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Regulations of Brain Functions by Estrogens

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Abstract

Oestrogen, the female reproductive hormone has many direct and indirect effects on various body systems. Hence, scientists were interested in understanding the role of oestrogen in many brain functions and related diseases, neuroprotective, cognitive functions, Alzeimer's disease, Schizophrenia and depression. Though encouraging results were obtained and the data proved that oestrogen has a role in aetiology of these diseases. However, the present evidences do not support its therapeutic usage or as an adjunct therapy in any of these diseases. Hence, further studies are needed to conclude its role in brain disorders.

Keywords: Oestrogen, Brain functions, Alzeimer's disease, Schizophrenia and depression

Introduction

In addition to promote growth for the female reproductive organs and triggering of a series of ovulation events, oestrogen has direct and indirect effects on various body systems. Specific oestrogen receptors mediate these changes in our body[1-3] and result in the activation and synthesis of oestrogen dependent proteins. The effects which indirectly influenced by oestrogen include the expressions of coagulant and fibrinolytic proteins and serum lipoprotein and triglyceride profiles. Later stage atherosclerosis and few progestins, however, may influence some of the oestrogen protective effects.

A high level of estradiol also mediates the expressions in the developing brain through nuclear transcription factors. These receptors stimulate signalling pathways by regulation of gene expression acting at the membrane level.[2] Sexual differentiation of the brain and a variety of nerve functioning including learning, memory, fine motor control, motor coordination, sensitiveness to pain and brain protection of Alzheimer's disease and stroke damage are regulated by estradiol.

The brain receptors for hormones include the metabolic hormone, insulin, insulin-like growth factor, ghrelin leptin, and steroid hormones. The gonadal hormones act in the brain as they do in peripheral target tissues by the binding the 'receptors'. From the blood, these hormones are received and act on neuronal membrane and affect the functions of neurone activity.

The aging and development of brain regions, which are important to memory like higher cognitive functions, are affected by estrogens and are also associated in neuropsychiatry disorders like Alzheimer's disease. The dendritic and synaptic density of spine in the hippocampus is raised by estrogens.

The nerve protection by steroids involves neurons, glial cells and blood vessels. These actions mediate through steroid receptor signalling which are started at the nuclear or membrane level. The neural injury attenuated by estrogen may be through ER-dependent and independent and genomic as well as non-genomic means. Overall, the dose of estrogen administered influences the pathway of estrogen activity.[4-5] Genomic, non-genomic and anti-inflammatory mechanisms are involved in the neuroprotection effect of oestrogens. It can cause overall protective actions in the brain[6] by acting directly on the neurons, and indirectly through astrocytes, endothelial cells and microglia. The neuroprotective actions of estrogen are also due to its actions against ischemia damage, amyloid protein damage, which is important in the pathogenesis of Alzheimer's disease and oxidative stress. It also helps in the promotion of growth, repair of neurons and stimulation of the nerve growth production factors.

Neural aging is one of the factors in causing age-related changes due to circulatory hormones, which affect functions of neuroprotection. Aging also declines the sensitiveness of glial cells and neurons, response to signals of some peripheral metabolic functions and neuro-protective agents. The hypothalamic control produced by the glands of peripheral endocrine system and systemic metabolism also affects neural aging. Hence, during the aging process, brain-body feed-back loops are positively changed causing neural dysfunction.

Neuro-inflammation is one of the major of age-related neurodegenerative diseases[7] including hearing function loss during aging.[8] The estrogens and mitochondrial function, which are related in the aged brain was described by Lejri[9]and Gaignard.[10] Mitochondria are involved in the sex steroidal hormone production in the body and these hormones in turn modify the mitochondrial function. More research was made in the neuroprotective actions of estrogens, particularly female aging on the use of brain-related neurotrophy factor and sirtuin-3 (SIRT3).

A review by Zarate[11] discussed the mechanisms involved in the promotion of neuroprotection by sex hormones. They also review the activity of sex steroidal hormones on DNA repairing enzymes and the involvement of decreased estrogen level in post-menopausal women in the decreased activity of repair of DNA during aging.

The decrease in endocrine function plays a major role in neural aging. The cognitive functions and psychological health is affected most in women during aging.[12] The attention by memory training, cognitive function and memory are improved with a reduction in circulatory amounts of cortisol and inflammatory cytokines.[13] With this background, the role of estrogen in brain functions, neuroprotective, cognitive functions, Alzeimer's disease, Schizophrenia and depression are discussed in this review.

