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Protective role of female estrogens and estrogen receptors especially GPER receptor activation on body systems and diseases: a review

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ABSTRACT

This review sheds light on the protective effect of estrogen and its receptors especially GPER activation on several diseases in previous studies. Activating estrogen receptors in different organs causes protection against kidney, liver, cardiovascular, and neurological diseases in addition to their protective role on metabolic disorders as insulin resistance. Estrogens are a class of female hormones, including estrone, estradiol, estriol, and estetrol. Estradiol is the most common circulating estrogen in humans, secreted by ovarian follicles and corpus lutea. Recent and previous studies have shown that estrogens are important regulators of many brain functions. It can also prevent hepatocellular carcinoma (HCC) from developing. Additionally, it is widely known that endogenous estrogen has a crucial role in lowering the incidence of cardiovascular disorders in women due to its antioxidant ability. Furthermore, estrogens have a direct pro-apoptotic effect on osteoclasts, which makes premenopausal women more protected than men from osteoporosis and bone disease. Estrogen also protects women from metabolic disorders as with the onset of menopause, metabolic abnormalities such as insulin resistance tend to increase markedly. Two different structural receptor classes, namely G protein-coupled estrogen receptor (GPER) and estrogen receptor (ER) α/β, mediate the effects of estrogen in both normal and pathological circumstances.

Keywords: *(Estrogens, GPER, health, Diseases)*

1. Introduction

Estrogen, a steroid, attaches to intracellular receptors that function as transcription factors (1). The name "estrogens" indicates a class of female hormones that includes estrone, estradiol, estriol, and estetrol. The ovaries create the majority of estrogens, but the adrenal glands and adipose tissue also produce some. In the early 1900s, ovarian extracts ("liquour folliculi") from cattle and hogs were injected into rodents and found to be efficient in causing sexual activity, or "estrus" (2). Furthermore, all four estrogens can work at nuclear and membrane estrogen receptors, with varying affinities and degrees of response (3). Many vital physiological processes are influenced by estrogen, including the development and progression of the endocrine, skeletal, circulatory, and metabolic systems (4). Women typically experience physical and psychological changes as a result of the loss in estrogen and decline in ovarian function during menopause, which can result in a range of symptoms (sweating, irritability, sleeplessness, hot flashes) that reflects dysfunction of autonomic nervous system (5). Furthermore, cardiovascular and brain vascular disorders, osteoporosis, and reduced immunity, that occur post-menopause, have become the primary risk factors affecting women's health (6). Two different structural receptor classes, namely G protein-coupled estrogen receptor (GPER) and estrogen receptor (ER) α/β, mediate the effects of estrogen in both normal and pathological circumstances (7). ERα and ERβ are two classical ER subfamily (8). GPER1 has been identified as one of the primary estrogen-sensitive receptors responsible for the rapid, non-genomic action of estrogen (9). GPER1 is also broadly expressed across numerous organ systems in the body, including the neurological system (10-14), reproductive system (10, 12, 14-17), gastrointestinal system (10, 12), and specifically in the cardiovascular and renal systems (10, 12, 17-19). Signaling pathways of three estrogen receptors were illustrated in Fig. 1. G-1 is a non-steroidal medication that was developed in 2007 by Bologa and associates as a GPER1 selective agonist (20). Collectively, this review aimed to shed light on the protective

action of estrogen and its receptors especially GPER activation on body systems and diseases in the previous studies and the role of ERs in some diseases was showed in table 1.

2. Estrogen, estrogen receptors and GPER activation protective role:

2.1. Nephroprotective role

Previous studies reveal that testosterone causes oxidative stress in the kidney, whereas estrogens mitigate it (56, 57). In a large amount of experimental research, females appeared to have better kidney transplantation outcomes than males due to improved IRI tolerance (58). Estrogen reduces renal IRI via activating PPARγ, a nuclear receptor that maintains renal metabolic balance (59-61), and notably, female ERα knockout mice had worsened renal IRI (58). Also, GPER1 activation reduces salt-induced renal damage and proteinuria in female mRen2.Lewis rats in a blood pressure-independent fashion (62). Furthermore, in ovariectomized Sprague-Dawley rats, systemic GPER1 activation guards against renal ischaemic damage (63). G1 infusion into the renal medulla elicits a natriuretic response in female, but not male, Sprague-Dawley rats (19). Additionally, GPER1 activation prevents podocyte death by lowering the generation of reactive oxygen species (ROS) (64) and G1 similarly enhances superoxide dismutase activity and reduces malondialdehyde levels in renal proximal tubular epithelial cells treated with methotrexate (65).

