-Fos) and cytokines (particularly connective tissue growth factor, which promotes cancer cell proliferation and migration).[199] These data indicate that tamoxifen treatment might have a cancer-promoting effect through GPER as discussed above. In support of this view, endometrial GPER expression also correlated with tamoxifen-induced uterine pathology, including bleeding and abnormal endometrial thickening,[189] which correlates with an increased incidence of endometrial cancer.[201,202]

The overall role of GPER in breast cancer progression is complex. Genistein stimulates the proliferation of MCF-7 cells through a GPER-dependent mechanism.[196] Moreover, GPER is implicated in 17β-estradiol-mediated activation of cancer-associated fibroblasts, which promote tumor cell proliferation and metastasis through direct association of GPER with chromatin.[200] GPER expression was induced in breast cancer cells under hypoxic conditions, which also suggests a cancer-promoting role for this ER, including a role in hypoxia-induced angiogenesis.[138] However, G-1 inhibits endothelial cell proliferation, which indirectly suggests that GPER activity also inhibits angiogenesis.[119] Despite these conflicting data on the role of GPER in cancer, targeting its activity represents an important new approach for cancer therapy.

Conclusions

The salutary effects of estrogens are well established in many diseases, and selective activation of GPER by G-1, phytoestrogens, SERDS, or SERMS can reproduce the beneficial effects of 17β-estradiol. The pace of research into the physiological and pathological functions of GPER has been accelerating over the past 5 years, and potential roles for GPER have now been identified in almost every system of the body. Thus, GPER-selective agents that mimic the beneficial effects of 17β-estradiol without its associated feminizing or other adverse effects could represent an important new family of drugs.

In addition, GPER-specific antagonists could be developed as important additions to the armamentarium of drugs used to treat estrogen-sensitive cancers and other diseases in which estrogen signaling is important. In this regard, the potential contribution of GPER-mediated signaling to the effects of existing clinically approved drugs, such as tamoxifen and fulvestrant, must be considered. GPER-mediated effects should also be taken into account in the future development of SERMs and SERDs. In addition, further research is required to determine to what extent the physiological effects of 17β-estradiol involve GPER signaling and the precise roles of nonselective estrogen receptor ligands in health and disease. The co-dependent, redundant and independent aspects of 17β-estradiol signaling through ERα, ERβ and GPER are likely to be very complex and specific to particular cell types, tissues, ligands and diseases. The data available to date nevertheless pose interesting questions about the therapeutic potential of specifically targeting GPER in disease.

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Biographies

Dr Eric R. Prossnitz received his PhD from the University of California at Berkeley, CA, USA, and carried out his postdoctoral studies at the Scripps Research Institute, La Jolla, CA, USA, where he became Assistant Professor in 1994. He relocated to the University of New Mexico, Albuquerque, NM, USA, in 1997. He has studied mechanisms of G-protein-coupled receptor function for over 20 years, with particular focus on the role of receptor regulation through phosphorylation and binding of arrestin. His recent research has centered on estrogen signaling through GPER, the identification of highly selective ligands for this receptor and the determination of its cellular and physiological functions.

Dr Matthias Barton obtained his MD from Hannover Medical School in Germany .He received a SCORE Career Development Award from the Swiss National Science Foundation in 1999 and is currently Professor of Cardiology at the University of Zürich in Switzerland. Dr Barton’s research relates to the molecular mechanisms involved in coronary artery disease and atherosclerosis, with a special interest in novel disease-modifying factors, obesity, and gender differences. Since 1990, Dr. Barton has studied vascular effects of estrogen. His laboratory was the first to report a regulatory role of GPER/GPR30 for vascular function.

Review criteria

A search for original articles was performed in PubMed. The search terms used included “GPER”, “GPR30”, “estrogen”, “rapid signaling”, “SERM”, “reproduction”, “immune”, “vascular”, “nervous”, “metabolism”, “bone” and “cancer” with no restriction on the publication year, language or article type. Additional abstracts were also identified by searching Google Scholar using similar keywords. Reference lists within identified papers were also searched.

