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REVIEW ARTICLE

Endocrine, Reproductive, Neurophysiologic and Extraneous Activities of Estrogen in Vertebrates

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SUMMARY

Estrogens are reproductive hormones synthesized in the gonads of both male and female vertebrates. This review is geared towards uncovering some endocrine, reproductive, neurophysiologic and extraneous activities of estrogen in vertebrates. The three most common naturally occurring estrogens are: Estrone (E1), estradiol (E2), and estriol (E3). In primates, estradiol is the most potent and predominant estrogen during reproductive years. Estrogens are synthesized primarily in the female ovaries and in small quantities in the male testes and the adrenal glands, brain, and fat of both sexes. Estrogens are steroid hormones. The adipose tissues are considered to be the major source of circulating estrogen after the gonads in both men and women. In essence, the presence of aromatase expression in a local tissue confirms extra-gonadal estrogen synthesis. In reproduction, estrogen promote secondary sexual characteristics in females and regulates maturation of sperm (spermiogenesis) in males. Neurophysiologically, estrogen promote glutamate activity in the central nervous system, facilitates dopaminergic neurotransmission but blocks gammaaminobutyric acid. Extraneously, estrogen decrease serum cholesterol and osteoporosis especially in menopausal females. However, acute estrogen drop postpartum leads to depressed mood experienced by most post parturient females. In this review, it is observed that, while serum estrogen decreases with age in females, in male it increases with age due to the extraneous synthesis of estrogen especially in the adipose tissue.

Keywords: Estrogen, Female, Aromatase, Male, adipose tissue

INTRODUCTION

Estrogens are the key hormones regulating the development and function of reproductive organs in all vertebrates. Estrogen is a generic term for estrus-producing compounds. Estrogen is produced by the ovaries and in smaller quantities, by the adrenal cortex, testes, and feto-placental unit (Azcoitia et al., 2011: Haraguchi et al., 2012).

Most animals depend on the versatile estrogens to influence growth, development, behavior, regulate reproductive cycles; and affect many other body systems (Juraska et al., 2013).

Understanding non-gonadal sites of estrogen synthesis and function is crucial and will lead to therapeutic interventions targeting estrogen signaling in disease prevention and treatment (Barakat et al., 2016).

Seventeen-beta (17-β) estradiol is the most abundant and potent natural estrogen in all vertebrates. The adipose tissues are considered to be the major source of circulating estrogen after the gonads in both men and women, and the contribution made by the adipose tissues to the total circulating estrogens increases with advancing age (Osterlund et al., 2000: Dieudonne et al., 2004).

Estrogens are synthesized in all vertebrates as well as some insects. Three major naturally occurring forms of estrogen in women are estrone (E1), estradiol (E2), and estriol (E3). Another type of estrogen called estetrol (E4) is produced only during pregnancy. Quantitatively, estrogens circulate at lower levels than androgens in both men and women. While estrogen levels are significantly lower in males compared to females, estrogens nevertheless also have important physiological roles in males (Marino et al., 2006).

Estrogens, in females, are produced primarily by the ovaries in non-pregnant animal species and the placenta during pregnancy. Follicle-stimulating hormone (FSH) stimulates the ovarian production of estrogens by the granulose cells of the ovarian follicles and corpora lutea. Some estrogens are also produced in smaller quantities by other tissues such as the liver, adrenal glands and the breasts. In females, FSH stimulates granulosa cells in the ovarian follicles to synthesize aromatase which converts androgens produced by the thecal cells to estradiol (Karligiotou et al., 2011: Anushka and Kumar, 2017).

In primates, estradiol is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in terms of estrogenic activity. During menopause, estrone is the predominant circulating estrogen and during pregnancy estriol is the predominant circulating estrogen. Estriol is the most abundant of the three estrogens, but it is also the weakest but estradiol is the strongest with a potency of approximately 80 times that of estriol. Thus, estradiol is the most important estrogen in non-pregnant females. All of the different forms of estrogen are synthesized from androgens, specifically testosterone and androstenedione by the enzyme aromatase (Hampson and Morley, 2013).

Some estrogen metabolites, such as the catechol estrogens, 2-hydroxyestradiol, 2-hydroxyestrone, 4-hydroxyestradiol and 4-hydroxyestrone as well as 16α-hydroxyestrone are also estrogens with varying degrees of activity. The biological importance of these minor estrogens is not entirely clear (Cornil et al., 2006).

Estrogen in men

Males secrete estrogens, too. About 70% of the estradiol in the plasma of adult men are formed by aromatization of circulating testosterone and androstenedione. The plasma estradiol level in men is approximately 2ng/dl which is equivalent to 70pmol/L and the total production rate is 0.05mg/d (0.18μmol/d). Estrogen influence fertility through the prostate, testis, and other sex tissues. Estrogen can be recovered from a man's urine. The concentration of estrogen in the fluid found in seminiferous tubules is quite high and plays a role in spermatogenesis (Cherrier et al., 2005i). Unlike women, there is a moderate increase in estrogen production in men with advancing years (Ganong, 1993: Hess et al., 1997).

Also, in male reproduction, the Sertoli cells possesses aromatase which converts testosterone to estrogen. Very large quantities of estrogen is found in stallions (male horse). Therefore, fertility of a horse can be assessed by measuring

circulating concentrations of either testosterone or estrogen (Bracket, 2004).

Estrogenic functions

Generally, estrogens have wide-range of effects throughout life and in both sexes. Most vertebrates depend on this hormones to control and regulate female development, reproduction, and sex characteristics. Their signals also affect blood fat levels (Bracht et al., 2019), enzyme production (Strehlow et al., 2003), water and salt balance (Santollo and Daniels, 2015), bone density and strength (Camacho, 2017), skin and blood vessel elasticity, heart muscle, and brain functions such as memory and sexual and maternal behavior (O'Lone et al., 2004).

