Role of Estrogen and Progesterone in Human Disorders – An Overview

Disha Parikh, *Priyanshee Gohil

Department of Pharmacology and Clinical Pharmacy, K. B. Institute of Pharmaceutical Education & Research, Kadi Sarva Vishva Vidhyalaya, Gandhinagar, Gujarat, India.

ABSTRACT

Estrogen and progesterone are considered to be female sex hormones and play a widespread role in human physiology. Apart from reproduction, they also have role in cardiovascular health, cognition, bone integrity, immunity and cell proliferative actions. Estrogen and progesterone exert their action through estrogen receptors (ER) α and β, and progesterone receptor (PR) A and B respectively via genomic and non-genomic pathways. In cardiovascular disorders such as atherosclerosis, these hormones are found to have cardioprotective as well as antioxidant effect. Beta amyloid accumulation reduces in presence of estrogen and progesterone thereby they decrease the progression of neurodegenerative disorder such as Alzheimer's disease. Additionally estrogen and progesterone are found to exert beneficial effect in Parkinson's disorder. Estrogen and progesterone affects calcium metabolism and thus prevent the occurrence and progression of Osteoporosis. However in diseases such as systemic lupus erythmetosus (SLE), these hormones aggravate immune response and play a pathological role in development of disease. These both female sex hormones are the key hormones to be involved in breast cancer. They are found to stimulate proliferation and enhance the invasiveness of breast cancer cells. Thus the role of estrogen and progesterone in occurrence and development of various diseases is complex and controversial. This review briefly summarizes the role of Estrogen and progesterone in development and progression of various diseases.

*Address for correspondence:
Dr. Priyanshee Gohil,
Department of Pharmacology and Clinical Pharmacy, K. B. Institute of Pharmaceutical Education & Research, Kadi Sarva Vishva Vidhyalaya, Gandhinagar, Gujarat, India.
E-mail: priyansheeg@yahoo.co.in

INTRODUCTION

Sex steroid hormones including estrogen and progesterone have been traditionally identified for their role in reproduction. The major endogenous estrogens include estradiol, estrone, and estriol whereas major progesterone is progestin [1]. The most potent and dominant estrogen in humans is 17-β estradiol (17β-E2), however lower levels of estrone and estriol are also present [2]. They act by paracrine manner or circulate to act on target tissue in endocrine manner [1]. From the past few decades, hormone replacement therapy (HRT) has been used for the treatment of the postmenopausal symptoms. Studies suggested that HRT may reduce the incidence of coronary heart disease (CHD), fractures, and colorectal cancer but may increase the incidence of endometrial cancer, breast cancer, stroke, and venous thromboembolism [3]. So, in present review, we summarize the pathophysiological and/or protective role of estrogen and progesterone in development and progression of various diseases.

Mechanism of Action of Estrogen and Progesterone Receptors

Estrogen and progesterone act via Estrogen and Progesterone receptors, the member of nuclear receptor superfamily. The biological effects of estrogen and progesterone is mediated through estrogen receptors (ER) α and β, and progesterone receptor (PR) A and B respectively through genomic and non-genomic pathways [2, 4]. The genomic

pathway includes binding of these hormones to specific ligand binding domain (LBD) and induce conformational changes in the receptors, followed by the separation of the receptor from cytoplasmic chaperone proteins such as heat shock protein 90 (Hsp90). This results in the dimerization of the ligand bound receptor and its binding to the steroid response elements on promoter region of target gene resulting in regulation of gene expression via interaction with transcription machinery [5]. Estrogen and progesterone also act via non-genomic mechanisms. The non-genomic actions are independent of gene transcription or protein synthesis and involve steroid-induced modulation of cytoplasmic or cell membrane-bound regulatory proteins. Regulatory cascades such as mitogen-activated protein kinases (MAPK), the phosphatidylinositol 3-OH kinase (PI3K) and tyrosine kinases are modulated through non-transcriptional mechanisms of steroid hormones [6]. This hormones have been found to be involved in the regulation of cell membrane ion channels, G-protein-coupled receptors (GPCRs), tyrosine kinases, MAPK and also have shown to activate adenylatecyclase production, as well as trigger activation of phospholipase C (PLC) [5] (**Fig. 1**).
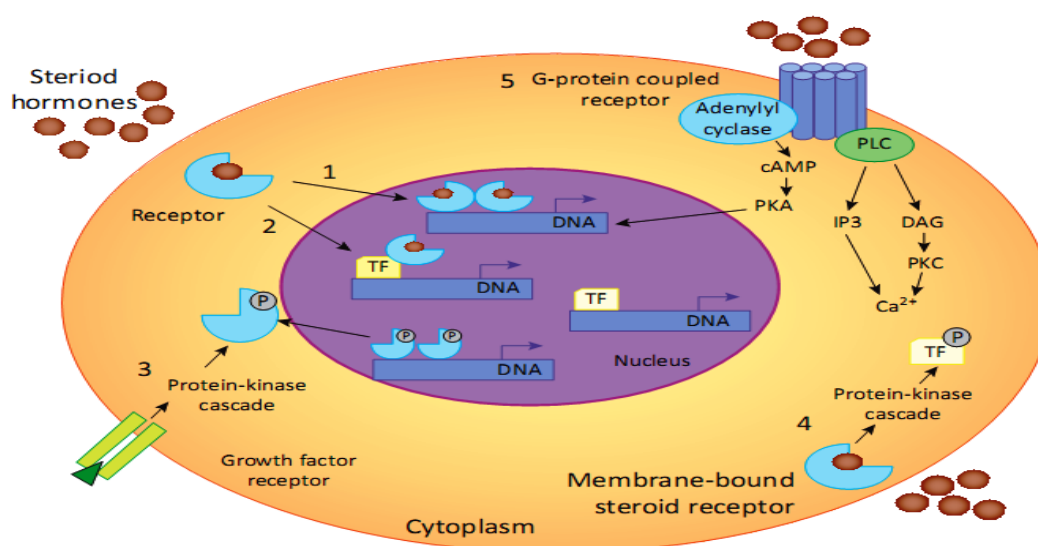