Key points

- Estrogen has critical nonreproductive roles in health and disease, including in the skeletal, nervous, endocrine, immune and cardiovascular systems, as well as in many diseases and cancers
- The estrogen receptors (ERs) include ERα, ERβ and G-protein-coupled estrogen receptor 1 (GPER); their expression and signaling mechanisms are complex, and potentially exhibit redundant, independent, synergistic and/or antagonistic actions
- Estrogenic compounds (selective ER modulators, ER antagonists, selective ER downregulators, phytoestrogens and xenoestrogens) have multifaceted effects on all types of ERs, as well as receptor-specific pharmacological profiles
- GPER -selective agonists, such as G-1, mediate many salutary effects of estrogen in various tissues and organs without having any reproductive effects
- GPER represents an important diagnostic, prognostic and therapeutic target; development of GPER-selective agonists and antagonists could contribute to the diagnosis and treatment of many diseases

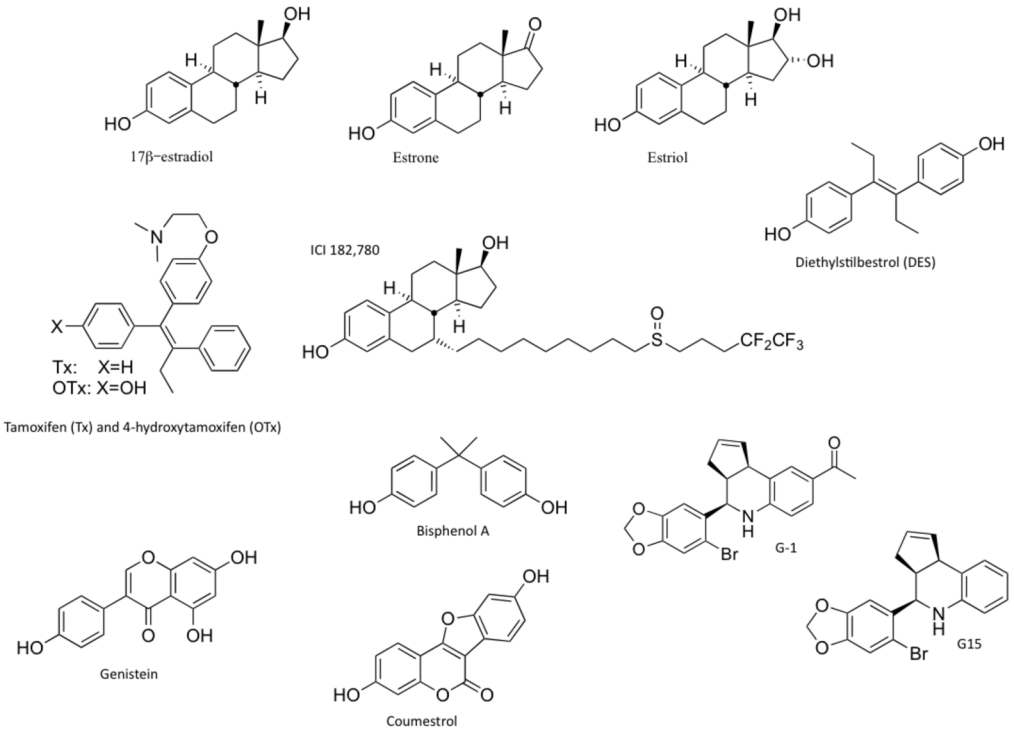

Figure 1.

Structures of selective and nonselective estrogen receptor ligands. Compounds shown include the three major physiological forms of estrogen (17β-estradiol, estrone and estriol); the anticancer agent tamoxifen and its active metabolite 4-hydroxytamoxifen (which is both a selective estrogen receptor modulator and an agonist for GPER); fulvestrant, a selective estrogen receptor downregulator and agonist for GPER; diethylstilbestrol, a nonselective GPER agonist; the phytoestrogens genistein and coumestrol; and the xenoestrogen bisphenol A. Also shown are G-1 (a selective GPER agonist) and G15 (a selective GPER antagonist). Abbreviation: GPER, G-protein-coupled estrogen receptor 1.