Like all steroid hormones, the receptor for estrogens are domiciled in the cell nucleus.

Estrogens readily diffuse across the cell membrane. Once inside the cell, they bind to and activate estrogen receptors (ERs) which in turn modulate the expression of many genes. Additionally, estrogens bind to and activate rapid-signaling membrane estrogen receptors (mERs) such as Guanoline-protein (G-protein) coupled estrogen receptor (GPER) which binds to 17-beta-estradiol (E2) with high affinity, leading to rapid and transient activation of numerous intracellular signaling pathways. G-protein coupled estrogen receptor 1 is also known as G-protein-coupled receptor 30 (GPER 30). GPER is ubiquitously expressed throughout the body, including the heart, brain, pancreas, skeletal muscle, kidney, vessels, and reproductive organs where it stimulates cyclic adenosine monophosphate (AMP) production, calcium mobilization and subsequent transactivation of the epidermal growth factor receptor (EGFR). Disease processes also regulate the expression of this receptor, as GPER is significantly up-regulated in lung cancer and endometriosis (Shang et al 2000: Prossnitz and Hathaway, 2015: Zimmerman et al., 2016: Yaser et al., 2017: Fuentes and Silveyra, 2019).

Endocrine activity of estrogen

Estrogens are steroid hormones. All steroid hormones are derived from cholesterol. The synthesis of estrogen is a one way chemical reaction. It is non-reversible (Cue et al., 2013). The precursor for estrogen and other steroid hormones is cholesterol. The synthesis of estrogen follows two pathways as shown below:

(1). Cholesterol, catalyzed by cholesterol desmolase give rise to Pregnenolone. Enzymatic catalysis of Pregnenolone by 17α-hydroxylase gives rise to 17-hydroxy-pregnenolone which also is catalyzed by 17, 20 lyase to give rise to Dehydroepiandrosterone which directly gives rise to Androstenedione in a non-enzymatic reaction. Androstenedione through a reversible non enzymatic reaction gives rise to Testosterone. Testosterone undergoes aromatization to yield estrogen in a non-reversible reaction (Sik Yoo and Napoli, 2019: Conklin and Knezevic, 2020).

(2). Cholesterol catalyzed by cholesterol desmolase give rise to Pregnenolone. Enzymatic catalysis of Pregnenolone by 3-β hydroxyl-steroid yields Progesterone. Progesterone catalyzed by 17-α hydroxylase yields 17-hydroxy-Progesterone which is catalyzed by 17, 20 lyase just as in step 1to yield Androstenedione which undergoes a reversible reaction to yield Testosterone. Testosterone through aromatization yields Estradiol in a non-reversible reaction (Santem and Simpson, 2019).

The half-life of estrogens is specie specific; about 1-3 hours. Like all steroid hormones, the receptor for estrogens are domiciled in the cell nucleus. The presence of aromatase expression in a local tissue confirms extra-gonadal estrogen synthesis (Shay et al., 2018). In the adipose tissues, estradiol stimulates the production of high density lipoprotein (HDL) and triglycerides and decreases low density lipoprotein (LDL) production (Ma et al., 1995).

Furthermore, aromatase expression in bone has been demonstrated in osteoblasts, chondrocytes, and fibroblasts where they convert circulating

androgens into estrogens. In the bone of pre-pubertal animals, the locally synthesized estradiol stimulates epiphyseal maturation during the growth phase. However, in both males and females, the massive pubertal increase of estradiol leads to increased apoptosis of chondrocytes in the epiphyseal plate, causing chondrocyte depletion leading to ossification and growth slow-down especially in the females (Song et al., 2019).

In females, synthesis of estrogens starts in theca interna cells in the ovary, by the synthesis of androstenedione from cholesterol. Androstenedione is a substance of weak androgenic activity which serves predominantly as a precursor for more potent androgens such as testosterone as well as estrogen. This compound crosses the basal membrane into the surrounding granulosa cells, where it is converted either immediately into estrone, or into testosterone and then estradiol in an additional step. The conversion of androstenedione to testosterone is catalyzed by 17β-hydroxysteroid dehydrogenase (17β-HSD), whereas the conversion of androstenedione and testosterone into estrone and estradiol, respectively is catalyzed by aromatase. These enzymes are both expressed in granulosa cells. In contrast, granulosa cells lack 17α-hydroxylase and 17, 20-lyase, whereas theca cells express these enzymes and 17β-HSD but lack aromatase. Hence, both granulosa and theca cells are essential for the production of estrogen in the ovaries (Nicol et al., 2009: Hu et al., 2010).

Estrogen in reproduction

During embryonic life, estrogens stimulate adrenal cortex growth during development by promoting cell proliferation and enhancing steroidogenic activity by increasing the steroidogenic acute regulatory protein (StAR) and steroidogenic factor-1 (SF-1) expression in the adrenal gland. In the fetal adrenal gland, estradiol and Adrenocorticotropic hormones (ACTH) form a positive regulatory loop in which estradiol increases ACTH secretion from adrenal cortex while ACTH increase estradiol in the ovary (Kaludjerovic and Ward, 2012).

In the females at puberty, increased estradiol synthesis as a primer for puberty, regulates growth hormone and determines final height, by shutting off bone growth at the ephiphysis of arms and legs in humans and fore and hind limbs in quadrupeds. Also, estrogens are responsible for the development of other female secondary sexual characteristics during puberty which include: widening of the hips and female fat distribution. At the other hand, androgens (testosterone and androstenedione) are responsible for pubic and body hair growth as well as acne and axillary odor observed in pubertal females (Blackburn, 2014).

