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A SYSTEMATIC REVIEW ON PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ROLES OF ESTROGEN IN HUMANS

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ABSTRACT

Estrogens are physiologically active hormones although present in small amounts but play vital roles in the maintenance of body health. In humans, two types of oestrogen receptors (ERs) have been identified ER- α and ER- β . The secretion and regulation of estrogen is controlled by hypothalamus via stimulation of anterior pituitary to secrete FSH and LH. Estrogen helps in regulation of various pharmacological activities in different body organs like CNS, cardiovascular system, gastrointestinal tract, immune system, lungs, female and male reproductive system and skeletal muscles. Estrogen also regulates various physiological processes like maintenance of cholesterol, coagulation, fluid balance, melanin, and secondary sexual characteristics. Both high and low level of the hormones can affect several physiological parameters. This review focuses on the various physiological as well as pathological roles of estrogen in humans.

Keywords: Estrogen, Estrogen receptors, Secretion and regulation, Pharmacological activities, Diseases

1. INTRODUCTION:

Estrogens are physiologically active hormones that are generated from cholesterol and produced in humans and animals by the adrenal cortex, testes, ovary, and placenta. Plants have also been shown to have estrogenic chemicals [1]. Some

tissues may synthesize estrogen on demand from the main circulating adrenal hormones dehydroepiandrosterone (DHEA), and androstenediol (A5), and testosterone (T) via aromatase [2]. Natural estrogens, in the conjugated form, can be excreted by women at quantities of 7.0, 2.4, and 4.4g/day of estrone, 17 β -estradiol, and estriol, respectively [3]. The most common estrogen found in nature are estrogen (E1), 17 β -estradiol (E2b), 17 α -estradiol (E2a), estriol (E3), 17 α -ethinylestradiol (EE2) [4]. Estrone (E1), Estradiol (E2), estriol (E3) are the three main estrogens found in animals [5]. In humans, two types of estrogen receptors (ERs) have been identified ER- α and ER- β [6]. Estrogen receptors ER α and ER β , which form homo- or heterodimers in the nucleus and influence expression of ER target genes by directly binding an estrogen response element (ERE) or indirectly regulating other transcription factors through protein-protein interactions [7]. ERs are found all over the body and have variety of roles in the cardiovascular, musculoskeletal, immune, and central nervous systems [8]. ER α is located in the CNS, cardiovascular system, lung, male reproductive organs, prostate, colon, kidney, ovary, and immune system, while ER β is found in the ovary, CNS, cardiovascular system, lung, white adipose tissue, and liver [9]. Metabolism of

Estrogen in peripheral tissue differs from that in the liver [10].

2. SECRETION AND REGULATION OF ESTROGEN

Hypothalamus secretes the Gonadotropin Releasing Hormone (GnRH) that stimulate the anterior pituitary which release the gonadotropins (LH and FSH). Estrogen is sex hormone which is produced by ovaries and its secretion is induced by FSH. Estrogen abolish increased level of GnRH and produce negative feedback mechanism (Figure 1).

3. ESTROGEN MECHANISM

Estrogen produces the response through two mechanisms: genomic and nongenomic action. In genomic mechanism estrogen ligand bind to estrogen receptors (ER- α or ER- β) and the dimer interact with DNA, dimer DNA complex further interact with target genes (Estrogen response element and activator protein-1) in cell nucleus as hetero or homodimer causing transcription activation in cytoplasm that results in cellular activity via protein synthesis. Nongenomic action appears when estrogen interacts with ERs or G protein couple receptor (GPCR30), at plasma membrane leading to secondary messenger system activation via MAPK or cAMP (Mitogen-activated protein kinase or cyclic adenosine 3', 5'- monophosphate) pathways. That also acts on transcription activation and show other response (Figure 2).