2.2. Neuroprotective role

In recent decades, growing research has revealed that estrogens are not just reproductive hormones but also key regulators of numerous brain activities, particularly learning and memory (66). In addition to the hypothalamus, which controls the reproductive neuroendocrine axis centrally, estrogens also target other extra hypothalamic brain areas linked to cognitive functions, including the hippocampus and cortex in both male and female brains (67). Many animal studies have shown that 17β-estradiol (E2) influences hippocampal neurogenesis and morphological plasticity (68, 69) along with synaptic transmission in the hippocampus (70). It has been demonstrated that E2 therapy not only reverses cognitive abnormalities brought on by ovariectomies (71), but also to provide ischaemic neuroprotection, which enhances behavioural recovery in mice following an experimental stroke (72). Recently discovered results proposed a unique E2-mediated neuroprotective impact throught modulation of microglial activation of the M2 anti-inflammatory phenotype in the brain of adult ovariectomized rats (73). Several investigations in invivo and vitro models have established that the anti-inflammatory action of estrogens is achieved throught suppression of microglial and astroglial inflammatory response, lowering the activity of NF-κB p65 and the release of pro-inflammatory cytokines (74-76). Numerous investigations suggested that ERα and ERβ have a role in mediating neuroprotective estrogen actions. However, selective activation of GPER1 mimic the estrogenic effects by enhancing the survival of murine cortical and hippocampal neurons exposed to neurotoxic insults (77). Additionally, the expression of GPER has been investigated in several areas of both male and female rodents central nervous systems (CNS), such as the hippocampus, cortex, hypothalamus, midbrain specific nuclei, and trigeminal nuclei (78). An increasing amount of data suggests that GPER has been connected to several brain disease experimental models, including global ischemia (79, 80), spinal cord injury (81), and parkinson′s disease (PD) (82-84). In the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) animal model of PD, prior research has demonstrated a crucial neuroprotective role for G1. This effect may be achieved by the increase of glial cell line-derived neurotrophic factor expression (83). Additionally, GPER in rat primary astrocytes has been linked to controlling glutamate transporter 1 expression, which is connected to the ex-citotoxic neurodegeneration of PD (85). E2 is a powerful modulator of the CNS that has a function in processes like neurogenesis, the regulation of the expression of neurotrophic factors, and the regulation of antioxidant mechanisms, according to studies conducted both in vivo and in vitro (72, 86, 87). Additionally, estrogens were linked to the control of cognitive function (88, 89), memory (90-95), and neurological diseases (96, 97). Activating GPER with its agonist G1 improves cognitive processes including learning and memory, similar to E2 (9).

2.3. Protective role on hepatocellular carcinoma

Major risk factors for hepatocellular carcinoma (HCC) have been identified, including hepatitis virus infection, alcoholism, aflatoxin exposure, autoimmune hepatitis, fatty liver disease, and male gender (98, 99). In female HCC patients, the rates of spontaneous survival and survival following resection are both higher (100, 101).