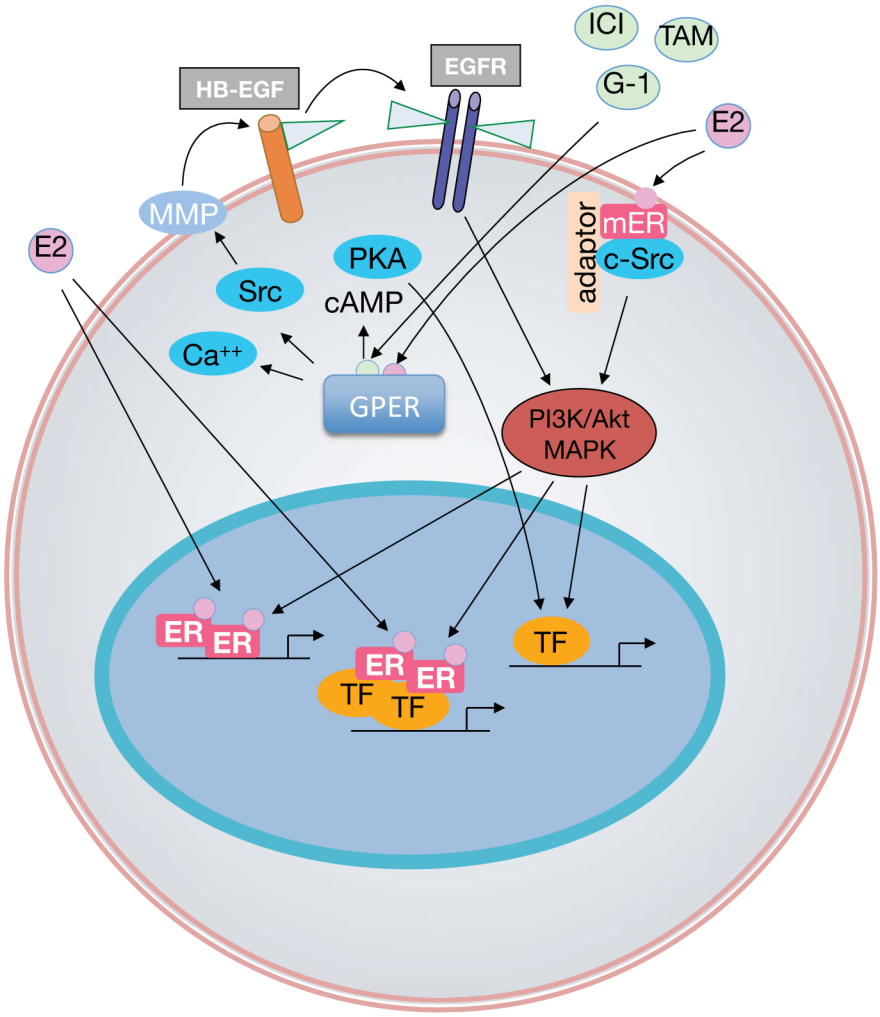

Figure 2.

Nongenomic and genomic estrogen signaling pathways. Endogenous estrogens including 17β-estradiol (E2) are nonselective activators of the three known estrogen receptors (ERs), ERα, ERβ and GPER. E2 activates nuclear ERs, inducing receptor dimerization, and binding of receptor dimers to the promoters of target genes. Alternatively, activated ERs modulate the function of other classes of transcription factors (TF) through protein–protein interactions. Subpopulations of ERs at the plasma membrane (mER) activated by E2 interact with adaptor proteins (adaptor) and signaling molecules such as c-Src, which mediates rapid signaling via PI3K/Akt and MAPK pathways. E2, or selective agonists such as G-1, or SERDs such as fulvestrant, or SERMs such as tamoxifen, also activate GPER, which is predominantly localized intracellularly. GPER activation stimulates cAMP production, calcium mobilization and c-Src, which activates matrix metalloproteinases (MMP). MMPs cleave pro-heparin-binding-epidermal growth factor (HB-EGF), releasing free HB-EGF that transactivates EGF receptors (EGFR). EGFR in turn activates MAPK and PI3K/Akt pathway, which can induce rapid (nongenomic) effects (X), or genomic effects regulating gene transcription. E2-mediated transcriptional regulation may involve phosphorylation (P) of ER or other TFs that may directly interact with ER, or bind independently of ER within the promoters of target genes.