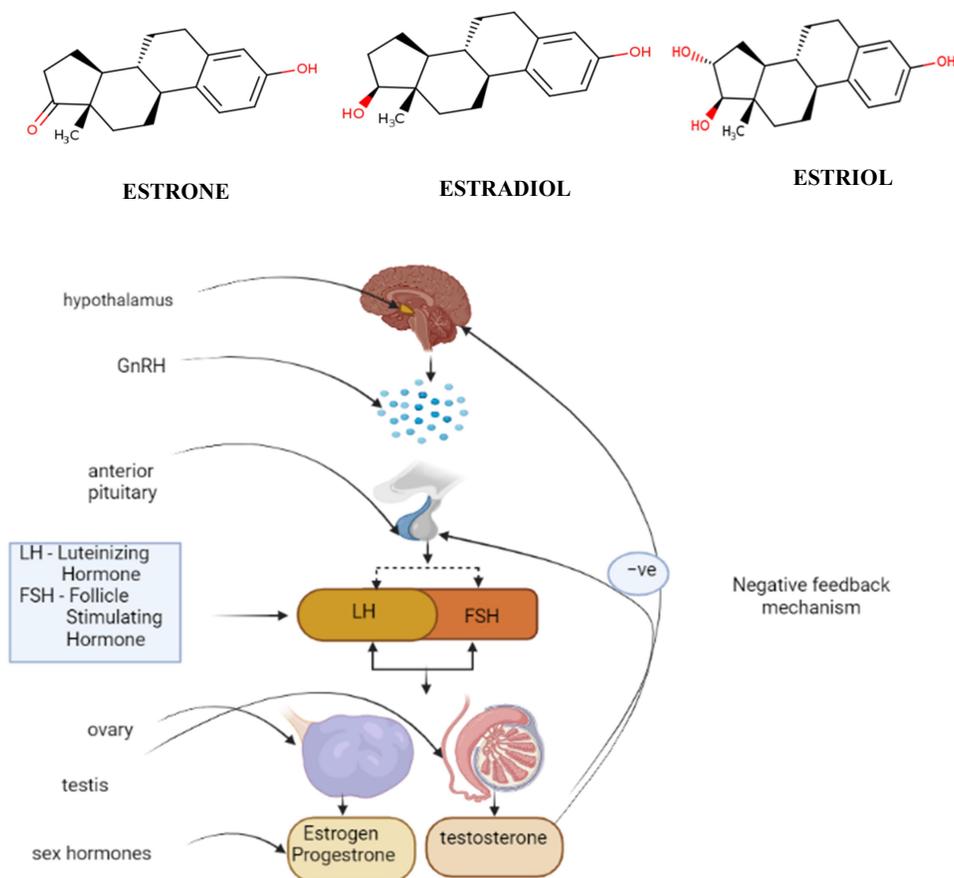


Figure 1: Secretion and regulation of estrogen

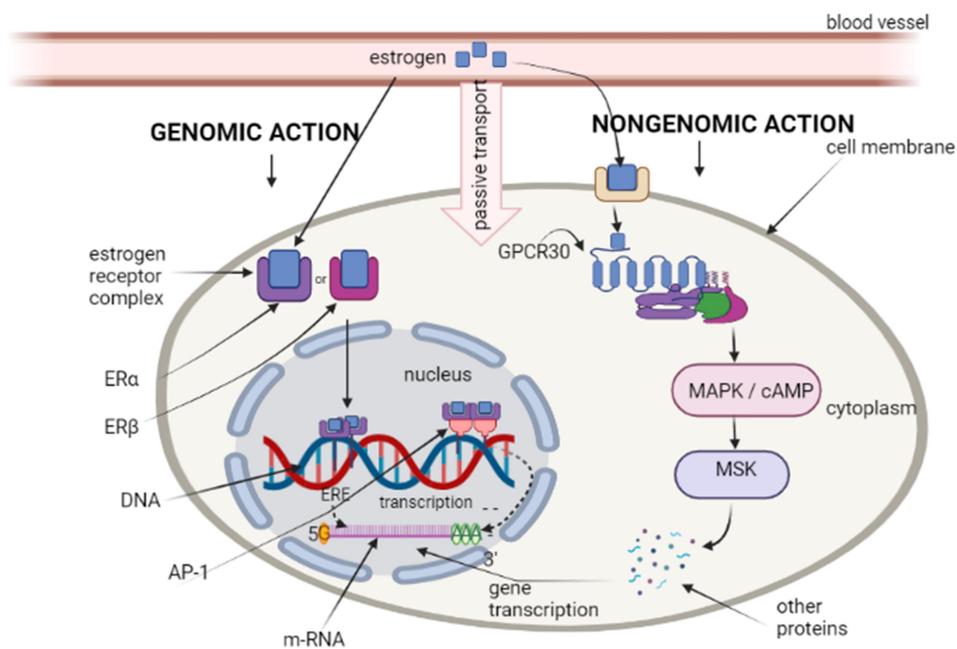


Figure 2: Genomic and nongenomic mechanism of estrogen

4. VARIOUS REPORTED PHARMACOLOGICAL ACTION OF ESTROGEN ON DIFFERENT BODY SYSTEMS

Estrogen regulates various pharmacological activities in CNS, cardiovascular system,

gastrointestinal tract, immune system, lungs, melanin, female and male reproductive system and skeletal muscles. Cholesterol, coagulation, fluid balance and secondary sexual characteristics.

