

## Estrogen and its neuroprotective action: a brief review

Anju Lata Rai

Assistant Professor, Dept. of Anatomy, PGIMER, Dr. RML Hospital, New Delhi

Email: anjulata72@gmail.com

### Abstract

Estrogens have been shown to affect the nervous system in many different ways. As the age advances especially in post menopausal women a significant decline in Cognition is observed. The low estrogen levels in postmenopausal females makes them vulnerable to neurodegenerative disorders. Estrogen has a neuroprotective role and this has been extensively studied in in-vitro or in rodents but the exact mechanism of action especially in humans is not completely understood. Several hypothesis have been documented by scientist to explain the neuroprotective mechanism of estrogens, they either 1) influence levels of neurotransmitter like GABA, Acetylcholine etc. 2) influence cerebral blood flow 3) alter growth proteins levels associated with axonal growth or lower the neurotoxic effects of  $\beta$ -amyloid. In this review, the author has tried to briefly describe the possible mechanism of action of estrogen in the nervous system, which may be significant in protecting against damage caused by ageing.

**Keywords:** Estrogen, Aging, Brain function

### Introduction

Estrogen a sex steroid not only controls the reproductive function but affects the nervous system in many different ways.

17 $\beta$ -Estradiol (E2), the most potent and predominant form of estrogen, has a number of effects on cognition and brain function. Estrogens act via two receptors the ER $\alpha$  and ER $\beta$  which are differently expressed throughout the rat brain. Immunohistochemical techniques have shown that in the hypothalamus ER $\alpha$  is present in the arcuate and ventromedial nuclei, whereas ER $\beta$  is mostly present in the paraventricular and ventromedial nucle, the cerebellum expresses only ER $\alpha$  and the hippocampus expresses both the subtypes but mainly has ER $\beta$ .<sup>(1-5)</sup> In some brain regions both the receptors have been localised i.e. in preoptic area, the bed nucleus of the stria terminalis, the lower brainstem and the dorsal horn of spinal cord. In females concentration of estrogens in blood decreases with age and the low estrogens levels in postmenopausal stage leads to decline in cognition and which affects the working memory, impairment of focus and attention and slowing of speed of information processing.<sup>(6-9)</sup> Normal ageing process is accompanied by changes in structure and function of those brain regions that are implicated in neuropsychiatric disorders, such as Alzheimer's disease (AD). Murphy et al<sup>(10)</sup> in a study measuring glucose metabolism, using positron emission tomography and 18F-2-fluoro-2-deoxy-D-glucose, observed that females had significant age-related decrease in hippocampal glucose metabolism, compared to men. The hippocampus part of limbic system is a crucial structure for the formation and processing of episodic memory and spatial memory.<sup>(11)</sup> It is also implicated in emotional behaviour.<sup>(12)</sup> The hippocampus is susceptible to damage during ageing and repeated stress.<sup>(13)</sup> It is well known that women have a higher age-related prevalence of AD than men and they also have a greater disease severity. In one of the study

done on postmenopausal women(n=425)  $\geq 65$  years of age it was observed that women with high concentrations of bioavailable estradiol had less decline on cognitive testing thereby, supporting the hypothesis that higher concentrations of endogenous estrogens prevent cognitive impairment.<sup>(14)</sup>

Several mechanisms have been postulated for neuroprotective role of estrogens, but the exact underlying mechanism of this effect in humans is not completely understood. Several studies on rodents and in vitro studies observed that E2 upregulates the excitatory action of neurotransmitters like acetylcholine.<sup>(15)</sup> In medial preoptic area levels of GABA increased with E2 levels<sup>(16)</sup> whereas in hippocampus it decreased GABA levels. E2 can augment neurosteroids synthesis and activity via neuroglia aromatase activity.<sup>(17-19)</sup> E2 also inhibits accumulation of  $\beta$ -amyloid.<sup>(20,21)</sup> It also reduces neuronal cell apoptosis mediated through ER $\beta$  (Nilsen *et al.*, 2000, Meda C *et al.*, 2000).<sup>(22,23)</sup> Estrogen acts on the mitochondria by stabilising its membrane potentials which prevents ATP depletion and hence reduces the generation of oxygen free radicals(Nilsen and Brinton, 2003).<sup>(24)</sup> Amongst the various neuroglia, estrogens have been shown to alter microglial expression of cytokines and growth factors and lack or low levels of estrogen, may restrict the immune responses and may hasten brain disorders.<sup>(25)</sup> One of the best-known processes regulated by estrogen hormone is the formation of excitatory synapses in the hippocampus.<sup>(26,27)</sup> Estrogen treatment increases dendritic spine density on CA1 pyramidal neurons in the hippocampus and also show cyclic variation .E2 can also influence levels of NMDA receptors ,earlier studies have shown that it down regulates activity of NMDA receptors.<sup>(28)</sup> and thereby reduces the chances of NMDA-induced neuronal death. In one of the epidemiological study done on postmenopausal women an improvement in verbal memory, reasoning and motor speed was seen when given hormone replacement therapy (HRT).<sup>(29)</sup> Studies

using Neuroimaging techniques done in females have confirmed that estrogens can increase cerebral blood flow, glucose metabolism.<sup>(30-31)</sup>

### Conclusion and Perspective

From the above review it is clear that estrogens have definite neuroprotective role and can be used as an important therapeutic agent to maintain normal neural function during ageing. Role of hormone replacement therapy in humans is an extensive and controversial subject and will be studied extensively in future studies.