Figure 1: Genomic and Non-genomic Actions of Steroid Hormones [7]

The events in (**Fig. 1**) are described as follows 1. In the nucleus the hormone bound receptor interacts with transcription factor and bind to responsive elements on DNA, controlling gene expression. 2. Non genomic actions are mediated by binding of hormones to membrane bound receptors and phosphorylation of steroid hormone receptor via protein kinase cascade thereby binding of phosphorylated receptor to DNA, regulating gene expression. 3. Hormone binding to membrane receptor may also phosphorylate transcription factors that bind to their own response element genome, via protein kinase cacade and regulate gene expression. 4. The effects that are not dependent on transcription and protein synthesis are mediated through the activation of G-protein coupled receptors by steroids. 5. Transcription factor(TR), cyclic adenosine monophosphate(cAMP), protein kinase A(PKA), phospholipase C(PLC), inositol 1,4,5-triphosphate(IP3), diacylglycerol(DAG), protein kinase C(PKC) [7].

The physiological effects of estrogen and progesterone are well known but limited information is available for their pathophysiological effect in genesis of various disorders. Estrogen and progesterone are considered to be involved in development and progression of following disorders.

Cardiovascular Disorders

Over a quarter million women aged 50–75 yr die of coronary artery disease (CAD) in the United States each year. This is due to the natural state of estrogen deficiency

during menopause. There are accumulating evidences about the protective role of estrogen in coronary artery disease. Estrogen have been found to increase high density lipoprotein (HDL) level as well as decrease low density lipoprotein (LDL) level and LDL oxidation. Action of progesterone is frequently described as opposite to that of estradiol. Progestins are found to decrease HDL level and increase LDL levels, however the effects of progesterone are controversial [8]. Estrogen relaxes the coronary artery system by acting through MAPK and PI3K, as well as reduces intracellular calcium levels [9]. Booth et al.2003, studied receptor mediated cardioprotective effects of 17β-estradiol in rabbits where it was found that estradiol decreased the myocardial infract size resulting from coronary artery occlusion and reperfusion, in a dose dependent manner [10]. Studies showed that estrogen reduces superoxide production by modulating nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase in endothelial and vascular smooth muscle; there by exerting antioxidant effect. Thus long term depletion of estrogen may result in endothelial dysfunction due to increased production of superoxide [11]. Estradiol cause hyperpolarization of vascular smooth muscle cells (VSMC) by acting on T and L type of calcium channels resulting in attenuation of myocardial and vascular contractility. Estradiol also inhibit VSMC and extracellular matrix formation suggesting its antiatherogenic effect of estradiol [8]. It was also found that hormone replacement therapy (HRT) with estrogen in postmenopausal women showed prolongation in QT- interval [12].

In contrast to estrogen, progesterone increase the degradation of HDL by inducing hepatic lipase activity however this effect depends on the biochemical structure and dose of progesterone e.g. medroxyprogesterone acetate (MPA) have little effect on lipid profile whereas levonorgestrel showed 20-30% reduction of HDL cholesterol [13]. Vázquez et al.1999, evaluated the effect of progesterone on endothelial cell proliferation and it was found that the rate of re-endothelialization decreased in wild-type mice in the presence of progesterone, whereas there was no difference between control and progesterone treated progesterone receptor knockout mice [14].

Neurodegenerative Disorders

Ion flux plays an important role in controlling neuronal function. Estrogen and progesterone activates the GPCR in rat neurons, thus rapidly suppress ion currents through L-type Ca^{++} channels. They have also been found to attenuate K+ conductance and to induce depolarization of hypothalamic neurons via cyclic adenosine monophosphate (cAMP) [15].

Female sex hormones have been found to play a role in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). Estrogen replacement therapy have also been suggested to postmenopausal women suffering from Alzheimer's disease as well as to decrease the progression of the disease indicating protective effect of estrogen in these diseases.

Studies showed that steroid deprivation via overiectomy (OVX) altered acetyltransferase (ChAT) activity and cholinergic receptor density in rats [16]. Muscarinic cholinergic M_4 receptors are found in abundance in neostriatum and in moderate levels in the hippocampus and cortex. Overiectomy showed significant up-regulation of muscarinic M_4 receptors in hippocampus, frontal cortex and hypothalamus. This suggested that estrogen receptor exist on the cholinergic neurone and due to OVX, estrogen deficiency failed to stimulate estrogen receptors which in turn failed to stimulate the release of acetylcholine [17].

Beta-amyloid protein (Aβ) accumulation in hippocampus and cerebrocortical regions plays a critical role in initiation and progression of Alzheimer's disease. Proteases involved in Aβ degradation and its clearance include insulin-degrading enzyme (IDE), neprilysin (NEP), endothelin-converting enzymes-1 (ECE1) and 2 (ECE2), angiotensin-converting enzyme (ACE) and transthyretin (TTR). Study of estrogen and progesterone on neuronal cultures showed that estrogen regulates the m-RNA expression of IDE, ACE, and ECE2 in dose and time dependent manners whereas

progesterone regulates the expression levels of IDE, ACE, and TTR mRNA [18].