Furthermore, in females, the ovaries are the prime location for estrogen production. The estrogens are released from ovarian follicles and the corpus luteum following the release of an egg from the follicle, and the placenta. Follicle-stimulating hormone (FSH) causes the release of estrogen and, conversely, estrogen inhibits the release of FSH in a negative feedback loop (Strauss and Barbieri, 2013).

Estrogens, in adult females, are produced primarily by the ovaries prior pregnancy and the placenta during pregnancy. Follicle-stimulating hormone (FSH) stimulates the ovarian production of estrogens by the granulose cells of the ovarian follicles and corpora lutea. Some estrogens are also produced in smaller quantities by other tissues such as the liver, adrenal glands and the breasts. (Simpson, 2003).

While estrogens are present in both male and female, they are usually present at significantly higher levels in females of reproductive age. They promote the development of female secondary sexual characteristics such as breast development, thickening of the endometrium, stimulates the growth of the vagina to its adult size and the thickening of the vaginal wall. It also plays a part in vaginal lubrication, stimulates the growth of the ovarian follicle, regulate the flow and thickness of cervical mucus secretion to

enhance sperm transport and stimulates the muscles in the uterus to develop and contract during parturition (Baker, 2013).

During pregnancy, estrogen is made and released by the corpus luteum of the ovaries and the fetal-placental unit. The fetal-placental unit is where the fetal liver and adrenal glands produce an estrogen called estriol. Generally estrogen levels increase throughout pregnancy and have the following effects: Supports, regulates, and stimulates the production of pregnancy hormone (progesterone), functions in the development of fetal organs such as the liver, kidneys, and lungs, facilitates placental growth and function and Prepares the mother for lactation (breast-feeding) by enhancing maternal breast tissue growth (Findlay et al 2016).

For commencement of parturition, Estrogen and oxytocin cause the release of prostaglandins in the uterus. In turn estrogen, oxytocin and prostaglandins stimulate the maturation of the cervix leading to successive dilation during parturition by relaxin. After expulsion of the placenta during parturition, the blood levels of progesterone and estrogen fall which allows the mother to produce colostrum, a high-density milk that is rich in proteins, minerals, and vitamins (specifically Vitamin A and K) and immunoglobulin for the neonate (Kota et al., 2013).

In males, estrogen exert pleiotropic effects by acting on several tissues and organs including the reproductive system (Rochira et al., 2016). Estrogen regulates certain functions of the reproductive system important to the maturation of sperm (spermiogenesis) and may be necessary for a healthy libido (cacciola et al., 2013). The Sertoli cells convert testosterone to estrogens. Estrogens move into the adluminal and basal compartments of seminiferous tubules and can move outwards to enrich estrogenic content in the blood stream (Lombardi et al., 2001: Brackett, 2004).

Estrogen affects sexual behavior

Apart from humans, female mammals have no mating desire except during estrus when there is estrogen surge. Estrogen promotes sexual receptivity of vertebrates in estrus and induces lordosis in some species; a behavior which is regulated by the ventromedial nucleus of the hypothalamus. Estrogen also regulates ovulation (Kow and Pfaff, 1998: Christensen et al., 2011).

In the male, sex drive thrives with increased androgen levels only in the presence of estrogen. Without estrogen, free testosterone level actually decreases sexual desire instead of increasing sex drive (Warnock et al., 2005).

Estrogens secreted from the ovaries fluctuate during the reproductive cycle, which may occur episodically in frogs mating in response to rainfall (Wilczynski and Lynch, 2011), bi-weekly in many marine animals (Bondesson et al., 2015), monthly in humans, semi-annually in cattle (Northrop, 2019), or even bi-annually in elephants (Kangwanakadzo, 1996). Estrogen levels rise in response to internal or external cues which include: temperature, light cycle or presence of potential mates (Heiman et al., 2011).

Neurophysiologic activity of estrogen

Estrogen has multiple effects on the brain (Zarate et al., 2017), including priming the body for sexual reproduction. In the brain estrogen functions in maintenance of body temperature. Estrogen may delay memory loss (Henderson, 2009), regulates parts of hypothalamus and limbic system which prepare the body for sexual and reproductive activity, increases serotonin and the number of serotonin receptors in the brain, modifies production and the effect of endorphins in the brain, protects nerves from damage and possibly stimulates nerve growth (Rettberg et al., 2014).

High levels of estrogen receptors are expressed during brain development in both male and female. In fact 17β-estradiol plays critical organizational role during early brain development and has been shown to be pivotal in

the sexually dimorphic development and regulation of the neural circuitry underlying sex-typical and socio-aggressive behaviors in males and females (Denley et al., 2018). During this period, sex hormones determine apoptosis, neuronal migration, neurogenesis, axonal guidance, and synaptogenesis. Estradiol induces sexual differentiation in the developing brain. Aromatase mRNA expression in the hypothalamus of males peaks before and after birth, inducing sexual differentiation of the brain. In the brains of both males and females, estradiol provides a neuroprotective effect. It prevents neurodegeneration in brain tissues (Azcoitia et al., 2003).

Estradiol regulates neuronal metabolism by modulating the expression of metabolic enzymes such as GLUT (glucose-transporter), glycolytic enzyme hexokinase, pyruvate dehydrogenase (PDH), aconitase (an enzyme involved in tricarboxylic acid cycle), and adenosine triphosphste(ATP) synthase (Mela et al., 2016).

Effect of estrogen on neurotransmitters

The tropic effects of ovarian hormones emerge early in brain development and remain throughout adolescence and adulthood. Many of these actions occur in brain regions involved in learning and memory (the cerebrum), emotion (hypothalamus and limbic system), motivation (hypothalamus and limbic system), motor control (medulla oblongata and midbrain), and cognition (limbic system). Furthermore, several lines of evidence support a main impact of ovarian hormone (estrogen and progesterone) on brain development and plasticity. Specific structural effects of estrogen and progesterone include neurite outgrowth and synaptogenesis, dendritic branching and myelination (Denley et al., 2018).

