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The Impact of Sex Hormones on Cognition and Treatment: A Review

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Abstract *— Hormones serves as natural chemical triggers that regulate various processes within the human body, including growth, emotional states, and cognitive processing. Extensive research has been conducted to explore the correlation between hormonal effects and cognitive function; these studies have examined a variety of factors such as aging, pregnancy, post-natal states, emotions, and stress. This article focuses on the impact of hormonal changes on neuronal networks and the mechanisms underlying cognitive function. Hormones possess the ability to influence multiple processes in the human body, including emotions and cognition. The effects of hormones on cognitive function vary depending on the specific hormone involved. Furthermore, hormone levels that are too low or too high can lead to both positive and negative outcomes. Therefore, understanding the influence of sex hormones on cognition is a valuable endeavor.*

Keywords *— **Cognition, Cognitive Decline, Phytoestrogens, Sex Hormones, Treatment.***

I. INTRODUCTION

Cognition refers to a wide scope of mental processes including the ability to gain knowledge, comprehend, remember, and problem-solving. Thus, cognitive abilities are higher level brain-based skills one needs to perform daily tasks and are directly related to how one learns, reason and remember rather than with information itself [1,2]. Moreover, specific neural pathways support cognitive abilities. For example, parts of the temporal and frontal lobes, specialized regions of the brain, are the domain for memory skills [3]. In these areas, neuronal input provides the basis for neurotransmission that determines how the brain thinks, feels, behaves, and functions.The brain consist of numerous nerve cells, which communicate with each other by releasing chemicals, neurotransmitters, involving synapses to relay information between brain cells. Some of the most common neurotransmitters are acetylcholine, epinephrine, norepinephrine, dopamine, serotonin, glutamate, and γ- amino butyric acid (GABA) as well as steroids and sex hormones. These neurotransmitters either excite or depress the receptors and/or neurotransmission, which is affected by the quantity and quality of these chemicals. How well these neurotransmitters bind and fit into their receptors and whether there are enough receptors present or not determine their action [4]. This process could regulate brain functions especially cognition. This process can be affected by diet, exercise, hydration, nutrients supply, perfusion, and hormone balance. If brain cells do not get enough nutrients they need, it could affect the processing and release of neurotransmitters [5,6]. Further, more hypo perfusion may contribute in several ways to the status of brain nutrients and hence performance activity level, and thought processes begins to slow. Long term or chronic imbalances, particularly hormonal imbalances, can lead to serious effect on brain functioning. This is

termed as a "hormonal misconnection syndrome" characterized by symptoms like changes in thinking, speech, attention, memory, behavioral, altered sense of time, spatial skill changes which severely reflects cognition decline [7].

II. FACTORS AFFECTING COGNITION

Decline in cognition can be caused by diseases that affect the brain, which could be due to reduced availability of neurotransmitters, hormones that interact with specific brain receptors to activate the cognition processes. Other possibilities could be lack of responsiveness from hormones, neurotransmitters – receptor interaction, lack of appropriate nutrition or nutrients needed to synthesize neurotransmitters and hormones leading to lack of essential nutrients of neurotransmitter synthesis. Aging conditions like menopause and andropause in both women and men could adversely affect cognition. Elderly people typically need more time to remember things than younger ones as their ability to concentrate, tends to decline with age, this is called Mild Cognitive Impairment (MCI) [8]. In this case poor nutrition, dehydration, and hormone imbalances are considered as precursors for the decline. All these conditions are severe concern of dementia/ Alzheimer's. There are many factors that causes cognitive disorders. Some are due to hormonal imbalances in the womb, genetic predisposition, and others to environmental factors considerably during infancy lack of proper nutrients and interaction during vulnerable stages of cognitive development [9]. Hypoxia induced dysregulation of brain function and cerebrovascular diseases can leads to vascular dementia. For example, stroke which prevents normal blood flow and brain perfusion, due to Ischemia/hypoxia alters brain cellular function. Other common causes of cognitive disorder include Prion disease, HIV infection - how the virus damages brain cells are not certain, substance abuse (drugs, medicines, and alcohol) and physical traumatic brain injuries. Considering all these factors, which could also affect the function of sex hormones, might lead to cognition decline.