Estrogen and progesterone activate tyrosine kinase and MAPK thereby exerting neuroprotective effect against glutamate induced excitotoxicity. However progesterone and 19-norprogesterone, and not medroxyprogesterone acetate (MPA), decreased neuronal damage induced by glutamate excitotoxicity. 17β-estardiol has been found to increase the expresion of antiapoptotic protein Bcl-2 in neuronal cultures and neural cell lines. Progesterone or 19 norprogesterone, administered alone or in conjunction with 17β-E2, showed increased Bcl-2 expression [19].

17β-estradiol has shown to prevent the formation of Aβ by promoting the non-amyloidogenic α-secretase processing of amyloid precursor protein (APP) [20]. The non-amyloidogenic APP processing involves MAPK signaling including activation of extracellular-regulated kinases 1 & 2 (ERK1/2) [21]. Besides estradiol also has the ability to increase amyloid beta-protein (Aβ) uptake by microglia as well as prevent Aβ peptide formation by neurons [22] (**Fig. 2**).
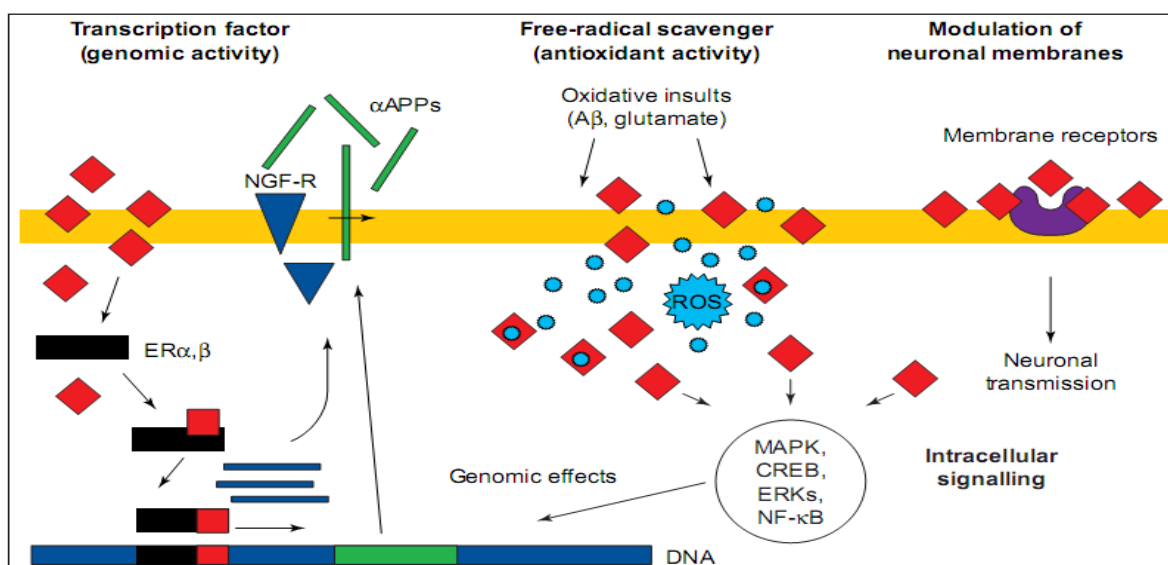

Figure 2: Estrogen Exerting Multiple Neuroprotective Functions [20]

Estrogen and estrogen receptors (ERα,β) complex translocate to the nucleus and bind to ER-responsive elements on the genomic DNA leading to the transcription of neuro protection modulators, such as nerve growth factor receptors (NGF-R) and the induction of non-amyloidogenic amyloid β protein precursor protein (APP) processing, leading to the generation of soluble APPs (αAPPs) [transcription factor and genomic activity]. The phenolic structure of estrogen has antioxidant activity that is independent of ER activation. Therefore, estrogen is a free-radical scavenger of reactive oxygen species (ROS) produced by amyloid β protein (Aβ) or glutamate [free-radical scavenger and antioxidant activity]. Estrogen modulates the function of membrane receptors that might modulate neuronal transmission. Estrogen might interact with various intracellular signaling pathways such as mitogen-activated protein kinase (MAPK), cAMP-response-element-binding protein (CREB), extracellular regulated kinases (ERKs), nuclear factor kB (NF-kB, and indirectly exert genomic effects by modulation of various transcriptional program (intracellular signalling) [20].

Estrogen has been shown to maintain the dopaminergic neurons in substantia nigra of primates. Overiectomy resulting in estrogen deficiency showed decrease in density of dopaminergic neurons in substantianigra suggesting the role of estrogen in Parkinson's disease. The exact mechanism of protective action of estrogen on dopaminergic neurone is not known however the antiapoptotic activity of estrogen might be responsible for exerting the neuroprotective action against the 1-methyl-4-phenyl-1,2,3,5-

tetrahydropyridine (MPTP) induced neurotoxicity [22, 23]. Estrogen also act indirectly by activating the insulin-like growth factor-1(IGF-1) receptor to protect against 6-hydroxdopamine (6-OHDA) induced neuronal loss in PD animal model [22].