Both estrogen and progesterone act through classical genomic receptors as well as non-classical membrane-associated receptors. The classical estrogen receptors (ERα/β) and progesterone receptors ($PR_{A/B}$) are highly expressed in brain areas involved in emotion and cognition, such as hippocampus and amygdala (Lymer et al., 2018). Ovarian hormones can act on multiple receptor types, such as voltage-gated ion channels, including Gamma-amino butyric acid A ($GABA_A$) N-methyl-D-aspartate (NMDA), serotonin and dopamine receptors (Li and Tsien, 2009). While these genomic actions of sex hormones require a comparably long time (from minutes to hours) and are limited by the rate of protein biosynthesis, non-genomic modulation of the membrane receptors is mostly faster and requires only milliseconds to seconds (Hara et al., 2015).

Both estrogen and progesterone exert acute effects on synaptic physiology through the activation of multiple intracellular signaling pathways which includes the MAPK/ERK and the Akt pathway which are both part to a non-genomic signaling cascade linked to the promotion of cell survival. MAPK/ERK is a chain of proteins in the cell which communicates a signal from a receptor on the cell surface to the DNA in the nucleus. The pathway includes many proteins such as Mitogen activated protein kinase (MAPK) originally called Extracellular signal-regulated kinase (ERK) which communicates through phosphorylation (Lavoie et al., 2020). Also Akt is a serine/threonine kinase previously known as protein kinase B (PKB), consisting of three isoforms (Akt1, Akt2 and Akt3), with a crucial role in major cellular functions including cell size, cell cycle progression, regulation of glucose metabolism, genome stability, transcription, protein synthesis and neovascularization (Nitulescu et al., 2018). A distinct progesterone-binding protein different from the classical PR was identified as a membrane protein, known as 7TMPR: a G-protein coupled progesterone receptor (Brinton et al., 2008) which mediates non-genomic actions through second-messenger cascades. However, genomic and non-genomic actions of hormones may also be coupled, so the distinctions are not as clear-cut as was first thought (Singh, 2001).

Estrogens also exhibit profound effect on neurotropins such as brain-derived neurotropic

factor (BDNF). BDNF has been shown to play a key role in neuronal survival, in promoting neuronal regeneration following injury and regulating neurotransmitter system (Kwakowsky, et al., 2016). Estrogen treatment seems to increase BDNF expression in several brain regions including hippocampus, amygdala and cortex. Estrogen has also been shown to decrease the risk for neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (Handa et al., 2012).

Although estrogen and progesterone target multiple regions in the brain, one brain region that has been the focus of many studies investigating potential neurotropic effects of these hormones is the hippocampus, a brain region associated with various memory functions. Both, acute estrogen and progesterone treatment have been shown to increase synapse density and spine formation in hippocampal structures in rodents respectively (Sheppard et al., 2019). However, the generative effects of progesterone seem to disappear after chronic treatment. Furthermore, progesterone has also been shown to down-regulate estrogen-induced synapses when added to estrogen-administration chronically (Karpinski et al. 2017). Thus, the duration and combination of ovarian hormone supplementation seems to be essential for its neuroplastic effects on brain structures, such as the hippocampus. Therefore, the overall modulatory effect of ovarian hormones is more complex than simple mechanistic processes of up- and down-regulation of expression patterns in isolated brain regions (Yague et al., 2008).

In humans, evidence for hormone-dependent modulatory effects on brain structure stems from hormonal replacement therapy (HRT) studies. The importance of ovarian hormones has led to its use as HRT, primarily to treat menopausal and postmenopausal symptoms such as hot flashes and night sweat. However, structural and functional changes associated with HRT regimens have sparked a heightened interest in ovarian hormone effects in the human body (Labhart, 2012).

Beyond structural changes mediated by HRT, estrogen supplementation is also known to have prominent effects on mood and cognitive functioning in domains such as working memory and executive control (Uban et al., 2012).

Estrogen and glutamate interaction

Glutamate acts as the main excitatory neurotransmitter in the Central Nervous System (CNS) and is a proximal regulator of cognitive domains such as learning and memory. The integration of glutamatergic transmission is fundamental for normal cognitive functioning and mental health. The cortical glutamate projections are organized in descending and ascending pathways that project throughout much of the telencephalon (the lobes of the cerebral cortex). The impact of ovarian hormones (estrogen and progesterone) on the glutamatergic system has been studied extensively, especially in cell cultures and animal models. Both stimulatory and inhibitory effects of ovarian hormones have been reported (Bethea and Reddy, 2012).

In rodents, several mechanisms through which ovarian hormones may influence glutamatergic neurotransmission have been studied; progesterone has been shown to suppress the excitatory glutamate response in a dose-dependent fashion while estrogen exhibits facilitating effects on glutamate transmission (Farkas et al., 2018). A physiological dose of progesterone in ovariectomized rats has been reported to reduce glutamate-response by 87% through attenuation of non-NMDA receptors (AMPA- Kainate). N-methyl-D-aspartate (NMDA) receptors are glutamate receptors and ion channel protein found in nerve cells while AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) is a sub-type of glutamate receptor responsible for the majority of fast-excitatory transmission in the central nervous system. The kainite receptor which is an ionotropic receptor that respond to the

neurotransmitter; glutamate is similar and the term AMPA-kainate is sometimes used to describe them collectively (Lerma and Marques, 2013). The magnitude of the attenuation of the non-NMDA receptors seems directly proportional to the progesterone dose. Whereas progesterone mainly impacts non-NMDA receptors, the mechanisms underlying estrogen effects on cognition are related to NMDA glutamate receptors. Estrogen has been shown to promote an increase in NMDA receptor subunit expression binding sites and neuronal sensitivity to synaptic input mediated by NMDA glutamate receptors. The blockade of NMDA receptors with antagonists attenuates the effects of estrogen on neuronal correlation of memory, such as long-term potentiation (Abdallah et al 2014).