Sex Hormones

It has been evident that hormonal regulation of brain region is critical for cognitive function and plays significant role in memory, decision making [10,11]. Many hormones that regulates cognition particularly sex hormones act on central nervous system (CNS) and regulates cognitive as well as sexual function [12]. The gonads produce gonadal hormones which includes both steroid hormones (sex hormones) and peptide hormones e.g., adrenocorticorticotropic hormone (ACTH), insulin, oxytocin, vasopressin, thyrotropin releasing hormone (TRH), thyroid stimulating hormone (TSH). The main steroid hormones estradiol and progesterone produced by the ovaries, and testosterone by the testes. Gonadal hormones generally exert their effects via the nuclear receptors and readily crosses blood brain barrier to modulate neuroendocrine functions in the CNS [13]. The binding of hormone to its receptors results in alterations of biochemical, physiological, and behavioral functions. Outside of the reproductive functions, brain is the main target for the actions of sex hormones. The effects of sex hormones emerge early in brain development and remain throughout adolescence and adulthood. These effects are also regulated through aging as the hormones fluctuate, as well as controls memory, motivation, emotion, cognition, and motor functions. Many literatures indicate that age related depletion of sex hormones both estrogen and progesterone at menopause in women, and testosterone at andropause in men affects the regulation of cognition [14, 12]. Aging associated hormonal depletion causes disease in hormone responsive tissues, including brain, for example, in women following menopause increased risk of stroke and cardiovascular diseases have been reported [15]. Also, menopause or oophorectomy women experience relatively quick loss of the ovarian sex hormones, progesterone (P4) and 17beta-estradiol (E2). Men also experience a significant age-related loss (or orchiectomy reported men) in circulating testosterone levels known as andropause or androgen deficiency in aging males (ADAM). However, in contrast to menopause, andropause is necessarily coupled with the loss of reproductive function and hormonal changes are gradual, with bio-available testosterone levels declining 2-3% annually from approximately 30 years of age [9]. The differences in sex hormone levels among conditions associated with cognitive decline, such as Alzheimer's and Parkinson's, suggest a possible

connection between sex hormones and cognitive decline.

Despite the significant global health burden of cognitive impairment in aging populations, researchers have made substantial progress in understanding the causes of cognitive decline, although certain aspects continue to be actively studied and explored. Several animal studies and theoretical frameworks have strongly suggested that sex steroid hormones play a role in cognitive functioning [13].

Men and women's physiological levels of sex hormones change significantly as they age. Aging results in both subjective and objective cognitive changes. Women experience monthly hormonal regulation during the menstrual cycle and pregnancy, which commonly leads to hormonal imbalance that can impact cognitive function and emotions [12]. However, it is important to note that hormonal imbalances can also affect men. [14]. Previous studies have predominantly focused on maternal hormones, resulting in limited research on the impact of hormones on male cognitive function. However, due to the different abilities of sex hormones to induce neurogenesis in the hippocampus, it suggests that the hormonal influence on cognitive function between genders may be relevant [16, 12].

Many biological studies suggest that sexual hormones are involved in the development of cognitive decline. Estrogen receptors are expressed in many key brain regions involved in cognitive function, including the hippocampus and other limbic structures, the cingulate, and the frontal cortex [17, 45]. Genetic factors may influence gonadal hormones, in which encoded genes in sex chromosomes act directly on the brain to influence neural development, and neural spatial explain the differences in sexual behavior between genders [18]. Progesterone and its metabolite, allopregnanolone, have neuroprotective properties, as well as the ability to promote nerve regeneration and myelination [19]. Testosterone can be converted to estradiol by aromatase or metabolized to dihydrotestosterone (DHT) and bind to androgen receptors. As a result, testosterone can influence cognition via androgen or estrogen receptors [20, 12]. Estrogens and androgens have numerous neuroprotective and neuromodulatory actions that are directly related to cognition.

Alzheimer's disease (AD) is the most prevalent cause of dementia. It is an age-related neurodegenerative disease. Abnormal amyloid- (Aβ) accumulation is thought to initiate a cascade of events in AD etiology, including oxidative damage, inflammation, neurodegeneration, and cognitive impairment. Several clinical studies have investigated the relationship between serum androgen concentrations and Aβ protein, which revealed that reductions in both serum and brain androgen levels in males are associated with increased amyloid- (Aβ) accumulation [21, 12].

III. TREATMENT

The Hormonal Therapy and Cognition

Hormone therapy is the most recommended treatment for menopause and andropause in women and men respectively. According to some studies, increased concentrations of endogenous steroid hormones may have prevented cognitive decline. For example, estrogen deficiency caused by ovariectomy (OVX) raises brain Aβ levels in many wild-type rodents and transgenic models of AD, which can be partially reversed with E2 supplementation [22]. In male rats, supplementation with DHT but not E2 prevented elevated levels of Aβ caused by castration, indicating a prominent role for androgen pathways [23]. However, Aβ burden was reduced not only by testosterone and DHT, but also by E2 in castrated male triple-transgenic mouse model of AD (3xTg-AD), indicating that both androgens and estrogens can reduce Aβ in male brain [24].

There is growing evidence that the cognitive effects of hormone formulations are heavily influenced by the progestin formulation. One small study included postmenopausal women (50 to 55 years old) who all received 12 weeks of estrogen therapy as well as micronized progesterone, resulting in a small decrease in delayed verbal memory scores as well as a significant increase in working memory scores [25].