### References

- Shughrue PJ, Komm B, Merchenthaler I. The distribution of estrogen receptor- $\beta$  mRNA in the rat hypothalamus. *Steroids* 1996;61:678-681.
- Mitra SW, Hoskin E, Yudkovitz J, Pear L, Wilkinson HA, Hayashi S, et al. Immunolocalization of estrogen receptor  $\beta$  in the mouse brain: comparison with estrogen receptor  $\alpha$ . *Endocrinology*. 2003;144(5):2055-67.
- Mitterling KL, Spencer JL, Dziedzic N, Shenoy S, McCarthy K, Waters EM, et al. Cellular and subcellular localization of estrogen and progesterin receptor immunoreactivities in the mouse hippocampus. *J Comp Neurol*. 2010;518(14):2729-43.
- Rai AL and Jeswar U. Immunolocalization of estrogen receptor alpha in adult female rat hippocampus. *Int J Morphol*. 2010;28:483-487.
- Shughrue PJ, Merchenthaler I. Distribution of estrogen receptor beta immunoreactivity in the rat central nervous system. *IJ Comp Neurol*. 2001 Jul 16;436(1):64-81.
- Craik FIM, Byrd M, Ageing and cognitive deficits: the role of attentional resources. In Craik FIM, Salthouse TA (eds), *Ageing and cognitive processes*. New York: Plenum Press, 1982, pp, 191-211.
- Rabbitt P. An age decrement and the ability to ignore irrelevant information. *J Gerontol*. 1965;20:233-236.
- Rogers W, Fisk AD. Age-related differences in the maintenance and modification of automatic processes: Arithmetic Stroop interference. *Human Factors* 1991;33:45-56.
- Cerella J. 1990. Aging and information processing rate. In Birren J, Schaie KW (eds) *Handbook of the Psychology of Aging*, San Diego, CA: Academic Press.
- Murphy DGM, et al. Sex differences in human brain morphology and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. *Arch Gen Psychiatry*. 1996;53:585-594.
- Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev*. 1992;99:195-231.
- Sahay A, Hen R. Hippocampal neurogenesis and depression. *Novartis Found Symp*. 2008;289:152-160. discussion 160-164, 193-195.
- Halbreich U. Possible acceleration of age effects on cognition following menopause. *J Psych Res*. 1995; 29:153-163.
- Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women. Effects on Cognitive Function and Dementia. 1998; *JAMA* 279:688-695.
- McMillan PJ, Singer CA and Dorsa DM. The effects of ovariectomy and estrogen replacement on *trkA* and choline acetyltransferase mRNA expression in the basal forebrain of the adult female Sprague-Dawley rat. *J Neurosci*. 1996;16:1860-1865.
- Herbison AE. Estrogen regulation of GABA transmission in rat preoptic area. *Brain Res Bull*. 1997;44(4):321-6.
- Baulieu EE, Robel P and Schumacher M. Neurosteroids: beginning of the story. *Int Rev Neurobiol*. 2001;46:1-32.
- Genazzani AR, Gambacciani M, Simoncini T and Schneider HPG. 'Controversial issues in climacteric medicine' series 3rd 'HRT climacteric and aging brain'. *Maturitas*. 2003; 46:7-26.
- Genazzani AR, Bernardi F, Pluchino N, Begliuomini S, Lenzi E, Casarosa E and Luisi M. Endocrinology of menopausal transition and its brain implications. *CNS Spectr*. 2005; 10:449-457.
- McEwen BS, Alves SE, Bulloch K and Weiland NG. Ovarian steroids and the brain: implications for cognition and aging. *Neurology*. 1997;48:8-15.
- Greenfield JP, Leung LW, Cai D, Kaasik K, Gross RS, Rodriguez-Boulan E, Greengard P and Xu H. Estrogen lowers Alzheimer beta-amyloid generation by stimulating trans-Golgi network vesicle biogenesis. *J Biol Chem*. 2002 ;5:12128-12136.
- Nilsen J, Mor G and Naftolin F. Estrogen-regulated developmental neuronal apoptosis is determined by estrogen receptor subtype and the Fas/Fas ligand system. *J Neurobiol*. 2000; 43:64-78.
- Meda C, Vegeto E, Pollio G, Ciana P, Patrone C, Pellicciari C, Maggi A. Oestrogen prevention of neural cell death correlates with decreased expression of mRNA for the pro-apoptotic protein *nip-2*. *J Neuroendocrinol*. 2000 Nov;12(11):1051-9.
- Nilsen J and Brinton RD. Mechanism of estrogen mediated neuroprotection: regulation of mitochondrial calcium and Bcl-2 expression. *Proc Natl Acad Sci USA*. 2003b;100:2842-2848.
- Mor G, Nilsen J, Horvath T, Bechmann I, Brown S, Garcia-Segura LM and Naftolin F. Estrogen and microglia: a regulatory system that affects the brain. *J Neurobiol*. 1999; 40:484-496.
- Woolley C and McEwen BS. Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. *J Neurosci*. 1992; 12:2549-2554.
- Woolley C and McEwen BS. Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. *J Comp Neurol*. 1993; 336:293-306.
- Weaver CE Jr, Park-Chung M, Gibbs TT, Farb DH. 17beta-Estradiol protects against NMDA-induced excitotoxicity by direct inhibition of NMDA receptors. *Brain Res*. 1997; 761:338-341.
- LeBlanc ES, Janowsky J, Chan BK, Nelson HD. 2001. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA*. 1997; 285:1489-99.
- Dietrich T, Krings T, Neulen J, Willmes K, Erberich S, Thron A, Sturm W. Effects of blood estrogen level on cortical activation patterns during cognitive activation as measured by functional MRI. *Neuro Image*. 2001; 13:425-432.
- Eberling JL, Reed BR, Coleman JE, Jagust WJ. Effect of estrogen on cerebral glucose metabolism in postmenopausal women. *Neurology*. 2000; 55:875-877.