Table 1: Various pharmacological action of estrogen on different body systems

Organ System	Physiological process	Estrogen	Activity studied	Reference
Central nervous system		17 β estradiol(E2)	Neuroprotective, Antioxidant.	Chakrabarti M <i>et al.</i> (2014) ¹¹
		Estradiol (E2)	Anti-inflammatory.	Kawasaki T <i>et al.</i> (2012) ¹²
		ER β	Diminish BBB disruption.	Shin JA <i>et al.</i> (2013) ¹³
Cardiovascular system		E2	Forbid Atherosclerosis, Increased relaxation and nitric oxide production.	Knowlton AA <i>et al.</i> (2012) ¹⁴
		E2	Cardioprotective effect via inflect the action of ROS.	Lagranha CJ <i>et al.</i> (2018) ¹⁵
		ER α	Hypertension via inflect the renin-angiotensin aldosterone system	Prabhushankar R <i>et al.</i> (2014) ¹⁶
Cholesterols		E2	Decrease low density lipoprotein fat deposition via GPER (G-1)	Ghaffari S <i>et al.</i> (2018) ¹⁷
		ER α	Stimulate high density lipoprotein, Cholesterol uptake in liver.	Zhu L <i>et al.</i> (2018) ¹⁸
Coagulation		E2	Reduce clotting time.	Lemini C <i>et al.</i> (2013) ¹⁹
		E2	Raise the level of factor VII, VIII, X, XII fibrinogen. Platelets adhesiveness increased.	Del Principe D <i>et al.</i> (2015) ²⁰
Fluid balance		ER β	Cortisol level increased, Sex hormone-binding globulin (SHBG) expression enhanced	Gebhart VM <i>et al.</i> (2014) ²¹
Gastrointestinal tract		E2	Sustain mucosal barrier function (like epithelial and physiological function).	Nie X <i>et al.</i> (2018) ²²
Immune system		E2	Estrogen has anti- inflammatory properties which provide mobilization of neutrophils.	Nadkarni S <i>et al.</i> (2013) ²³
Lungs		E2	Estrogen stimulate lung function by maintain alveoli in rodents.	Ticconi C <i>et al.</i> (2013) ²⁴
Melanin		E2	Estrogen enhance pheomelanin content in female hair and decrease pheomelanin and eumelanin in male hair.	Hirobe T <i>et al.</i> (2010) ²⁵
Female Reproductive system Fallopian tubes		ER α	In fallopian tube Estrogen stimulate the embryos and help in maturation of eggs.	Cunha GR <i>et al.</i> (2018) ²⁶
Uterus		ER α	Embellish and maintain the mucous membrane.	Cunha GR <i>et al.</i> (2018) ²⁶
Vagina		ER β	Estrogens support the vaginal wall thickness and contribute in lubrication.	Li S <i>et al.</i> (2018) ²⁷
Male reproductive system Corpus cavernous		E2	High absorbance over neurovascular bundles	Kataoka T <i>et al.</i> (2013) ²⁸
Testis		E2	Modulation of spermatogenesis.	Hess RA (2003) ²⁹
		E2	ERs provide germ cell progress and spermatogenesis progression.	Verderame M <i>et al.</i> (2018) ³⁰
Secondary sexual characteristics		ER α	Estrogen receptor alpha develop the secondary sexual characteristic in females and for feminine body.	Bulun SE(2014 feb) Fuentes N (2019 jan) ³¹
		E2	Provide allocation of adipose tissues in the breasts.	Gerard C(2018 may) ³²
Skeletal muscles		ER α	Estrogen protect cortical bone mass via help of ER α	Manolagas SC <i>et al.</i> (2013) ³³
		ER	Estrogen help in increase bone resorption. Provide bone formation at the cellular level.	Khosla S <i>et al.</i> (2012) ³⁴

5. PATHOPHYSIOLOGICAL ROLE OF ESTROGEN

Estrogen affects the body either because of the high level or low level of it. The high level of estrogen may cause many type of cancers and thyroid dysfunction and the deficiency of estrogen leads to obesity, osteoporosis or osteopenia and cardiovascular disease.