Osteoporosis

In postmenopausal women, the rate of bone resorption increases rapidly, resulting in calcium imbalance, leading to osteoporosis. Estrogen and progesterone affects the calcium metabolism thereby suggesting their role in osteoporosis. Estrogen such as 17β-estradiol and progesterone such as gestronolhexanoate and norethisterone are used as hormone replacement therapy in osteoporosis of postmenopausal women [24]. Estrogen via ERα signaling exert collagen type –II and cartilage protective actions in collagen induced arthritis (CIA) thereby reducing the severity of arthritis and progression of osteoporosis in mice [25]. It has also been found that decrease in progesterone in postmenoposal women cause decrease in bone mineral density (BMD) leading to rapid bone loss [26].

Pro-inflammatory cytokines induced osteoclast cells (OC) formation is responsible for bone resorption in osteoporosis. Osteoclast formation occurs when monocytes are co-stimulated by osteoclastogenic factors such as receptor activator of nuclear factor-kappa B ligand (RANKL), and macrophage colony stimulating factor (M-CSF)[27]. These factors via acting through RANK and TNF receptors activate nuclear factor-kappa B (NFκB) and Jun N-terminal kinase (JNK) intracellular signaling thus increases the differentiation and activity of OC and decrease the apoptosis of OC. Cytokines such as interleukin-1 (IL-1), interleukin -6 (IL-6) and tumor necrosis factor-α (TNF-α) increases the signaling of RANKL and M-CSF whereas prostaglandin E_2 increase RANKL signaling. Transforming growth factor-β (TGF-β) increase the apoptosis of OC and osteoprotegerin (OPG), a soluble decoy receptor neutralizes RANKL thereby decreasing bone resorption[28-30].

Estrogen has been found to inhibit IL-1 and TNF-α mediated stimulation of IL-6, thus regulate differentiation and expression of osteoclast cells thus improving the bone mineral density [31, 32]. Estrogen also increase the activity of OPG and TGF-β [28]. Progesterone has been found to upregulate TGF-β isoforms such as β1, β2 and β3 in human osteoblasts thus contributing to promote bone formation [33] (**Fig. 3**).
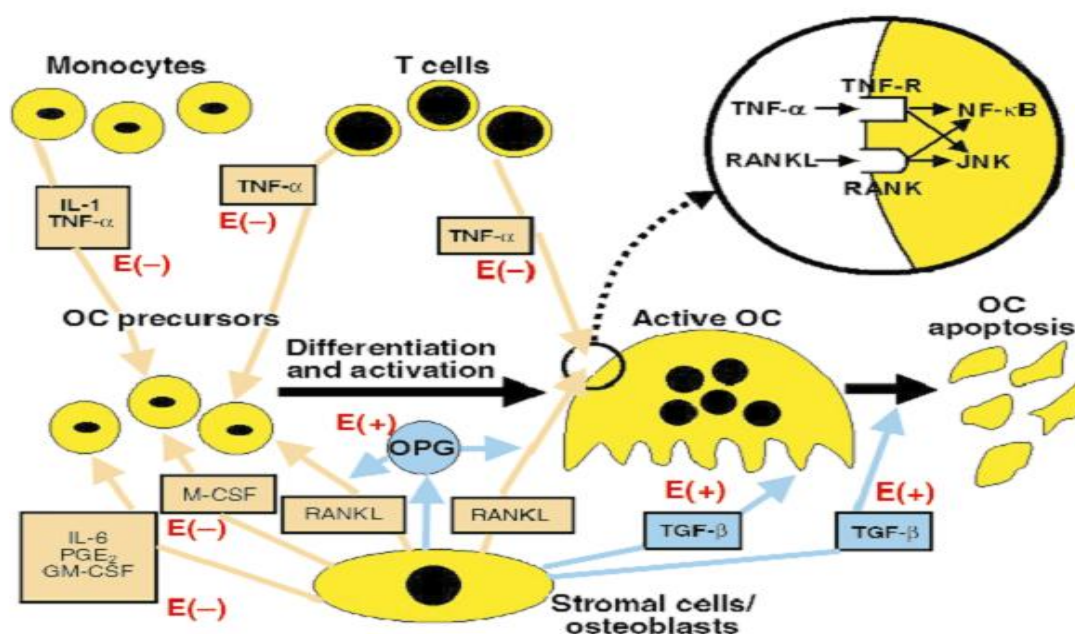

Figure 3: Positive (+) and Negative (-) Effect of Estrogen on Cytokines involved in Regulation of Osteoclast Cell Function [28]

Stimulatory factors for osteoclastogenesis are shown in orange and inhibitory factors are shown in blue.