Apart from the androgen axis, epidemiological research has also indicated that the estrogen axis functions in controlling the gender difference in HCC. However, the higher female estrogen activity appears to have a protective effect on hepatocarcinogenesis, in contrast to the androgen axis' tendency to promote tumours. Yu et al., 2003 research demonstrated an inverse relationship between the age at menopause and the number of full-term pregnancies in females and the risk of HCC (102). It's interesting to note that all these benefits for female HCC patients diminish post-menopause, with older females experiencing a rise in cirrhosis and HCC instances (103). Regardless of the etiology, persistent chronic inflammation predisposes to HCC. Since sex discrepancy starts at the chronic hepatitis stage, we anticipate that the estrogen axis may begin to work as an antitumor early on in the process and fighting inflammation. Major regulators regulating the inflammation process during liver inflammation are immune-related cells and the inflammatory substances they produce, which are abundant in the local inflammatory microenvironment. When macrophages (Kupffer cells), T cells, and other immune cells are drawn to the microenvironment, they release proinflammatory factors such chemokines (like interlekin-8 (CXCL8), C-X-C chemokine receptor type 4 (CXCR4), and tumor necrosis factor alpha (TNF-α)), cytokines (like interlekin-1(IL-1), interlekin-6 (IL-6), and TNF-α), and other cytokines (104-106). In this microenvironment, there is a communication between the hepatocytes and the inflammatory cells. Protumorigenic factors secreted by immune cells, are able to target and activate various transcriptional activators present in hepatocytes, such as Nuclear factor kappa B (NF-κB), Signal transducer and activator of transcription 3 (STAT3), hypoxia-inducible factor 1 (HIF-1), and so on (105). In addition to increasing the tumorigenic activity of hepatocytes, activation of these transcription factors may also leads to synthesis of additional inflammatory mediators, which in turn attract and activate more immune cells inside the liver tissues (104-106). Different estrogen receptors contribute in different ways to the development of HCC (107). It has been demonstrated that E2 dramatically reduces the malignant activity of HCC cells by upregulating NLRP3 inflammasomes, which are regulated by ERβ /mitogen activated protein kinases (MAPK) signal pathway (108). Subsequent investigation revealed that the E2/ERβ/AMPK/mTOR pathway was used by the NLRP3 inflammasome to suppress the tumors' protective autophagy. E2 can often prevent HCC from starting by promoting caspase1-dependent apoptosis and preventing autophagy (109). The estrogen membrane receptor GPER is found in the plasma membrane and is not highly expressed in the tissues of liver cancer. Knocking down the GPER gene can greatly increase the incidence of liver cancer in the mouse liver cancer model caused by the carcinogen diethylnitrosamine. This is followed by fibrosis, immune cell infiltration, and the generation of inflammatory molecules (like IL-6). Moreover, GPER knockdown prevents the selective GPER agonist G-1 from decreasing the expression of IL-6 in bone marrow-derived macrophages. Nevertheless, in vitro tests have demonstrated that GPER has no direct impact on the survival and growth of liver cancer cells (54). These findings suggested that rather than directly affecting tumor cells, GPER might suppress HCC by controlling the inflammatory response. In contrast to matched non-tumor tissues, a new research discovered that GPER was dramatically down-regulated in HCC tissues. GPER positive HCC patients had significantly higher overall survival rates, smaller tumor sizes, low blood alpha-fetoprotein levels, female sex, and hepatitis B surface antigen negative status as compared to GPER negative patients. Both in vitro and in vivo, GPER/EGFR/ERK signaling, which is elicited by G1, a GPER-selective agonist, was essential in reducing the tumor viability of HCC. Clinical research revealed that improved prognosis for HCC was predicted by concurrently high expression of GPER and phosphorylated ERK (P-ERK). These results imply that targeting the GPER/ERK axis specifically may be a therapeutic goal (110).

2.4. Protective role on cardiovascular system

It is commonly recognized that the primary component contributing to sex differences is sex steroid hormones. It is well known that endogenous estrogen has a preventive function in women and lowers the incidence of cardiovascular disorders in women (111). Premenopausal women have a lower incidence of hypertension, atherosclerosis, myocardial dysfunction, ventricular hypertrophy, heart failure, and myocardial ischaemia compared to their age-matched male counterparts (112). However, the advantage in women gradually fades post-menopause, increasing the risk of CVD in postmenopausal women than in males of the same age. This trend is primarily assigned to the role of female estrogen in this process (113). Estrogen and the body's antioxidant ability decreases as menopausal women grow older, while the body's nicotinamide adenine dinucleotide phosphate (NADPH) and other oxidase activities increase, which results in an inability to clear ROS in time (114). Oxidative stress is then induced by the accumulation of ROS, which results in osteoporosis and CVD (115). GPER is abundantly expressed throughout the cardiovascular system of mammals, which includes the arterial wall and the heart (116). Physiological roles of GPER in the cardiovascular system include inhibition of inflammation, angiogenesis, myocardial contractility, and regulation of arterial blood pressure (116). GPER activation causes acute vasodilation of human, pig, rat, and mouse arteries (117-119). Direct effects on vascular

smooth muscle are among the underlying mechanisms (117, 118, 120) and endothelial L-arginine–NOS3–NO–cGMP pathway activation (121-123).