A plethora of animal studies have shown that estrogen with and without progesterone increases dendritic spines through the up-regulation of AMPA and NMDA receptors in the hippocampus and prefrontal cortex (PFC) but ovariectomy reduced synaptic markers in these regions (Zhou et al., 2005: Alexander et al., 2018).

Apart from cellular effects, recent studies report that the interaction between estrogen and glutamate can affect cognitive domains such as working memory and executive function under harmful conditions. Brain regions hypothesized to underlie these cognitive domains, for instance; the pre-frontal cortex (PFC) and hippocampus, seem largely dependent on normal estrogen signaling to counter insults such as stress. In a repeated stress paradigm, Wei et al., (2014) found a beneficial effect of endogenous estrogen on glutamate receptors in the PFC in female rats compared to male rats. Some authors propose that detrimental effects of repeated stress are present in females when estrogen signaling is blocked. Also, detrimental effects of stress are blocked in males when estrogen signaling is activated (Jacobs et al., 2015: Yuen et al., 2016).

Blocking estrogen synthesis enzyme aromatase with formestane in pre-frontal cortex (PFC) showed stress-induced glutamatergic deficits and memory impairment in female rats. This suggests that the female rodent PFC has an endogenous capacity to generate estrogen that provides protection against sub-chronic repeated stress. However, there is gender differences in response to stressors and they are modulated by hormonal status. However exogenous administration of estrogen seems to increase resilience to stress and preserve hippocampal functioning in rats (Cohen and Yehuda, 2011: Bredemann and McMahon, 2014).

Although animal studies assessing electrophysiological, biochemical and behavioral markers for sex hormonal impacts on the glutamatergic system provide useful insights on underlying mechanisms, extrapolation to humans is difficult. Some of the beneficial effects of estrogen on cognitive function have also been shown in humans. Pre-menopausal women who were treated with a gonadotropin releasing hormone analog which chemically suppressed ovarian function experienced significant deterioration of mood and worsening of performance in working memory tasks (Freeman et al., 2006: Grigorova and Sherwin, 2006: Soares, 2014).

A large number of studies with behavioral testing during hormonal transitions such as the menstrual cycle or post-menopause, point toward an estrogen-dependent improvement in memory but the neurochemical pathways underlying these changes remain to be identified. A useful approach to assess glutamate release *in vivo* in humans might be a pharmacological stimulation of the glutamatergic system with positron emission tomography (PET) using a glutamate-receptor radio ligand. In conjunction with MR-Imaging it could link glutamate release to brain activation during working memory tasks (Mcewen et al., 2012). Such methods may lead to a better understanding of the interaction between sex hormones and glutamatergic neurotransmission in humans (Holmseth et al., 2012: Li and Huang, 2014).

Estrogen and gamma-aminobutyric-acid interaction

Gamma-amino butyric acid (GABA) is the most abundant and widely distributed inhibitory neurotransmitter in the Central Nervous System (CNS). GABAergic neurotransmission through interneurons is known to modulate local neuronal circuits through activation of dopaminergic and serotonergic neurons. GABAergic interneurons can be differentiated into two types, each acting through its receptor-subtype. GABA receptors are highly distributed in cortical, hippocampal, thalamic, basal ganglia and cerebellar structures (Sieghart and Sperk, 2002: Zhou and Danbolt, 2013).

$GABA_A$ receptors mediate major inhibitory GABAergic actions in the central nervous system (CNS) and are putative sites for ovarian hormone effects. Estrogen modulates the dynamics of surface $GABA_A$ receptors hence efficacy of inhibition through a postsynaptic mechanism (Mukherjee et al., 2017). Whereas estrogen seems to suppress GABA inhibitory input, progesterone and its neuroactive metabolites (allopregnanolone and pregnanolone) seem to facilitate GABAergic transmission through their action at $GABA_A$ receptors. Allopregnanolone acts like a positive modulator and potentiates the inhibitory action of GABA by increasing channel openings of the GABA-gated chloride channels and augmenting other inhibitory neuronal responses to GABA. This facilitation of GABA-mediated Chloride ion current can result in inhibitory effects on neuronal function (Murphy et al., 1998a: Marshal, 2008).

Estrogen and dopamine interaction

Dopamine (DA) is a key neurotransmitter that is implicated in motor control, learning, motivation, reward, decision-making and working memory. Brain areas that show rich dopaminergic innervation include the striatum, substantia nigra and hypothalamus. Estrogen can impact dopaminergic neurotransmission through a multitude of mechanisms which include: synthesis, release, degradation and pre-and postsynaptic receptor transmissions (Quinlan et al., 2013). There is evidence for stimulating as well as inhibiting effects of estrogen on dopaminergic neurotransmission. The impact of estrogen on the DA-system depends on dose as well as time of testing, mode of administration, duration of exposure, and time after exposure. Estrogen has an overall facilitating effect on dopaminergic neurotransmission. Priming with estrogen can also influence the impact of progesterone on dopaminergic transmission (Barth et al., 2015).

Recent studies report on the interaction between estrogen and dopamine on cognitive domains, such as decision-making, fear extinction and memory. There seems to be an agreement that estradiol affects decision-making toward smaller, more accessible rewards and a low-estrogen state during fear extinction is detrimental for an optimal freezing suppression after extinction, which is mediated by DA1-receptor signaling and that memory is mediated by the interaction of estradiol and dopamine in the dorsal striatum. Thus, optimal signaling may depend on the levels of estrogen to best interact with dopamine levels in the median range for optimal striatal function and optimal performance during a task (Rey et al., 2014).