Estrogen effects on Brain Functions

Among the scientific community the interest on neurobiological effects of ooestrogen is increasing and more research is being done. Estrogen helps in the higher cognitive functions by producing effects on brain parts like hippocampus and prefrontal cortex. Spinogenesis and synaptogenesis in the brain regions are induced by oestrogen and also a complex series of signal transduction pathways are initiated through receptors of estrogen.[14] Therefore, now more women are suggested estrogen and progesterone hormonal replacement therapy (HRT) not only to treat reduced bone loss and vasomotor instability, but also in several disorders of neuropsychiatry.

Estrogen as a Neuro – protectant

The regions related to the development and aging in brain are involved in higher cognitive functions like memory and are involved in neuropsychiatry disorders like Alzheimer's disease are affected by estrogens. For example, dendritic and synaptic densities in the hippocampus are increased by estrogens. In animal studies it was proven that ovariectomy cause a reduction in density of dendritic spine in CA3 pyramidal cells. However, it is not observed when estrogens are administered to the ovariectomized animals.

Circulating estradiol levels are related to synaptic spine density. However, it is also found that high N-methyl-D-aspartate (NMDA) receptors induced by estrogen hippocampal neurons in rat in the same region, where a rise in dendritic spines are found, indicating that the "new" estrogen-induced spines are excitatory.[14] Research also established that in healthy women during menstrual cycle estrogen modulates central cholinergic function by affecting the response of growth hormone to pyridostigmine and a significant correlation exists between cholinergic responsivity and estradiol

levels.[15] The relationship between estrogen and the serotonergic (5-hydroxytryptamine, 5-HT) system was well established in various studies.[16,17]

Estrogens exert their actions on pathology and physiology in women through serotonin also, though the primary action of estrogen is reproductive, the mediation of serotonin on estrogenic system, which produces reproductive benefits are not yet known. Apart from direct actions on neurons, estrogens also have indirect effects on neurotrophins to potentiate growth of nerve cells.

Co-expression of estrogen and neurotrophin receptors on rat neurons in cerebral cortex, forebrain, and hippocampus, and this co-localisation may be essential for the existence of neurons. Additionally, estrogen can also prevent activity of neuro- toxins, which are involved in the increase of free radical production and affect nerves.[18] It also decreases the β amyloid neuronal generation and act as an antioxidant.[19]

Estrogen and Cognitive Function

The activity of oestrogen on verbal memory is its most robust effect on cognitive function. A significant +ve activity of oestrogens on verbal memory was evidenced in randomised, prospective studies of Hormone Replacement Therapy versus placebo using total abdominal hysterectomy and bilateral salpingo-ophorectomy.[20,21] In healthy premenopausal women, the outcome in few tasks, cognitive also differs as a menstrual cycle function. Luteal phase which is characteristic of high secretion of oestrogen and progesterone is seen with improvement of verbal articulation and reduced spatial ability.[22] During the follicular phase, characteristic of low oestrogen and progesterone, a reversal of this pattern is seen. When subjects are tested during the surge of pre-ovulatory oestradiol to control for the potential actions of progesterone on cognitive effects, a similar effect of cognitive outcome is seen, indicating that oestrogen not the progesterone is responsive for the shown cognitive actions.

A crossover, placebo controlled, randomised and recent study using functional MR imaging[23] showed that estrogen induces changes in activation of brain results during encoding and retrieval of both verbal and non-verbal stimuli. More recently, Maki and Resnick[24] used PET and 15O to study longitudinal changes in regional cerebral blood flow (rCBF) over a 2 year period in women on and off HRT (both with and without adjuvant progesterone therapy). However, using higher samples, further prospective and randomised studies are required.