2.5. Protective role on bone

The fast decrease in serum estradiol levels that occurs after menopause in women is intimately linked to a higher rate of osteoclastic bone resorption. Postmenopausal women's low estrogen levels cause circulating macrophages to release osteoclastic cytokines, which in turn activate receptor activator of nuclear factor-κB (RANK) and encourage the activation of osteoclasts (124). Furthermore, the absence of the direct pro-apoptotic effects of estrogens on osteoclasts results in the lengthening of osteoclast lifespan, accelerating trabecular bone loss (125). It has been proven that estrogens play a major role in controlling bones remodeling in both sexes (126). In relation to connective tissues, human bone and growth plate cartilage have previously shown evidence of ERα, ERβ, and GPER1 expression (22, 127) as well as in the growth plate chondrocytes of the rat spinal and tibial (128). Furthermore, human osteoblasts, osteocytes, and osteoclasts have been shown to express GPER1 in the cytoplasm (22). GPER-1 deficiency results in specific metabolic changes, body weight loss, and decreased bone formation in global GPER-1 KO mice, indicating that GPER-1 may be involved in skeletal development (11). Recent study by Fan et al., 2018 demonstrated how GPER-1 increases chondrocyte proliferation (129).

2.6. Protective role on metabolic disorders as insulin resistance

Males are more prone to developing metabolic syndrome than premenopausal women, while protection in women is dramatically diminished when estrogen levels decline (130). Menopause can increase the likelihood of developing insulin resistance regardless of age, most likely due to a decrease in circulating estrogens (131). With the onset of menopause, metabolic disturbances such as insulin resistance grow considerably; however, the risk of metabolic syndrome is significantly reduced with estrogen replacement therapy (131, 132). Furthermore, timing is important since hormone replacement therapy (HRT) has a different impact on glucose homeostasis and insulin sensitivity in women who are early menopausal compared to those who are established postmenopausal and for whom HRT has no effect at all (133). Exogenous estrogen dramatically increases insulin sensitivity and reduces the incidence of diabetes in women receiving estrogen replacement therapy (134). According to a recently published cross-sectional analysis, estrogens significantly reduce the etiological components of metabolic syndrome in both groups of Korean women with and without diabetes. This finding agreed with previous research on the effect of hormone replacement treatment on metabolic syndrome (135).

Insulin stimulates the synthesis of endothelial nitric oxide by means of the PI3K-Akt pathway. Nitric oxide, a vasodilator which increases blood flow and the body's ability to absorb glucose by different organs and tissues (136, 137). In addition, nitric oxide stops smooth muscle cell proliferation, platelet aggregation, and leukocyte adherence (136, 137). Reduced nitric oxide generation by endothelial cells is a characteristic of endothelial dysfunction, a trait of insulin resistance that can set off the processes leading to atherosclerosis and the emergence of cardiovascular diseases (137, 138). Evidence from multiple clinical trials suggests that endothelial vascular tissue may be negatively impacted by estrogen deprivation, since post-menopausal women have a greater degree of endothelial dysfunction than premenopausal women (139-141). Studies on male Zucker rats that were insulin-resistant and given estradiol demonstrated a marked increase in endothelial function through the induction of nitric oxide synthase production, vasodilation responses, and a decrease in vasoconstriction (142). Male mice lacking GPER may develop pathological alterations as insulin resistance, dyslipidemia, and inflammatory responses (143). Reduced insulin sensitivity, increased abdominal fat accumulation, poor glucose tolerance, and systemic inflammation are the outcomes of losing E2 (as in postmenopause) or ER function (as in ERα knockout mice) (144, 145). Nevertheless, new research also points to the GPER; formerly known as GPR30 as having a function in the control of metabolism (116). Compared to wild type (WT) mice, mice without GPER had a higher risk of developing diabetes caused by streptozotocin (146). Furthermore, the protective effect of E2 in double-KO animals lacking both ERα and ERβ after treatment with streptozotocin suggests a function for GPER in islet survival (146). Finally, G1, the GPER-selective agonist (20) Reduces β-cell death in MIN6 pancreatic β-cells, as well as mouse and human islets (146) and increases islet survival after transplantation in a mouse model of type 1 diabetes (147). Mice lacking in GPER put on more weight (117) and in comparison to WT mice, female GPER KO mice exhibit glucose intolerance (11).

