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Estrogen Response in Correlation with Women Memory: A Review

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ABSTRACT

Aim: To review the estrogen responses in correlation with women memory.
Data sources: A search of PubMed was conducted using the search terms estrogen, memory and mood. Clinical and observational studies were selected from the past year articles. Theories on mechanisms of action of estrogen signaling, and its effect on various disease were discussed.
Results: On an observational study by using various tests, the findings suggest that estrogen may facilitate the automatic activation of verbal representations which is similar to our study but it has shown a negative influence on spatial memory.
Conclusion: From this study, it concludes that estrogen plays a major role in the enhancement of verbal memory; on other side it has a negative influence on spatial memory. In females, sexually dimorphic cognitive skills have enhanced because of the influence of estrogen such as verbal articulation and fine motor skills.

Keywords: Estrogen, Mood, Memory, Women, Alzheimer's disease.

INTRODUCTION

Human memory can be considered as a system for storing and retrieving senses acquired information.[1] The aim of this review is to find the effect of estrogen in women memory. Visual and auditory memory, systems have been the most completely explored. Short term, visual memory means that the trace of visual memory disappears after a fraction of second to several seconds, and long-term visual memory describes the ability to identify a visual stimulus for days, months, or years after exposure.[1]

Women are more twice as likely to develop depression than men[2] and are three times more to be diagnosed with Alzheimer's disease[3] and also experience neurological disorder as Alzheimer's disease progresses.[4] Both estrogens and androgens are involved in the incidence and symptomatology of these disorders.[5] The process of development of new medical technology and a concentrated research initiative have combined to provide substantial new knowledge about the mode of action of estrogen in central nervous system (CNS) that may underlie its possible influence on cognitive functioning.[5]

Estrogen preserves mental features, it can help preserve these functions and delay the beginning of dementia during the latter one third of women's lives.[6] Gonadal hormones may affect the nervous system in controlling gonadotropin and prolactin production and modulating sexual behaviour.[6] It has also been documented that estrogens and androgens affect verbal fluency, performance on spatial tasks,[7] verbal memory tests, and fine motor skills.[8] Estrogens are also correlated with depression symptoms and depressive disorder treatment.[9] Gender differences in brain function also include gender differences in the prevalence of

psychopathologies such as bipolar disorder, which is more common in women, substance abuse, pain tolerance, and antisocial behavior, which is more common in men.[10]

MECHANISMS OF ESTROGEN ACTION

Transsynaptic control by synapse forming estrogen occurs in hippocampus, the recognition, and mapping of estrogen receptors (ERs) in brain culminated in the discovery that these proteins are located in the hypothalamus and the pituitary[11] and then in the hippocampus, the cerebral cortex, midbrain, and brain stem. Two types of intracellular ERs have now been identified, ER alpha and ER beta.[12] The use of [125I]estrogen, which labels ER with a higher specific radioactivity than [3H]estradiol (E2), led to detection of label in pyramidal cells of CA1 and CA3 in the ventral hippocampus,[13] areas were shown to be important for memory.

It has become clearly seen that certain essential steroidal acts involve the coparticipation of certain neurotransmitters, which involves hormone activities on cells that do not tend to have the genomic steroid receptors within them; instead, the effects can be transmitted through other steroid-sensitive neurons. An important example is the Gonadotropin-Releasing Hormone (GnRH) system of hypothalamus.

The function of GnRH neurons is controlled by ovarian steroids; in vivo, these cells have not been found to concentrate estrogen or express the classical ER alpha, ER beta or progesterone receptors(PR).[14] Nonetheless, it has been found that different populations of adjacent cells, immunoreactive to neurotensin, galanin,[15] g aminobutyric acid (GABA), or glutamate, express ER alpha and PR protein.[16] Furthermore, it is known that GnRH release is controlled by hypothalamic amino acid transmitter systems.