Autoimmune Disease

Female sex hormones have been studied for many years for its role in immune system. Estrogen receptors ER-α and ER-β are also expressed in immune cells such as T, B lymphocytes, natural killer (NK) cells, macrophages and dendritic cells (DCs) where as progesterone receptors are expressed in NK cells and tissue macrophages [34-36]. Estrogen and progesterone had shown modulatory effect on functions on cells of the immune system, including macrophages, NK cells, DCs, T cells and B cells (**Fig. 4**). It was found that 17β-estradiol modulate the ability of macrophages to produce various cytokines such as IL-1, IL-6 and TNF-α. During pregnancy at the foetal-maternal interface, natural killer (NK) cells possess high concentrations of perforin that mediates NK cell cytotoxicity. Progesterone lowers the NK cell activity and thereby contributes to successful continuation of pregnancy. Thus estrogen and progesterone have shown immunomodulatory effects [36-38].
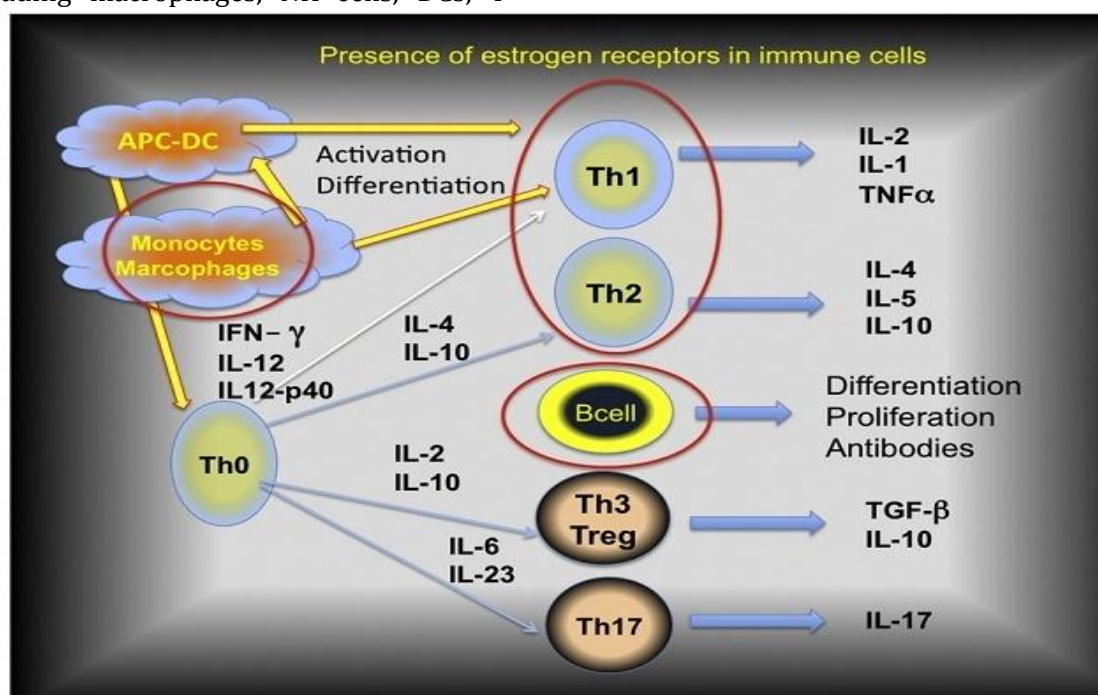

Figure 4: Estrogen Receptors in Immune cells. Functional Receptors are found in Macrophage, T-cells and B-cells (red circles)[35]

Role of estrogen and progesterone have been widely studied for autoimmune disease such as systemic lupus erythematosus (SLE). Estrogen have been found to involved in the development of T helper cell-2 (Th2) and induce B-cell hyperactivity leading to generation of more auto-antibodies [39]. Estrogens and their catechol metabolites alter immunogenicity of DNA leading to induction and elevation levels of SLE autoantibodies crossreacting with native DNA [35]. Further estradiol and progesterone have been found to increase the expression of antigen presenting dendritic cells resulting in production of IL-1, IL6 and TNF-α [35, 39]. Estradiol also upregulate the m-RNA expression of T-cell markers such as calcineurin and CD154 in patients with SLE [34]. This suggests that exogenous estrogen and progesterone may aggravate the inflammatory response in SLE [40].

Breast Cancer

Estrogen and progesterone are the major hormones involved in growth and regression of breast cancer. Both estrogen and progesterone receptors are involved in breast cancer. It was found that breast tumor regression was higher in estrogen and progesterone combination treatment than in progesterone alone. A moderate to higher dose of estrogen alone can cause mammary gland tumor, however patients, who were found to fail to regress towards estrogen alone, responded towards estrogen and progesterone combination

[41, 42]. Progestins are found to stimulate proliferation, inhibit apoptosis and enhance invasiveness of breast cancer cells [43]. Estrogen receptors are directly targeted in breast cancer using selective estrogen receptor modulators (SERM) such as tamoxifen and reloxifen as competitive antagonist or by pure antiestrogens such as fluvestrants. [44]

It has been suggested that estrogen metabolites are also responsible for breast cancer. Estrogen metabolites like catechol estrogen-3,4-quinones (CE-3,4-Q) and to a much lesser extent, catechol estrogen-2,3-quinones (CE-2,3-Q) affecting the formation of DNA adducts, carcinogenicity, mutagenicity, and cell transformation can result in critical DNA mutations that initiate breast, prostate and other cancers [45].

Estrogen receptors and progesterone receptors are expressed in both normal breast and in breast carcinoma. Esterogen receptor-α expression dramatically increase in early hyperproliferative premalignant phase. Progesterone receptor is an estrogen regulated gene, and requires estrogen and ER for its synthesis in normal and cancer cells. Interaction of ER and PR with breast cancer susceptibility gene 1(BRCA1) have been studied in development of breast cancer. Breast cancer susceptibility gene 1 is the ligand independent co-repressor of ER and PR. Mutation of BRCA1 has been implicated for the development of breast cancer. Excessive signaling of ER and PR lead to mutation in BRCA1 leading to

BRCA1 mutant cancer [46-48]. Moreover mifepristone (antiprogestin) treatment in mice that lack the murine homologues of BRCA1 and p53, two tumour suppressors that are frequently mutated in breast cancer, has been shown to prevent mammary tumourogenesis, suggesting the role of progesterone in breast cancer [49].