3. Side effects of estrogen hormone replacement therapy:

- Case-controlled studies appeared strongly linking postmenopausal estrogen use to endometrial cancer (148-150).
- Oral contraceptive studies have provided significant data on the link between estrogen treatment and thromboembolic and coagulation problems (151).
- Some studies in postmenopausal women do document an increase in blood pressure with low doses of conjugated estrogens (152, 153).
- Postmenopausal estrogen therapy increases the risk of cholelithiasis (154).

4. Conclusion

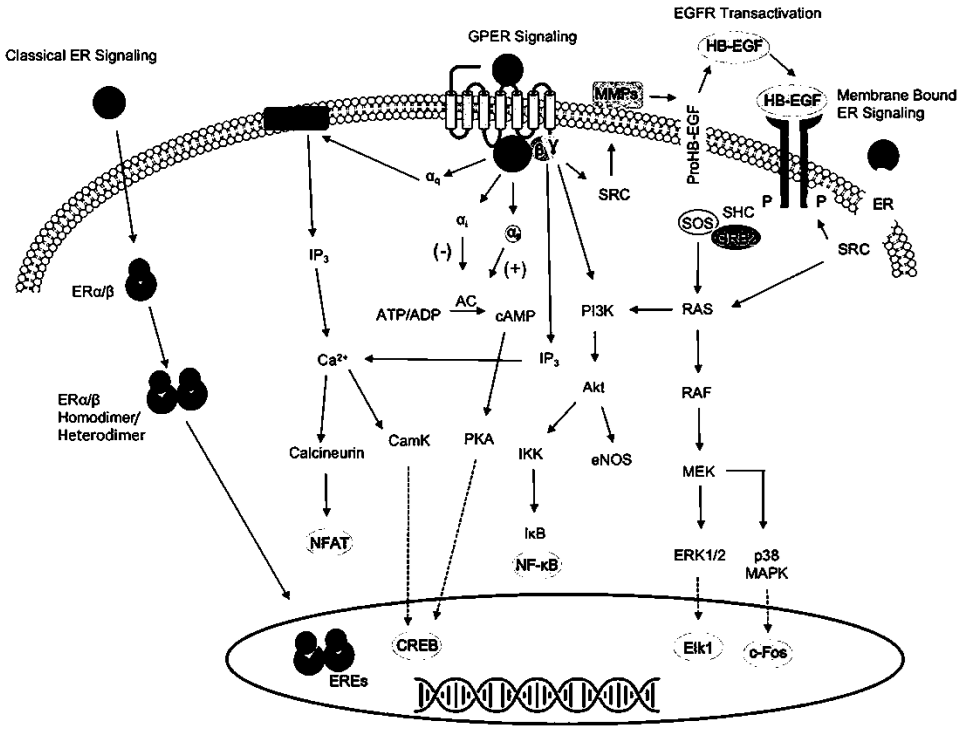
Female estrogens may exert a protective effect against some diseases through its anti-inflammatory, antioxidant, and vasodilator action which making the premenopausal females more protected from various diseases than their age-matched men. Additionally, estrogen receptors especially GPER activation different organs cause protection against kidney, liver, cardiovascular, and neurological diseases in addition to its protective role on metabolic disorders as insulin resistance.

Disclosure

The author reports no conflicts of interest in this work.