Estrogen and Alzheimer's disease

More research support that estrogen affects the aging of brain

systems that are both important to higher cognitive function and involved in mood and neuropsychiatric disorders like Alzheimer's disease. Epidemiological evidence have suggested that the incidences of Alzheimer's disease are significantly reduced in women on HRT, and that these women with the disease on HRT treatment had lesser symptoms than those who were not.[25]

A new longitudinal study concluded that long term use of HRT reduced the risk and prolonged the start of Alzheimer's disease (relative risk = 0.40; 95% confidence interval, 0.22 to 0.85); moreover, the use of oestrogen for higher than one year decreased the chances of getting Alzheimer's disease by 5%.[26] However, the observational results from such studies are often hard to interpret. For example, women using oestrogen are usually educated, healthier, and depressed less than non-users—a factor called as "the healthy user bias". Thus, for the effects observed for the uses of oestrogen, an unidentified bias may exist.[26,27]

According to current proofs, there is no usage for oestrogens to treat later stage Alzheimer's disease, though it is well established that in healthy brain, estrogen is a neuroprotectant and late start of Alzheimer's disease. In the developed disease, the potential therapeutic window might be missed and the rest of neurons are refractory to the positive effects of estrogen. However, estrogen may be helpful as an augmentation strategy in those using acetyl cholinesterase inhibitors.

Estrogen and Schizophrenia

The outcome of Schizophrenia is related to age of onset and symptomatology of sex and sex differences in premorbid functioning. For example, the disease onset in men has a single peak at their early twenties and the onset for women is at a later age and women between the ages of 45 and 55 years have a second peak in incidence.

The schizophrenic family history and display of atypical or affective features affect women more and they also show a seasonal pattern of hospital admission. It is suggested that women estrogens may be responsible for the delay in onset of first schizophrenic peak and also may be due to putative anti-dopaminergic/antipsychotic actions of oestrogens. The second onset of schizophrenic peak may be due to the decline in oestrogen levels at the menopause. Research suggests that protection of nigrostriatal dopaminergic system is done by estrogen against the neurotoxic effects of MPTP in rats.[28-30]

Clinical studies also support the antipsychotic action of estrogens considering the fact that the rates of admission for psychosis around the menses is raised for women[29] and that psychotic symptomatology differs with the menstrual cycle phase.[30,31] Also, schizophrenic women show decreased levels of concentrations of oestradiol as compared to controls.[31] Contrary to these claims, therapeutic usage of oestrogen in schizophrenia is not supported by evidences. For example, adjunctive oestrogen treatment to women with schizophrenia slight improvement in speed of recovery was observed, but when compared to antipsychotic drug treatment alone, no overall improvement was seen.[32] Though there is less evidences for the use of oestrogen as an antipsychotic drug, it remains plausible that the therapy of oestrogen replacement may protect only against delay of schizophrenia in postmenopausal women by decreasing changes related to age in brain structure and neurochemistry (for example, in the hippocampus).

Estrogen and Depression

Epidemiological studies support that, not only psychosocial reasons, periods of changes in levels of oestrogenare likely to cause depression in a vulnerable women subgroup. For example, depression affects twice in women after puberty than men[33] and reaches its peak during the postpartum period.[34] However, increased mild symptoms of depression are common during the perimenopausal period, postmenopausally such an increase is not observed[33] and research suggests that prevalence of depression reduces postmenopausally.[35]

Although these studies claim that oestrogen may be effective as an antidepressant, methodological difficulties don't allow accepting the claims. These difficulties include the lack of control groups, few subjects, the use of multiple HRT preparations and in the findings of menopausal depression, aninadequate or variable definition of the menopause.

Oestrogen treatment may be useful in postpartum depression both as prophylaxis and in vulnerable individuals[36] and as a treatment.[37] Large doses of oestrogen are helpful in non-postpartum treatment of resistant depression in women[38]but the paper suffers from small group and no repetition done.

The research also suggests that women under estrogen replacement therapy respond well to fluoxetine, an antidepressant drug.[39] Estrogen replacement therapy, in the perimenopause, is useful in decreasing the symptoms of mild depression[33] and research claims that it is a better treatment for depression.[40,41] But it is hard to conclude from these results that whether the oestrogen is useful in the treatment of the symptoms of menopause such as deprivation of sleep and anergia or the depression *per se.*

However, there is no sufficient support to prove the usefulness of oestrogen in the treating of depression in the menopausal or at other times. However, scientists suggest that oestrogen replacement or HRT can't be considered as a priority for treating depression in depressed women, though in non-depressed women, in the perimenopausal period, it may produce a sense of "psychological wellbeing".[33] However, in peri-postmenopausal women, in the treatment of resistant depression or in reducing of milder mood symptoms, oestrogen may have a limited role in adjunct to antidepressants.