In order to study the molecular mechanisms of estrogen, progesterone and their receptors, nuclear-initiated steroid signaling (NISS) and membrane-initiated steroid signaling (MISS) pathways have been elucidated using breast cancer cells [46, 50] (**Fig. 5**). Growth factors, such as insulin-like growth factor-I(IGF-I), epidermal growth factor (EGF), heregulin, and transforming growth factor alpha, neurotransmitter such as dopamine, signaling molecules such as cyclic adenosine monophosphate, and membrane-permeable phosphatase inhibitors via NISS pathway increase the phosphorylation of ER and its co-regulator (CoR). Several key signaling kinases, including the mitogenic ERK1/2, the stress-related kinases I kappa B kinase, c-Jun NH2 terminal kinase (JNK), and the p38 MAPK, have all been suggested to phosphorylate members of the p160 SRC family of co-activators [44,46, 51].

Through the MISS events estradiol was found to activates the SHC1/MAPK1/3 and phosphoinositide-3-kinase/AKT1 pathways that are likely to be the major effectors of cell proliferation and cell survival in cancer [50].
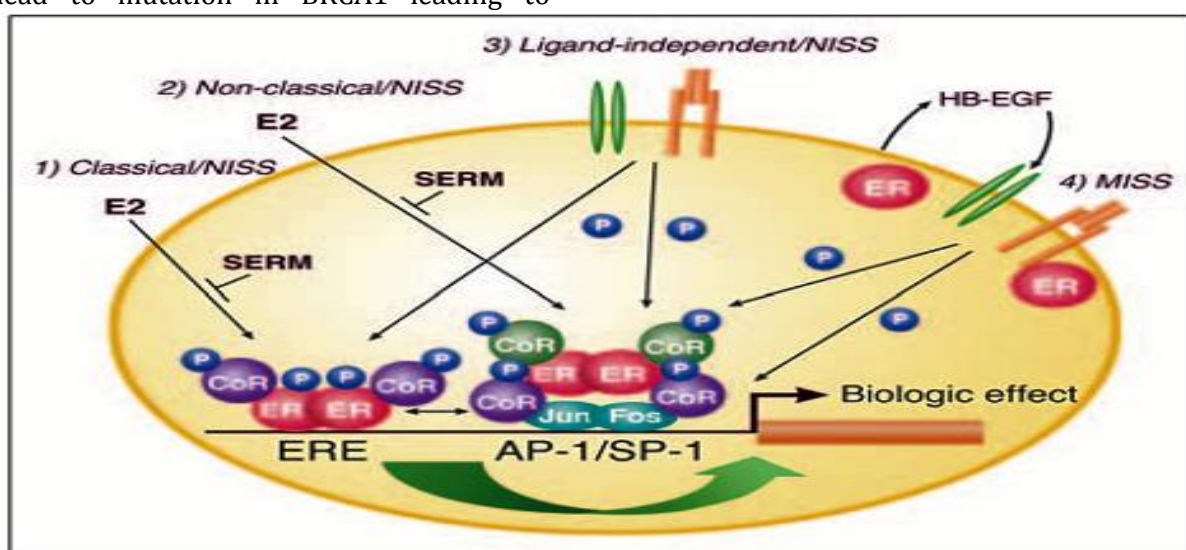

Figure 5: Major pathways for action of ER in breast cancer cells [46]

NISS (Nuclear-Nitiated Steroid Signaling), HB-EGF (Heparin Binding Epidermal Growth Factor), MISS (Membrane-Initiated Steroid Signaling), SERM (Selective Estrogen Receptor Modulator), P (Progesterone), CoR (Co-Regulator), E2 (Estradiol), ERE (Estrogen Response Element).

All three members of the steroid receptor co-activator (SRC) family have been found to interact with the PR and enhance its transcriptional activation in a ligand-dependent manner [48]. Progesterone has been found to induce cell proliferation via activation of endothelial growth factor (EGF) and transforming growth factor-α (TGF-α) [52].

It has also been found that ERα, PRA, and PRB induce robust proliferation in both the normal mammary gland and hormone-dependent mammary cancers through the induction of amphiregulin (Areg) which acts as an autocrine/paracrine EGFR ligand and result in activation of intracellular signaling pathways (Erk, Akt, JNK) downstream of EGFR that regulate proliferation in breast cancer [53].

Conclusion

Estrogen, Progesterone and their receptors have been implicated for development and progression of various disorders. They have been found to exert protective effects in cardiovascular disorder such as atherosclerosis, neurodegenerative as well as disorders such as osteoporosis. However, a detailed investigation on diseases such as cardiac arrhythmia, neuropsychiatric disorder and rheumatoid arthritis is needed. Estrogen and progesterone receptors also play a role in pathogenesis of disease like breast cancer. Targets for estrogen receptors in breast cancer are documented but estrogen receptor targets for prostate cancer, ovarian cancer and colon cancer are yet to be established. Further, estrogen and progesterone have been identified to aggravate autoimmune disease such as systemic lupus erythmatosus. Future studies to understand how the hormonal changes regulate immune response must be considered. Thus activation or inactivation of ER and PR can be used as new therapeutic strategies for the prevention and treatment of diseases.

The traditional estrogen and progesterone agonist and antagonist used for treatment of certain disorders aggravate complications in the therapy by acting on other tissues, thus development of tissue specific agents might dampen the risk associated with the conventional therapy. Thus, further research at molecular level may provide important insights to clarify the role of estrogen and progesterone in various human disorders.