Some studies have found that testosterone treatment in postmenopausal women to restore physiological levels to premenopausal levels has some benefits for verbal learning and memory [26]. Studies have shown that testosterone supplementation improves

memory in cognitively normal older men with low testosterone [27].

Estrogen Receptor Modulators-Phytoestrogens

The human consumption of diverse foods, drugs, and dietary supplements derived from plants has the potential to modulate the functioning of the central nervous system (CNS). A growing number of herbal remedies, dietary supplements and natural medical foods are promoted as cognition boosters or memory enhancers. Phytoestrogens are herbal components, which have structural and functional similarities with mammalian estrogens and considered to be important in regulation of many dysfunctions including cognition [28]. This structural similarity enables phytoestrogens to cause estrogenic effects by binding to estrogen receptors (ERs). Phytoestrogens have been proposed as potential substituents to hormonal replacement therapy [29]. There is evidence, that consumption of herbal components or their molecules could prevent and treat several dysfunctions and diseases related to aging, mental processes, and menopausal symptoms [30, 31]. Different levels of estrogens in nervous system and its response to those hormones discriminates sex in brain cognitive functions [32]. There is epidemiologic evidence and clinical studies demonstrated that phytoestrogens improved cognitive brain function among Western and Asian populations [33].

Many plants have been shown to have phytoestrogens e.g., fruits, seeds, vegetables, and wholegrains consumed by humanbeings. These plant derived phytoestrogens have been classified as coumestans, isoflavones, lignans etc.. Plants belongs to Leguminosae family, mostly soybean contains highest concentrations of soy isoflavones and coumestans [34]. Soybeans are a rich source of isoflavones, a class of phytoestrogens found predominantly in legumes and beans. Soy isoflavones are heterocyclic phenols with structural similarity to estradiol-17beta and selective estrogen receptor modulators [35]. Lignans mainly found in vegetables, fruits, seeds (flaxseeds) and cereals. Coumestans are significantly present in clover, alfalfa, and soybean sprouts. Plant extracts with potential estrogenic activities include soy, red clover, kudzu, hops, licorice, rhubarb, yam, and chaste-berry [36].

Phytoestrogens - Mechanisms of action

Both genomic and nongenomic mechanisms have been proposed to explain phytoestrogenic effects on human health. Because of their stable structure and low molecular weight, phytoestrogens can interact with enzymes and receptors. These interactions allow them to bind to ERs, induce specific estrogen-response. The level of endogenous estrogens and the type of estrogen receptor can also influence phytoestrogen biological activity [37].

Due to structural and functional similarity of Phytoestrogens with mammalian estrogen, estradiol they bind to estrogen receptors α and β having great preference for recently described estrogen receptor β. Binding to these receptors causes transcription of nucleotides (DNA and RNA) and leading to expression of specific estrogen responsive genes [38,39].

Phytoestrogens are able to bind cell membrane receptors, which promotes formation of cytoplasmic cyclic nucleotides and related protein kinases, which controls the expression of target genes via transcription factors [40]. Hence, phytoestrogens potentially regulate all processes regulated by estrogens including induction sex hormone binding globulin and inhibition of aromatase [41]. Phytoestrogens may exert tissue specific hormonal effects, because of estrogen receptors presence in different tissues – central nervous system (including hypothalamic-pituitary axis), gonads, reproductive tract, placenta, mammary gland, gastrointestinal tract, lung and bones [42,43]. Other than estrogen receptor modulation phytoestrogens are also responsible for other biological effects by acting on other cellular receptors.

Also, there are many natural testosterone-boosting remedies that have been around for centuries. Plant extracts such as chrysin and certain plant lignans inhibit the aromatization (conversion) of testosterone to estrogen, effectively enhancing free testosterone levels [44]. Nettle root liberates testosterone in the body by preventing it from being bound to sex hormone-binding globulin [45].

Alternative Treatment for Cognitive Decline

There is evidence that some cognition enhancing drugs produce their beneficial effects on learning and memory by increasing the availability of glucose for

uptake and utilization into the brain. Some studies denoted that many cognition-enhancing drugs act through a peripheral mechanism rather than directly on the brain and hypothesized as cognitive function is correlated with glucose regulation in aged animals and humans [46].

IV. CONCLUSION

Sex hormones play an important role in maintaining neuronal health, which supports cognitive processes. Hormonal changes not only affect negatively but act as a neuroprotector. As a result, maintaining healthy hormone levels throughout life is critical for both male and female cognitive abilities. More research is necessary to understand the role of sex differences, sex hormones, gender, and psychosocial factors in cognitive functioning, especially in relation to cognitive decline. Depending on the underlying causes of hormonal imbalance, treatment for cognitive issues associated with sex hormones may include hormone replacement therapy and estrogen receptor modulators. It is possible to positively impact hormonal balance and cognitive function by adopting a healthy lifestyle. The regular practice of exercise, a balanced diet, stress management techniques, and adequate sleep can assist in optimizing hormone levels and promoting cognitive health.

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