Conclusion

The basic research conducted thus far supports the multiple roles of oestrogen on brain aging, brain function, glucose metabolism, modulating aspects functions of neurotransmitter and synaptogenesis. Supporting the same, epidemiological research indicates oestrogen in the aetiology of disorders of neuropsychiatry. But, these evidences are not enough for the use of oestrogen in therapy. The research findings prove that only oestrogen has no activity in treating late stage Alzheimer's disease, but may delay the start of the disease. Oestrogen as an adjunct therapy also can't be used along with neuroleptics in schizophrenia or in treating depressions of postnatal and perimenopausal, as current evidences arenot enough to support analteration in clinical practice. Further high level researches are required to establish whether oestrogen has an activity in the prevention and treating of these disorders.

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Conflicts of Interest

The author declares that there are no conflicts of interest.

References

1. Gupta PD. Molecular Biology of steroid and nuclear hormone receptors *Ind J Expt. Biol.* 1999;37:622.
2. Shashi Singh, Shaul Philip W, Gupta PD. Conventional oestrogen receptors are found in the plasma membrane of vaginal epithelial cells of the rat. *Steroids.*2002;67:757-764.
3. P D Gupta , Kaid Johar Sr, K Nagpal, et al. Sex hormone receptors in the human eye. *Surv Ophthalmol.* 2005;50:274-284.
4. Garcia-Segura LM, Balthazart J. Steroids and neuroprotection: New advances. *Front Neuroendocrinol* 2009;30(2):5-9.