Several neuropsychiatric pathologies that display a substantial sexual dimorphism have been linked to abnormal dopaminergic function, such as schizophrenia, Parkinson's, or Alzheimer's disease. Thus, a better understanding of the interaction between estrogen and dopaminergic neurotransmission could help to improve pharmacological treatment regimens for these diseases and significantly impact women's mental health (Reeves et al., 2009).

Estrogen and serotonin interaction

The effect of estrogen on serotonin expression seems to depend on several factors such as: receptor subtype, brain area and duration of estrogen treatment. Chronic estrogen administration has been found to increase tryptophan hydroxylase (TPH) messenger

ribonucleic acid (mRNA). TPH is a serotonin synthesizing enzyme. These enzymes include: 5-hydroxytryptamine 2A (5-HT_{2A}) mRNA levels in brain areas relevant for the control of mood, mental state and cognition and 5-hydroxytryptamine transmission (5-HTT) mRNA (Wu et al., 2019). However, acute estrogen treatment leads to decrease in mRNA related to serotonergic neurotransmission. For instance, 5-HT1B auto-receptor mRNA in dorsal raphe and Mono amino oxidase A (MAO A) mRNA activity are decreased after estrogen treatment (Amidfar et al., 2016). Furthermore, acute estrogen administration decreases 5-HTT mRNA levels and 5-HT_{1A} mRNA levels and binding. The latter effect disappears after a more chronic treatment-regimen. Thus, assigning the effects of estrogen on serotonin to a homogenous functional class of stimulation or inhibition seems not to be feasible (Michopoulos et al 2011).

Extraneous activities of estrogen

Apart from reproduction and modulations in the brain, estrogen has been implicated in many other bodily function**:**

Effect of estrogen in cardiovascular system

Estrogen therapy in postmenopausal women decreases the serum levels of both total and low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol and triglycerides by influencing the expression of hepatic Apo protein genes. Two estrogen receptor (ER) subtypes, ERα and ERβ, have been identified and are expressed in the vasculature. However, estrogen supplementation in ovariectomized monkeys reduces the formation of plaques independent of changes in total plasma cholesterol or HDL levels. In contrast, protection against the development of atherosclerotic plaques by estrogen in intact female monkeys is associated with a concomitant decrease in plasma HDL (Meyer et al., 2014). Estrogen enhances endothelium-dependent vesorelaxation through increased release of nitric oxide (NO) (Akinshita and Yu, 2012). Estrogen inhibits calcium influx and stimulates calcium efflux in vascular smooth muscle cells leading to endothelium-independent vasodilation. Endothelial regeneration, inhibition of endothelial apoptosis and inhibition of vascular smooth muscle cell migration and proliferation may account for the inhibitory effects of estrogen on neointima formation (Krom et al., 2007). Analyses of knockout mice for ERα and ERβ have provided more information regarding the molecular mechanism of estrogen's action on the blood vessels. Recent progress in nuclear receptor research has also clarified the non-genomic action of estrogen on the vasculature such as the direct interaction of ERα with the regulatory subunit of phosphatidylinositol-3-OH kinase (Wu et al., 2005: Akishita and Lu, 2012: Reslan et al., 2013).

Effect of estrogen on bones

Estrogen has various actions that are related to bone development and bone maintenance. Aromatase expression in human bone has been demonstrated in osteoblasts, chondrocytes, and fibroblasts where they convert circulating androgens into estrogen (Gennari et al., 2004). In the bone of prepubertal animals, the locally synthesized estradiol stimulates epiphyseal maturation during the growth phase. However, in both males and females, the massive pubertal increase of estradiol leads to increased apoptosis of chondrocytes in the epiphyseal plate, causing chondrocyte depletion and hence, ossification and slow down of growth. In adults, estradiol increases bone formation and mineralization and reduces bone resorption, thus reducing the risk of osteoporosis (Zhong et al., 2011).

Effect of estrogen on appetite

There is a correlation between estradiol levels and appetite. Food intake is significantly decreased during the preovulatory period when estradiol levels are increasing. These actions are attributed to estradiol inhibiting appetite indirectly through cannabinoid receptors which are a class of cell membrane receptors in the

guanoline protein-coupled superfamily located throughout the body involved in appetite, pain-sensation, mood and memory (Mela et al., 2016). When estrogen receptors are blocked with estrogen receptor antagonist such as ICI182, 270, any action of estradiol on appetite is removed. Alternatively, appetite is influenced by the microbiome which are ecological communities of commensals, symbiotic and pathogenic microorganisms present in the gastrointestinal tract (GIT). Bacterial peptides signal hunger or satiation; which means that bacteria control the desire of an animal or humans to eat. Interestingly, locally synthesized estrogen produced in response to microbiome composition influence immune responses to the bacterial load (Blaut, 2015).

Regulation of adrenal function by estrogen

Estrogens stimulate adrenal cortex growth during development by promoting cell proliferation and enhancing steroidogenic activity by increasing steroidogenic acute regulatory (StAR) protein and steroidogenic factor-1(SF-1) expression in the adrenal gland. The steroidogenic acute regulatory protein, commonly referred to as StAR is a transport protein that regulates cholesterol transfer within the mitochondria. StAR is a rate limiting step in the production of steroid hormones. StAR is primarily present in steroid producing cells which includes: theca and luteal cells in the ovary, Leydig cells in the testis and cell network in the zona reticularis of the adrenal cortex (Roostaee et al., 2008). There is need to transfer cholesterol from the outer mitochondrial membrane to the inner membrane where cytochrome P450scc enzyme (CYP11A1) cleaves the cholesterol side chain, which is the first enzymatic step in all steroid synthesis. P450scc is a member of the cytochrome P450 superfamily of enzymes (family 11, subfamily A, polypeptide 1). The gene name is CYP11A1 (Choi et al., 2019). The aqueous phase between these two membranes cannot be crossed by the cholesterol. StAR is the carrier protein which mediates this process (Tyczewska et al., 2014).