REFERENCES

1. Wierman ME. Sex steroid effects at target tissues: mechanisms of action. Advances in Physiology Education. 2007 January 1, 2007;31(1):26-33.
2. Bjornstrom L, Sjoberg M. Mechanisms of estrogen receptor signaling: convergence of genomic and nongenomic actions on target genes. Mol Endocrinol. 2005;19(4):833-42.
3. Michels KB, Manson JE. Postmenopausal Hormone Therapy: A Reversal of Fortune. Circulation. 2003 April 15, 2003;107(14):1830-3.
4. Leonhardt SA, Boonyaratanakornkit V, Edwards DP. Progesterone receptor transcription and non-transcription signaling mechanisms. Steroids. 2003;68(10-13):761-70.
5. Simoncini T, Genazzani AR. Non-genomic actions of sex steroid hormones. Eur J Endocrinol. 2003;148(3):281-92.
6. Simoncini T, Mannella P, Fornari L, Caruso A, Varone G, Genazzani AR. Genomic and non-genomic effects of estrogens on endothelial cells. Steroids. 2004;69(8-9):537-42.
7. Laurentino S PP, Correia S, Cavaco JE, Canrio AVM, Socorro S. Structural variants of sex steroid hormone receptors in the testis: from molecular biology to physiological roles. OA Biotechnology 2012 Dec 17;1(2):4.
8. Skafar DF, Xu R, Morales J, Ram J, Sowers JR. Clinical review 91: Female sex hormones and cardiovascular disease in women. J Clin Endocrinol Metab. 1997;82(12):3913-8.
9. Chambliss KL, Shaul PW. Estrogen Modulation of Endothelial Nitric Oxide Synthase. Endocrine Reviews. 2002 October 1, 2002;23(5):665-86.
10. Booth EA, Marchesi M, Kilbourne EJ, Lucchesi BR. 17β-Estradiol as a Receptor-Mediated Cardioprotective Agent. Journal of Pharmacology and Experimental Therapeutics. 2003 October 1, 2003;307(1):395-401.
11. Dantas AP, Tostes RC, Fortes ZB, Costa SG, Nigro D, Carvalho MH. In vivo evidence for antioxidant potential of estrogen in

microvessels of female spontaneously hypertensive rats. Hypertension. 2002;39(2 Pt 2):405-11.

12. Shufelt CL, Bairey Merz CN. Contraceptive Hormone Use and Cardiovascular Disease. Journal of the American College of Cardiology. 2009;53(3):221-31.

13. Rosano GM, Sarais C, Zoncu S, Mercuro G. The relative effects of progesterone and progestins in hormone replacement therapy. Hum Reprod. 2000;1:60-73.

14. Vázquez F, Rodríguez-Manzaneque JC, Lydon JP, Edwards DP, O'Malley BW, Iruela-Arispe ML. Progesterone Regulates Proliferation of Endothelial Cells. Journal of Biological Chemistry. 1999 January 22, 1999;274(4):2185-92.

15. Deroo BJ, Korach KS. Estrogen receptors and human disease. J Clin Invest. 2006;116(3):561-70.

16. Simpkins JW, Green PS, Gridley KE, Singh M, de Fiebre NC, Rajakumar G. Role of Estrogen Replacement Therapy in Memory Enhancement and the Prevention of Neuronal Loss Associated With Alzheimer's Disease. The American journal of medicine. 1997;103(3):19S-25S.

17. El-Bakri NK, Adem A, Suliman IA, Mulugeta E, Karlsson E, Lindgren JU, et al. Estrogen and progesterone treatment: effects on muscarinic M(4) receptor subtype in the rat brain. Brain Res. 2002;948(1-2):131-7.

18. Jayaraman A, Carroll JC, Morgan TE, Lin S, Zhao L, Arimoto JM, et al. 17β-Estradiol and Progesterone Regulate Expression of β-Amyloid Clearance Factors in Primary Neuron Cultures and Female Rat Brain. Endocrinology. 2012;153(11):5467-79.

19. Nilsen J, Brinton RD. Impact of progestins on estrogen-induced neuroprotection: synergy by progesterone and 19-norprogesterone and antagonism by medroxyprogesterone acetate. Endocrinology. 2002;143(1):205-12.

20. Behl C, Holsboer F. The female sex hormone oestrogen as a neuroprotectant. Trends Pharmacol Sci. 1999;20(11):441-4.

21. Barron AM, Pike CJ. Sex hormones, aging, and Alzheimer's disease. Front Biosci. 2012;4:976-97.

22. Spence RD, Voskuhl RR. Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration. Front Neuroendocrinol. 2012;33(1):105-15.

23. Leranth C, Roth RH, Elsworth JD, Naftolin F, Horvath TL, Redmond DE. Estrogen Is Essential for Maintaining Nigrostriatal Dopamine Neurons in Primates: Implications for Parkinson's Disease and Memory. The Journal of Neuroscience. 2000 December 1, 2000;20(23):8604-9.

24. Christiansen C. Hormone replacement therapy and osteoporosis. Maturitas. 1996;23:S71-S6.

25. Jochems C, Islander U, Erlandsson M, Engdahl C, Lagerquist M, Gjertsson I, et al. Role of endogenous and exogenous female sex hormones in arthritis and osteoporosis development in B10.Q-ncf1*/* mice with collagen-induced chronic arthritis. BMC Musculoskelet Disord. 2010;11(284):1471-2474.

26. Seifert-Klauss V, Prior JC. Progesterone and bone: actions promoting bone health in women. J Osteoporos. 2010;31(845180):845180.