Due to the widespread existence of ERs throughout the brain in their various forms, estrogen activities are also common and influence other neurotransmitter systems including catecholaminergic, serotonergic, cholinergic and aminobutyric acid systems.[17] Several effects of estrogen on brain structure and function provides the mechanism of action by which this steroid hormone can affect women's cognitive function.[18] One of the behavior of estrogen is to increase dendritic spine density in 24 to 72 h after acute administration of CA1 pyramidal neurons in hippocampus. Estrogen raises the production of choline acetyltransferase, the acetylcholine synthetic enzyme,[19] a neurotransmitter that is centrally involved in memory functions and whose levels in Alzheimer's disease (AD) are significantly reduced.[20] The various neurotrophic effects of estrogen may explain how this hormone would protect against declines in cognition with aging.[21] Estrogen also have neuroprotective effects through the regulation of molecules involved in apoptosis and through its function as an antioxidant.[22]

VERBAL MEMORY AND FLUENCY

Verbal memory is significant because it is a cognitive feature that with estrogen therapy has been shown to improve and predict the risk of Alzheimer's disease. Estrogen interacts with cholinergic and serotonergic systems to affect the hippocampal and frontal cortical brain areas and thus improves memories, particularly during recovery.[23]

In average, women are better at remembering words from spoken lists and having verbally paired partners than men.[24] Such gender disparities occur before puberty[25] and contribute to older age.[26] Adult estrogen and progesterone levels are linked to verbal memory and fluency performance,[27] because hormone therapy (HT) enhances verbal memory in postmenopausal or surgically menopausal women.[28]

In addition, variations in verbal fluency performance can be seen throughout the menstrual cycle, with high estrogens associated with improved performance and

low estrogens associated with poorer performance in and between subjects during the menstrual period.[29]

ESTROGEN RECEPTOR SIGNALING

The recognized pattern of activation of estrogen receptors (ER) is similar to that of the receptors of androgen (AR). Once estrogen binds to ERs in the nucleus or cytoplasm, there is a conformation shift that results in the recruitment of coactivator (or corepressor) proteins and dimerisation with other ligand ERs.[30] The complex then travels into the nucleus to bind to the estrogen sensitive genes (EREs).[31] Nevertheless, ERs, independent of direct interaction with an ERE, may control the genetic transcription of target genes by controlling other transcription factors which bind to cognate response elements that differ from those of ERE.[32]

This transcriptional cross talk[33] acts by direct protein interactions between an activated ER and a transcription factor, such as AP-1,[34] to control a multitude of non-ERE genes.[35] ERs are also documented to have rapid, nongenomic effects that induce protein production. Estradiol is to improve intracellular calcium release and trigger the cascade of mitogen-activated protein kinase (MAPK).[36] Therefore, while estradiol can lead to the activation of a response component through the initiation of second messenger systems, estradiol mediated nongenomic effects occur too quickly to stimulate protein production and instead use the existing intracellular protein machinery.[36]

It has been proposed that estradiol's classic genomic and nonERE effects are mediated by intracellular ERs (α and β), with nongenomic effects regulated by the G-protein coupled estrogen (GPER) membrane-bound receptors.[37] This complex signaling mechanism helps estradiol to control a wide range of genes, and molecular events will facilitate the production of drugs targeting individual components of the signaling system.[37]

ESTROGEN AND MOOD

Estrogen boosts women's mood and interacts with many mental neurotransmitters. It modulates mood at cellular and synaptic levels through the serotonergic process. And tryptophan depletion during functional magnetic resonance imaging (FMRI) decreased neural activation during a verbal memory task.[38] Estrogen contributes to the upregulation of serotonin 5-HT1 receptors and to downregulation of 5-HT-2 receptors and monoamine oxidase activity. A serotonin agonist, estrogen responds through multiple mechanisms in brain regions supporting mood regulation.[38] It also seems clear that while physiological doses of exogenous estrogen given to postmenopausal women alleviate depressive symptom without significant effect on more profound mood disturbances that fullfill diagnostic criteria for a majordepressivedisorder.[39] On the other hand, it has been shown that very high, supraphysiological doses of estrogen relieve a medical severity of depression. Estrogen improves women's mood and also memory functions, it can separately and directly affect various psychological processes.[39]

ESTROGEN ACTIONS IN CENTRAL NERVOUS SYSTEM

Estrogens function in early embryonic or neonatal development of the brain's sexual differentiation. The cycle of sexual differentiation includes the release of testosterone in fetal or early neonatal life and the actions of testosterone in the defeminization and masculinization of brain structures and function either through androgen receptors or through aromatization to estrogen.[40] Although initially believed to be confined to the hypothalamus, structural and functional sex differences have been found in higher cognitive centers and in sensory and autonomic ganglia and structures of a limbic system of the brain and the midbrain, brainstem, and basal forebrain structures.[40]