5.1 AFFECTS OF HIGH LEVEL OF ESTROGENS

5.1.1 Estrogen and breast cancer:

Estrogen promotes breast cell growth and milk ducts. The long term exposure of estrogen without intermission leads to an increased risk of breast cancer [35]. The women with high concentration of estradiol, estrone, androstendione and estrone- sulfate in postmenopausal state are at breast cancer risk [36]. ER β - selective agonist diarylpropionitrile (DPN) restrain cell growth and causes apoptosis whereas E2 or ER α agonist propyl-pyrozol-triol (PPT) stimulate proliferation in mammary call lines [37]. The genotoxic metabolites of estradiol can damage DNA along with formation of estradiol-adenine-guanine adducts and generation of oxygen free radicals. Estrogen receptor mediated proliferation of breast cells and continuous formation of estradiol metabolites can result in neoplastic transformation over subsequent period of time [38]. Estrogen-induced ROS have a significant role in

breast cancer cell transformation, cell cycle, migration, and invasion by increasing genomic instability and transducing signal via redox sensitive transcription factors [39].

5.1.2 Estrogen and uterus cancer:

Progesterone inhibits estrogen – induced endometrial growth while simultaneously converting the endometrium to affected state during the luteal phase. When it comes to blastocyst implantation estrogen, which stimulate growth, and progesterones, which restrict growth, are commonly used together. Estrogen is a hormone that is present in animals and is responsible for the development of cancer [40]. E2 stimulate cathepsin D production in a kind of serious carcinoma ovarian cancer cell, much as it does in ER-positive breast cancer cell. Estrogen may influence tumour growth by boosting cell proliferation, as well as encouraging invasion and cytokinesis, via influencing the expression of these genes [41]. Endometrioid endometrial cancers with estrogen receptor alpha negative are more likely to be diagnosed with a higher grade and stage of cancer [42]. ER β has a comparable binding affinity for estrogen as ER α . It has been claimed that ER β has a role in myometrial invasion progression, surprisingly and unexpectedly [43].

5.1.3 Estrogen in thyroid dysfunction:

Estrogen is a significant growth agent for thyroid cells, both benign and cancerous. It

promotes development through both genomic and non-genomic route, which is regulated by a membrane-bound oestrogen receptor, a chromosomal rearrangement of the tyrosine receptor kinase TRKA that may activate these pathways in papillary thyroid carcinomas⁴³. ER subtype expression with Ki-67, mutant P53, VEGF expression, and ETE indicate that estrogen activated ER α may have stimulatory effect on thyroid cancer progress and expansion whereas ER β has some inhibitory effects [44].

5.2 affects of low level of estrogen

5.2.1 estrogen and obesity: estrogen deficiency has the potential to affect adiposity via mrna expression in 3t3 adipocytes [13] and leptin secretion in omental adipose tissue and have been found to be increased by 17 β -estradiol [45]. low level of estrogen affects adiposity primarily in abdominal fat depots instead of subcutaneous fat depots [46].

5.2.2 estrogen and osteoporosis or osteopenia: deficiency of estrogen may exacerbate osteocyte-mediated bone formation activation resulting in decreasing bone mass and anatomy [47]. estrogen loss result in immunological dysregulation, as evidenced by a skewed distribution of t-helper cell subset and increased responsiveness of t helper-17 (th17) cells [48]. insufficiency of estrogen enhance osteoclast formation by increase tnf and rankl level as well as quantity of osteoclast

precursor and it contribute in bone mass loss [49]. the majority of estrogens affect in bone appear to be mediated by er α [50]

5.2.3 estrogen and cardiovascular diseases: deficiency of estrogen cause blood vessels to become thicken and less permeable and this can lead to hypertension, triggering damage to blood vessels and elevating the risk of cardiac arrest [51] low estrogen level can increase ldl level and decrease hdl level and cholesterol in arteries that cause ischemic stroke [52].

6. CONCLUSION:

In present review the various physiological and pathophysiological roles of estrogen, an insight into estrogen receptors, secretion, regulation, mechanism, pharmacological activities and various affects of rise and fall in levels of estrogen leading to various diseases has been presented. The high level of estrogen can lead to breast cancer, uterus cancer and thyroid dysfunction and the deficiency of estrogen can lead to obesity, osteoporosis or osteopenia and cardiovascular disease. More studies are still needed to understand the estrogenic role in various disease and use of estrogen replacement therapies in treatment of this hormone related disorders.

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