5. Dubal DB, Wise PM. Oestrogen and neuroprotection: from clinical observations to molecular mechanisms. *Dialogues Clin Neurosci*. 2002;4(2):149-161.
6. Brann DW, Dhandapani K, Wakade C, et al. Neurotrophic and neuroprotective actions of oestrogen: basic mechanisms and clinical implications. *Steroid.* 2007;72(5):381-405.
7. Arroba AI, Campos-Caro A, Aguilar-Diosdado M, et al. IGF-1, Inflammation and Retinal Degeneration: A Close Network. *Front Aging Neurosci.* 2018;10:203.
8. Varela-Nieto I, Chowen JA, García-Segura LM. Editorial: Hormones and Neural Aging: Lessons From Experimental Models. *Front Aging Neurosci.* 2018;10:374.
9. Lejri I, Grimm A, Eckert A. Mitochondria, Oestrogen and Female Brain Aging. *Front Aging Neurosci.* 2018;10:124.
10. Gaignard P, Liere P, Thérond P, et al. Role of Sex Hormones on Brain Mitochondrial Function, with Special Reference to Aging and Neurodegenerative Diseases. *Front Aging Neurosci.* 2017;9:406.
11. Zárate S, Stevnsner T, Gredilla R. Role of Oestrogen and Other Sex Hormones in Brain Aging. Neuroprotection and DNA Repair. *Front Aging Neurosci.* 2017;9:430.
12. Navarro-Pardo E, Holland CA, Cano A. Sex Hormones and Healthy Psychological Aging in Women. *Front Aging Neurosci.* 2018;9:439.
13. Rajasundaram S, Rahman RP, Woolf B, et al. Morning Cortisol and Circulating Inflammatory Cytokine Levels: A Mendelian Randomisation Study. *Genes (Basel).* 2022;13(1):116.
14. Hara Y, Waters EM, McEwen BS, et al. Oestrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. *Physiol Rev.* 2015;95(3):785-807.
15. Cappa M, Loche S, Salvatori R, et al. The growth hormone response to pyridostigmine plus growth hormone releasing hormone is not influenced by pubertal maturation. *J Endocrinol Invest.* 1991;14(1):41-45.
16. Epperson CN, Amin Z, Ruparel K, et al. Interactive Effects of Estrogen and Serotonin On Brain Activation During Working Memory and Affective Processing in Menopausal Women, *Psychoneuroendocrinology*. 2012;37(3):372–382.
17. Pottoo FH, Javed MN, Barkat MA, et al. Estrogen and Serotonin: Complexity of Interactions and Implications for Epileptic Seizures and Epileptogenesis. *Curr Neuropharmacol*. 2019;17(3):214–231.
18. Picazo O, Azcoitia I, Garcia-Segura L M. Neuroprotective and neurotoxic effects of oestrogens. *Brain Research.* 2003;990(1–2):20-27.
19. Kontush A, Berndt C, Weber W, et al. Amyloid-beta is an antioxidant for lipoproteins in cerebrospinal fluid and plasma. *Free Radic Biol Med.* 2001;30(1):119-128.
20. Sherwin BB. Oestrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology.* 1988:13: 345–357.
21. Phillips SM, Sherwin BB. Effects of oestrogen on memory function in surgically menopausal women. P*sychoneuroendocrinology* 1992;17:485–495.
22. Hampson E**.** Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cogn.*1990*;* 14:26–43.
23. Shaywitz SE, Shaywitz BA, Pugh KR, et al. Effect of oestrogen on brain activation patterns in postmenopausal women during working memory tasks. *JAMA.* 1999*;*281:1197–1*202.*
24. Maki PM*,* Resnick SM. Longitudinal effects of oestrogen replacement therapy on PET cerebral blood flow and cognition. *Neurobiol Aging.* 2000*;*21:373–3*83.*
25. Henderson VW**,** Paganini-Hill A, Emanuel CK, et al. Oestrogen replacement therapy in older women: comparisons between Alzheimer's disease cases and nondemented control subjects. *Arch Neurol.* 1994*;*51:896–900.
26. Tang MX**,** Jacobs D, Stern Y, et al. Effect of ooestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet.* 1996*;*348:429–4*32.*
27. Liang J, Wang C, Zhang H, et al. Exercise-Induced Benefits for Alzheimer's Disease by Stimulating Mitophagy and Improving Mitochondrial Function. *Front Aging Neurosci.* 2021;13:755665.
28. Dluzen DE*,* McDermott JL, Liu B. Oestrogen alters MPTP-induced neurotoxicity in female mice: effects on striatal dopamine concentrations and release. *J Neurochem.*1996*;*66*:*658–666.
29. Hallonquist JD*, Seeman MV, Lang M,* et al. Variation in symptom severity over the menstrual cycle of schizophrenics. *Biol Psychiatry.*1993*;*33:207–20*9.*
30. Lindamer LA*,* Lohr JB, Harris MJ, et al. Gender, oestrogen, and schizophrenia*, Psychopharmacol Bull.* 1997*;*33*:*221–22*8.*
31. Riecher-Rössler A, Häfner H, Dütsch-Strobel A, et al. Further evidence for a specific role of estradiol in schizophrenia? *Biol Psychiatry.*1994*;*36:492–49*4.*
32. Kulkarni J*,* Riedel A, de Castella AR*,* et al. Oestrogen – a potential treatment for schizophrenia*. Schizophr Res.* 2001*;*48:137–1*44.*
33. Epperson CN, Wisner KL, Yamamoto B. Gonadal steroids in the treatment of mood disorders. *PsychosomMed. 1999;61:676–697.*
34. Kumar R**,** Robson KM. A prospective study of emotional disorders in childbearing women. *Br J Psychiatry.*1984*;*144:35–*47.*
35. Bebbington PE*,* Dunn G, Jenkins R, et al*.* The influence of age and sex on the prevalence of depressive conditions: report from the National Survey of Psychiatric Morbidity. *Psychol Med.* 1998*;*28:9–*19.*
36. Sichel DA*,* Cohen LS, Robertson LM*,* et al*.* Prophylactic oestrogen in recurrent postpartum affective disorder. *Biol Psychiatry.* 1995*;*38:814–818.
37. Gregoire AJP*,* Kumar R, Everitt B*,* et al. Transdermal ooestrogen for treatment of severe postnatal depression. *Lancet.*1996*;*347:930–933.
38. Klaiber EL*,* Broverman DM, Vogel W*,* et al. Estrogen therapy for severe persistent depressions in women*. Arch Gen Psychiatry.* 1979*;*36:550–55*4.*
39. Schneider LS*,* Small GW, Hamilton SH, et al. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Fluoxetine Collaborative Study Group*. Am J Geriatr Psychiatry.* 1997*;*5:97–*106.*
40. Schmidt PJ*,* Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report*. Am J Obstet Gynecol.* 2000*;*183:414–4*20.*
41. Soares CN*,* Almeida OP, Joffe H, et al. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo–controlled trial*. Arch Gen Psychiatry.* 2001*;*58*:*529–5*34*.