Estrogen may affect areas of the brain that are not initially involved in reproduction, such as the cholinergic system of the basal forebrain, hippocampus and cerebral cortex, caudate-putamen, midbrain raphe and locus coeruleus and the spinal cord.[41] Both processes are involved in a number of moodrelated estrogen behavior, locomotive activity, pain tolerance, epilepsy susceptibility, and mechanisms and awareness of attention. Estrogen have effects in a variety of nonreproductive brain functions on many other brain regions and neurochemical processes. In many of these brain regions, the expression of Estrogen Receptor mRNA has increased the potential for functional ERs in these brain areas.[41]

At the same time, the presence of a few nerve cell Estrogen receptors has led to the discovery, for instance in the hippocampus, that these few nerve cells can have strong transsynaptic effects on neighboring neurons.[40]In the corpus striatum and nucleus acumens, actions of estrogens on dopaminergic activity tend to be regulated by membrane actions in absence of any expression of either ER alpha or ER beta in the cell nuclei of these brain regions. On the other hand, estrogen activities at dopaminergic cholinergic, noradrenergic, serotonergic and hypothalamic systems are likely to be regulated by known intracellular nuclear ER alpha or ER beta.[40]For the serotonin system, this will be identified. Endothelial cells and at least some glial cells should be regarded as targets for estrogen activity influencing the absorption of glucose and processes promoting cell membrane replenishment, and even synaptogenesis and other types of structural plasticity.

ESTROGEN AND ALZHEIMER'S DISEASE (AD) IN WOMEN

The most common cause of dementia is AD, the earliest symptom of which is the inability to learn and remember new knowledge, which is accompanied by a gradual loss of other cognitive abilities. Several lines of evidence indicate that replacement therapy with estrogen (ERT) can delay the onset of AD in women.[42] First, results from basic neuroscience that estrogen has a beneficial effect on many of the brain structures and functions in AD neuropathology (such as neuron degeneration in the basal forebrain, the origin of cholinergic projections in cortical, hippocampal and amygdala regions) offered biological plausibility for this hypothesis.[42] Second, the gender disparity in the prevalence of AD, has been found a higher incidence of AD in women compared to men while increasing female longevity.[43] Finally, the findings that ERT preserved the very aspects of cognition in stable, elderly women who deteriorate most deeply in AD (memory and learning) patients raised the possibility that ERT could protect women against AD.[43]

ESTROGEN IN VARIOUS DISEASES

ERs and BREAST CANCER

Estrogen in breast cancer growth and breast cancer risk factors, indicates an accumulated exposure to estrogen from breast epithelium.[44] There are two existing theories for this relationship.[45] In the first theory, binding estrogens to ER may promote mammary cell proliferation, increasing the target cell number in the tissue, and increasing cell division and DNA synthesis increases the risk of replication errors, which can lead to the development of detrimental mutations that interfere with normal cellular processes such as apoptosis, cell proliferation, or DNA repair. In the second theory, metabolism of estrogen contributes to the development of genotoxic by-products that could damage DNA directly, leading to point mutations again.[45]

ERs and OSTEOPOROSIS

In both men and women, estrogen controls the skeletal homeostasis. Osteoporosis is caused by increased bone resorption in both males and females and associated with estrogen deficiency.[46] By reducing osteoclast-mediated bone resorption and increasing osteoblast

mediated bone formation, estrogen reduces bone turnover. The treatment of postmenopausal bone loss is recommended for both estrogen and raloxifen.[46]

ERs and ALZHEIMER'S DISEASE

Many mechanisms can include estrogen in Alzheimer's disease. It may be protective for atherosclerosis and may enhance the blood flow of the brain.[47] Because vascular factors has in Alzheimer's disease, the use of estrogen may have a beneficial effect on its progress. Estrogen can promote growth factor activity,[48] increases the viability of neurons, and sustain neuronal interconnections in cognition-related brain areas. It also affects many neurotransmitter systems, especially cholinergic system.[49] Estrogen can alter the production of amyloid precursor protein, thus reducing the accumulation of a-amyloid. However, the putative exictotoxic effects of beta-amyloid may be decreased by estrogen.[50] The reversal of glucocorticoid damage and anti-inflammatory effects are other potential mechanisms.

CONCLUSION

Estrogen plays a major role in the enhancement of verbal memory; on other side it has a negative influence on spatial memory. In females, sexually dimorphic cognitive skills have enhanced because of the influence of estrogen such as verbal articulation and fine motor skills.

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