In the fetal adrenal gland, estradiol and adrenocorticotropic hormone (ACTH) form as a positive regulatory loop in which estradiol increases ACTH secretion from adrenal cortex while ACTH increase estradiol in the ovary (Kariyazono et al., 2015)

Effect of estrogen in pancreas

Estradiol increases insulin gene expression and insulin content in β-cells of the pancreas. Also, estradiol increases β-cell proliferation during pancreatic development and recovery from injury and prevents apoptosis of β-cells upon inflammatory insult through estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) mediated pathways (Yuchi et al., 2015).

Effect of estrogen in adipose tissue

Estradiol stimulates the production of high density lipoprotein cholesterol (HDL) and triglycerides in adipose tissues but decreases low density lipoprotein (LDL) production and fat deposition. However, in an experiment conducted by Barakat et al., 2016, both male and female aromatase-deficient (Cyp19KO) mice exhibited obesity and dyslipidemia proving that estradiol plays a beneficial role in lipogenesis. At the other hand, estradiol is indicted in the pathogenesis of breast cancer because adipose tissues proximal to the breast tumor exhibit higher aromatase activity than those distal to it (Miller, 1991: Rochira and Carani, 2009: Hess and Cooke, 2017)

Effect of estrogen in the skin

Aromatase expression in the skin occurs mainly in hair follicles and sebaceous glands. Estradiol enhances collagen synthesis, increases skin thickness, and stimulates blood flow in the skin. Estradiol also prolongs the anagen phase of the hair cycle and therefore enhances hair growth by increasing the synthesis of essential growth factors stimulating the proliferation of hair follicle cells. As a result estrogen is used in

cosmetics as hair shampoo. But the danger is that the estrogen component of the cosmetic can induce premature development in the girl child and cause feminization in the male fish that comes in contact with it in fresh water during the germination period of the reproduction (Nelson and Bulun, 2001: Jobling et al., 2006: El-Safoury et al ., 2010).

Effect of estrogen in the liver

In the liver, estradiol regulates protein synthesis, including lipoprotein and proteins responsible for blood clotting (factors II, VII, IX, X, plasminogen). Estrogen signaling is also essential in regulating glucose homeostasis, thus improving glucose tolerance and insulin sensitivity (Barros and Gustafsson, 2011). Estrogens are metabolized through hydroxylation by cytochrome P450 enzymes such as CYP1A1 and CYP3A4 through conjugation by estrogen sulfotransferases and Uridine 5-diphospho-glucoronyl transferases (UDP-glucoronyl transferases). In addition, estradiol is dehydrogenated by 17β-hydroxysteroid dehydrogenase into estrone which is less potent. These reactions occur primarily in the liver. Estrogen receptor beta (ERβ) is implicated in mediating the protective role that estradiol plays under pathogenic condition in the liver as it shows potent anti-proliferative and anti-inflammatory properties (Iavaroneet al., 2003). ERβ is also known to mediate the anti-tumor action of estrogens in intrahepatic cholangiocarcinoma (Marzioni et al., 2012).

Effect of estrogen in immunity

Estrogens play an important role in the inflammatory response by regulating development, proliferation, migration, and apoptosis of immune cells. Lymphocytes have been shown to express estrogen receptors (ERα and ERβ), but the expression levels of both receptors vary among cell types. CD4＋ T-lymphocytes (which are white blood cells that are an essential part of the human immune system. They are often referred to as CD4 cells, T-helper cells or T4 cells). They express ERα whereas B-lymphocytes express ERβ. However, CD8＋ T-lymphocytes which are lymphocytes that kill cancer cells, cells infected with virus and/or damaged cells express both receptors at low but equal levels (Uzhachenko and Shanker, 2019). Estradiol inhibits lymphopoiesis and influences T helper (Th) lymphocyte responses inhibiting the production of Th1 cytokines such as interleukin-12 (IL-12) (which is produced by activated antigen-presenting cells; dendritic cells and macrophages. It promotes the development of Th1 responses), tumor necrosis factor-α (TNF-α) and interferon gamma (IFN-γ); a dimerized soluble cytokine that is the only member of the type II class of interferon and stimulate Th2 anti-inflammatory cytokine production such as interleukin-10 (IL-10), IL-4, and transforming growth factor-β (TGF-β) (Salem, 2004: Fabregat and Caballero-Diaz, 2018). Estradiol has also been shown to modulate the maturation, differentiation and migration of myeloid cells, including monocytes, macrophages, and dendritic cells. In effect, estradiol negatively impact on immune cells and affects both the innate and the adaptive immune systems, which may account for its contribution in diseases associated with immune disorder (Mackern-Oberti et al., 2017).

Effect of estrogen post-partum

Estrogen levels decrease 100–1000-fold post-partum. This dramatic hormonal change induce a cascade of signaling that also affects the brain (Schiller et al., 2015). A study investigating the neurochemistry of the female brain in the immediate postpartum period found a substantial whole-brain increase in Monoamine oxidase A (MAO-A) in the brain in the first week postpartum compared to women who had not recently been pregnant. MAO-A is an enzyme that metabolizes monoamines, such as serotonin, dopamine and noradrenaline. A significant increase in MAO-A has been proposed to be predictive for the recurrence of major depressive disorder. These findings in humans are in line

with the inverse relationship between estrogen levels and MAO-A which has been observed in cell lines, as well as in rat and macaque models (Dowlati et al., 2017). The acute estrogen drop within the first week postpartum has been hypothesized to trigger the subsequent MAO-A peak that could explain the depressed mood that a majority of mothers experience during this time. Elevated MAO-A levels have also been found in prefrontal cortical regions and areas of the acuate nucleus in women with postpartum depression (PPD) and in women who do not meet criteria for a full PPD but report postpartum crying (Mbarak et al., 2019). Thus, the interaction between estrogen and MAO-A seems to be a crucial factor in balancing postpartum mood. Given the current lack of prevention strategies for PPD, translation of biological concepts to facilitate the normalization of MAO-A levels in the brain, including potentially attenuating the acute hormonal withdrawal that can precede such an MAO-elevation, represents a promising line of research (Suda et al., 2008).