Graphs

Fig.1. **Signaling pathways of three estrogen receptors.**



Signaling pathways of three estrogen receptors. The classical estrogen receptors, ESR1 and ESR2, primarily exist within the cytoplasm and nucleus, as well as interact with estrogen response elements (EREs) after dimerization to drive genomic signaling. Unlike the nuclear estrogen receptors, GPER1 signaling pathway occurs through various second messengers. Phospholipase C Beta (PLCβ), inositol triphosphate (IP3), nuclear factor of activated T-cells (NFAT), calcium/calmodulin-dependent protein kinase (CamK), cAMP response element-binding protein (CREB), adenylate cyclase (AC), protein kinase A (PKA), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), IκB kinase (IKK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), endothelial nitric oxide synthase (eNOS), non-receptor tyrosine kinase (SRC), matrix metallopeptidases (MMPs), heparin-binding EGF-like growth factor (HB-EGF), son of sevenless (SOS), Src homology 2 domain-containing transforming protein (SHC), growth factor receptor-bound protein 2 (GRB2), RAS protein (RAS), RAF kinase (RAF), mitogen-activated protein kinase kinase (MEK), extracellular signal-regulated kinases 1/2 (ERK 1/2), Elk-1 transcription factor (Elk1), p38 mitogen-activated protein kinase (p38 MAPK), and c-Fos transcription factor (c-Fos).

Tables

Table 1. The role of ERs in some diseases.

Number	Disease	ERα	ERβ	GPER
1	Bone	-ERα is expressed in osteoblast, osteocytes, and osteoclast (Bord et al., 2001). -ERα in cortical bone is higher than in trabecular bone (Bord et al., 2001).	-ERβ is expressed in osteoblast, osteocytes, and osteoclast (Bord et al., 2001). -ERβ in trabecular bone is higher than in trabecular bone(Bord et al., 2001).	-GPER1 is expressed in osteoblasts, osteocytes, and osteoclasts (Heino et al., 2008). -Loss of GPER1decreases the bone growth in female mice (Mårtensson et al., 2009) , increases the bone mass in male mice (Ford et al., 2011).
2	Cardiovascular Disease	-ERα is highly expressed in PASMCs and VSMCs (Wright et al., 2015, Ortmann et al., 2011). -ERα improves cardiac recovery (Ortmann et al., 2011, Schubert et al., 2016, Booth et al., 2005, Zhai et al., 2000, Westphal et al., 2012,	-ERβ is expressed in endothelial cells and VSMCs of arteries (Christian et al., 2006). -Improves cardiac recovery (Schubert et al., 2016, Pelzer et al., 2005, Iorga et al., 2018, Kararigas et al., 2011, Liu et al., 2011). , decreases	-GPER1 is widely distributed in the cardiovascular system (Delgado et al., 2021). -GPER1 improves cardiac recovery (Bopassa et al., 2010, Feng et al., 2017, Wang et al., 2018, da Silva et al., 2019, Kang et al., 2012). -decreases cell

		Mahmoodzadeh et al., 2006, Frump et al., 2015, Billon-Galés et al., 2009).	fibrosis, inflammation, vasoconstriction, and right ventricle hypertrophy (Shen et al., 2018, Umar et al., 2011, Lahm et al., 2008, Pedram et al., 2016)	proliferation of fibroblasts and VSMC(Wang et al., 2015)
3	Liver Disease	-inhibits liver cancer (Hou et al., 2013, Dai et al., 2014, Chen et al., 2015a).	inhibits tumor (Yang et al., 2012, Lin et al., 2013)	inhibits tumor (Wei et al., 2016)
4	Neurodegenerative Disease	ERα is expressed in cortical and hippocampal neural stem/progenitor cells. ERα levels in female are higher than that in male (Foster, 2012).	ERβ is widely distributed and expressed in the hippocampus and cerebral cortex, lateral septa, and medial and basolateral amygdala. ERβ expression levels are higher than that of ERα in hippocampi (Foster, 2012).	GPER1 is expressed in cortical and hippocampal neural stem/progenitor cells (Foster, 2012).

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