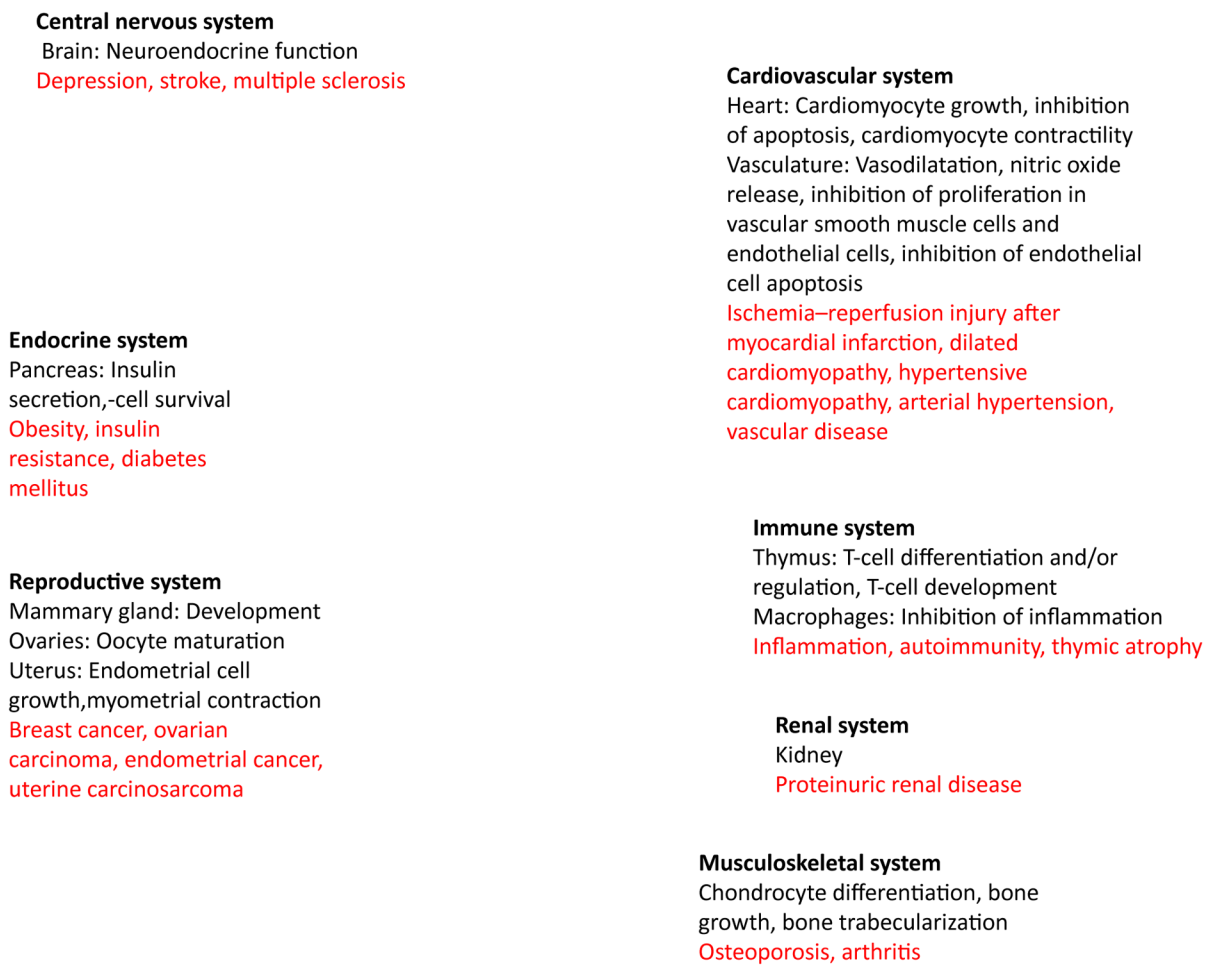

Figure 3.

Involvement of GPER action in regulation of physiological responses, including neuroendocrine and cerebral functions, immune cell function, endocrine regulation and metabolism, cardiovascular and kidney function, and reproductive functions. In addition, studies using experimental models of disease and/or human tissue suggest roles for GPER in diseases (such as diabetes, arterial hypertension, proteinuric renal disease, and immune diseases such as multiple sclerosis and cancer;) shown in red. Collectively, such studies suggest the therapeutic potential of regulating GPER activity as a novel approach for the treatment of these conditions.