Estrogenic deficiency

In vertebrates, estrogen deficiency occur due among others to: hypogonadism which is caused by ovarian failure, hypopituitarism (which makes it difficult to synthesize FSH and LH), polycystic ovarian syndrome, anorexia nervosa, extreme endurance exercise training post-partum and during lactation (Hill et al., 2004: Arenas et al., 2005).

The symptoms commonly observed in estrogen deficiency include: fatigue, depression, amenorrhea, lack of concentration, urinary tract infections, mood swings, hot flashes, breast tenderness, painful sex due to lack of lubrication, osteoporosis due to decreased bone density, compulsive behavior in male and ultimately infertility (Hill et al., 2007: Pinna et al., 2008).

Estrogen in disease

Estrogen is implicated in the development or progression of numerous diseases such as osteoporosis, breast cancer, endometrial cancer, ovarian cancer, colorectal cancer, heart disease and neurodegenerative diseases. Most women who take singe hormones as hormone replacement therapy (HRT) run the risk of coming down with cancer. The longer women take HRT, the more the risk increases. However, with stoppage of the treatment, the risk factor wanes off and returns to pre-treatment state (Ivarone et al., 2003: Sohrabji and Lewis, 2006: Deschamps et al., 2010).

Estrogen in Colorectal cancer

Studies have shown that combining two hormones as hormone replacement therapy (HRT) lowers the risk of invasive colorectal cancer in postmenopausal women. The two hormones commonly combined are estrogen and progestin. However, combination HRT does not lower the risk of dying from colorectal cancer (Prossnitz and Barton, 2011).

Estrogen in Treatment

Synthetic estrogen has numerous uses in medicine. The most common and notable uses of estrogen are in birth control pills or contraceptives and in hormone replacement therapy in humans. Estrogen is also used as a tool in estrous synchronization in animals (Pal and Dar, 2020). In humans, women between the ages of 25 to 50 who are estrogen deficient are generally prescribed a high dose of estrogen. This can reduce the risk of bone loss, cardiovascular disease, and other hormonal imbalances. The actual dose will depend on the severity of the condition and the method of application (Harman, 2014).

Mode of administration of estrogen

Estrogen can be administered through the oral route, intra vaginal, intra venous or topical.

Estrogen therapy is only recommended for one to two years. This is because estrogen therapy may increase the risk of cancer (Grodstein et al., 2006: Darabi et al., 2011).

Estrogen in Livestock

Human circulating estrogen are affected by diet and medication. Animal derived foods are rich in cholesterol, saturated fat and proteins. Cholesterol is the precursor for steroid hormones. In effect, cholesterol rich food leads to increase in estrogenic synthesis. This information is buttressed by the fact that changing diet regimen from animal products to vegetables in humans resulted in a significant reduction in estrogen (Carruba et al., 2006).

However, synthetic estrogens are used as growth promoters and anabolic agents for efficient conversion of feed into meat in livestock and poultry. These hormones mimic the action of endogenous estrogens and initiate signal cascades out of membranes of the alimentary tract which affects the physiology of consumers especially in pubertal females (Lykholat et al., 2016).

Most cattle producers in the United States of America, use hormone implants to improve production efficiency. Some of these hormones approved by Food and Drug Administration include: estradiol, progesterone, testosterone, trenbolone acetate and zeranol. It is important to note that implants reduce greenhouse gas emission, energy use, water use and reactive nitrogen loss when compare to beef raised without growth promoting hormones (Beef News, 2019).

Though implanted animals release minimal quantity of estrogen; about one nanogram per three-ounce serving when compared to non-implanted animals, some consumers of such meat especially the bone complain of massive weight gain (Okwudiri, 2020, Oral communication). This is understandable because for growth to occur, most of the estradiol released from the pellet accumulate in the bones and induce the periosteum to become osteoprogenitor (bone forming) cell which eventually give rise to osteoblasts at the point of ossification of the cartilage to become bone (Goff, 2015).

CONCLUSION AND RECOMMENDATION

Estrogen in women is responsible for women to multitask with ease (Wei et al., 2014).

Estrogen-dependent improvement in memory is observed but the neurochemical pathways underlying these changes have not been identified, therefore I recommend that researchers should turn their attention towards this vacuum with a view to fill it.

Postpartum depression (PPD) is a common occurrence in primipartum women (first parturition). However, it is not certain whether estrogen drop postpartum is a sequel to PPD due to increase in Monoamine Oxidase. Hence I suggest that researchers should establish the actual cause of PPD whether it is hormone induced or psychopathic or both by treating post parturient females with Gonadotropin Releasing Hormone, or Follicle Stimulating Hormone or Luteinizing Hormone which ultimately leads to increase in estrogen secretion.

Apart from United States of America that are clear about the use of hormone in livestock production, other countries should report drug use in animal production so that consumers will beware the consumption of some parts like the bone in order to avoid weight increase arbitrarily.

This review is just to bring out estrogenic functions aside from reproduction. I suggest that a critical review of estrogen should be done to harness the progress made so far with estrogen research, the vacuums and the way forward.

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