27. D'Amelio P, Grimaldi A, Di Bella S, Brianza SZM, Cristofaro MA, Tamone C, et al. Estrogen deficiency increases osteoclastogenesis up-regulating T cells activity: A key mechanism in osteoporosis. Bone. 2008;43(1):92-100.

28. Riggs BL. The mechanisms of estrogen regulation of bone resorption. J Clin Invest. 2000;106(10):1203-4.

29. Dougall WC. Molecular Pathways: Osteoclast-Dependent and Osteoclast-Independent Roles of the RANKL/RANK/OPG Pathway in Tumorigenesis and Metastasis. Clinical Cancer Research. 2012 January 15, 2012;18(2):326-35.

30. Pfeilschifter J, Koditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. Endocr Rev. 2002;23(1):90-119.

31. Kawai M, Modder UI, Khosla S, Rosen CJ. Emerging therapeutic opportunities for skeletal restoration. Nat Rev Drug Discov. 2011;10(2):141-56.

32. Girasole G, Jilka RL, Passeri G, Boswell S, Boder G, Williams DC, et al. 17 beta-estradiol inhibits interleukin-6 production by bone marrow-derived stromal cells and osteoblasts in vitro: a potential mechanism for the antiosteoporotic effect of estrogens. J Clin Invest. 1992;89(3):883-91.

33. Luo XH, Liao EY, Su X. Progesterone Upregulates TGF-b Isoforms (b1, b2, and b3) Expression in Normal Human Osteoblast-Like Cells. Calcif Tissue Int. 2002 2002/10/01;71(4):335-43.

34. Pierdominici M, Ortona E. Estrogen Impact on Autoimmunity Onset and Progression: the Paradigm of Systemic Lupus Erythematosus. International Trends in Immunity. 2013;1(2):24-34.

35. Cutolo M, Sulli A, Straub RH. Estrogen metabolism and autoimmunity.

Autoimmunity Reviews. 2012;11(6–7):A460-A4.

36. Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev. 2012;11(6-7):13.

37. Ansar Ahmed S, Penhale WJ, Talal N. Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action. Am J Pathol. 1985;121(3):531-51.

38. Menzies F, Henriquez F. Immunomodulation by the female sex hormones. Open Infect Dis J. 2009;3:61-72.

39. Lee T-P, Chiang B-L. Sex differences in spontaneous versus induced animal models of autoimmunity. Autoimmunity Reviews. 2012;11(6–7):A422-A9.

40. Buyon JP, Petri MA, Kim MV, Kalunian KC, Grossman J, Hahn BH, et al. The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomized Trial. Annals of Internal Medicine. [Article]. 2005;142(12):953-W-221.

41. McGuire WL, Horwitz KB, Chamness GC, Zava DT. A physiological role for estrogen and progesterone in breast cancer. Journal of Steroid Biochemistry. 1976;7(11–12):875-82.

42. McGuire WL, Horwitz KB, Pearson OH, Segaloff A. Current status of estrogen and progesterone receptors in breast cancer. Cancer. 1977;39(6):2934-47.

43. Kato S, Pinto M, Carvajal A, Espinoza N, Monso C, Sadarangani A, et al. Progesterone Increases Tissue Factor Gene Expression, Procoagulant Activity, and Invasion in the Breast Cancer Cell Line ZR-75-1. Journal of Clinical Endocrinology & Metabolism. 2005 February 1, 2005;90(2):1181-8.

44. Pearce ST, Jordan VC. The biological role of estrogen receptors α and β in cancer. Critical Reviews in Oncology/Hematology. 2004;50(1):3-22.

45. Russo J, Russo IH. The role of estrogen in the initiation of breast cancer. The Journal of Steroid Biochemistry and Molecular Biology. 2006;102(1–5):89-96.

46. Cui X, Schiff R, Arpino G, Osborne CK, Lee AV. Biology of Progesterone Receptor Loss in Breast Cancer and Its Implications for Endocrine Therapy. Journal of Clinical Oncology. 2005 October 20, 2005;23(30):7721-35.

47. Katiyar P, Ma Y, Fan S, Pestell RG, Furth PA, Rosen EM. Regulation of progesterone receptor signaling by BRCA1 in mammary cancer. Nuclear receptor signaling. 2006;4:e006

48. Gao X, Nawaz Z. Progesterone receptors - animal models and cell signaling in breast cancer: Role of steroid receptor coactivators and corepressors of progesterone receptors in breast cancer. Breast Cancer Res. 2002 2002/06/28;4(5):1-5.

49. Gellersen B, Fernandes MS, Brosens JJ. Non-genomic progesterone actions in female reproduction. Human Reproduction Update. 2009 January 1, 2009;15(1):119-38.

50. Song RX-D, Santen RJ. Membrane Initiated Estrogen Signaling in Breast Cancer. Biology of Reproduction. 2006 July 1, 2006;75(1):9-16.

51. Madak-Erdogan Z, Lupien M, Stossi F, Brown M, Katzenellenbogen BS. Genomic collaboration of estrogen receptor α and extracellular signal-regulated kinase 2 in regulating gene and proliferation programs. Molecular and cellular biology. 2011;31(1):226-36.

52. Graham JD, Clarke CL. Physiological Action of Progesterone in Target Tissues. Endocrine Reviews. 1997 August 1, 1997;18(4):502-19.

53. Kariagina A, Xie J, Leipprandt JR, Haslam SZ. Amphiregulin mediates estrogen, progesterone, and EGFR signaling in the normal rat mammary gland and in hormone-dependent rat mammary cancers. Horm Cancer. 2010;1(5):229-44.