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PROTECTIVE ROLE OF ESTROGEN IN THE NEURODEGENERATIVE DISORDERS

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Abstract : Estrogen is an anabolic hormone of gonadal cells and it also modulates the growth and differentiation of non-gonadal cells like neuron/glia and protects them against the injury. The anabolic or protective actions of estrogen on the neuronal cells are mediated by the modulation of intracellular factors such as insulin like growth factor (IGF-I), tyrosine kinase A (Trk A), nerve growth factors (NGF) etc. It also modulates the action of neurotrophins which inturn regulate the synaptogenesis, synaptic plasticity and synaptic functions. By these actions estrogen prevents or slows down the neurodegenerative process.

Key words : estrogen receptors; neurodegenerative diseases; amyotrophic lateral sclerosis; insulin like growth factor

INTRODUCTION

The existence of gender related differences reported in various neurological and cardiovascular diseases is well documented. The role of estrogen/testosterone for these differences have been speculated but the precise mechanisms for many of the conditions are not known. Recent literature supports for the action of estrogen in preventing the cellular apoptosis (programmed cell death) and prolonging the cell survival (1, 2). This is of great importance for the nervous tissue (1, 2). Thus, estrogen plays a vital role in the functioning of cells of different tissues especially the non-proliferative cells like nervous tissue.

General actions of estrogen

Estrogen is feminine hormone synthesized mainly by the granulosa cells and corpus luteal cells of the ovary. This hormone is essential for the oogenesis to fertilization and development of fetus at various stages of intrauterine life. Later on in extrauterine life, it is necessary for the nourishment of infant by means of lactation. Further, estrogen is anabolic to the Muellerian duct organs and also to the secondary sex organs in female. Further in males, the bio-feedback regulation of testosterone at the pituitary-hypothalamic axis is mediated by converting testosterone to estrogen (aromatization) to produce the desired negative feedback effect on the gonadotrophin secretion (3).

TABLE I: Actions of Estrogen.

1.	Growth of reproductive organs, external genitalia, and breasts.
2.	Growth of body hair.
3.	Growth of long bones and early closure of epiphyses.
4.	Female pattern of fat distribution.
5.	Exerts positive feedback for the secretion of gonadotrophins in follicular phase and negative feedback in luteal phase.
6.	Testosterone feedback in males by aromatization to estrogen.
7.	Decreases sensitivity of peripheral tissue to insulin.
8.	Protects against bone loss.

Besides being synthesized from the gonadal cells, estrogen is also synthesized by the suprarenal gland. The physiological actions of estrogen are summarized in the Table I. Basically, it is an anabolic hormone to primary and secondary sex organs of the female. It exerts action on the bone metabolism so as to prevent the osteoporosis.

Estrogen receptor and mechanisms of action

The actions of estrogen are mediated via the estrogen receptors (ER). These receptors are located on the nuclear envelope or within the nucleus of the cell. The ER protein consist of 595 amino acids with a molecular weight of 595 kDa (4). The ER receptors are distributed in all the cells of the body including neurons, astrocytes, endothelial cells (5). The ER molecule has been separated into 6 different functional domain (6, 7). These domains can be broadly grouped into two major groups, those bind with N terminal region and those bind with the C terminal region. The N terminal region binds with DNA and known as DNA binding domain. The C terminal region is available for binding with hormone and hence hormone binding domain (7). The hormone binding domain has ligand recognition sites and bestows specificity and selectivity to the ER. The hormone binding domain contains two separate regions, one is for the attachment with heat shock protein-90 and the other is for the nuclear localization of the signal region (8). The estrogen diffuses through the plasma membrane of target cells where it binds with the hormone binding domain of the ER (9). Upon binding with the ligand the coordination of hormone binding domain on DNA binding domain is lost. The DNA binding domain now becomestranscriptionally active (10). The heat shock protein-90 brings the conformational changes in the ER. The transcriptionally active process triggers the activation of phosphorylation. Several protein kinases such as ER kinase, DNA dependent kinase, ser-pro-kinase, protein kinase C, protein kinase A, casein kinase II, and MAP kinase are thought to be involved in this process (8).

The binding of estrogen to this receptor site causes conformational changes in the receptor such as the hormone/receptor complex then interacts with specific "acceptor site" on the nuclear DNA. This interaction initiates transcription of mRNA molecules that code the specific proteins. After transcription, the mRNA precursors are processed within the nucleus before moving to the cytoplasm of the cells. Because of the increased abundance of these particular mRNA molecules, the synthesis of specific proteins is increased. Increased synthesis of the particular class of proteins leads to altered cellular functions characteristically produced by the hormone. These changes produce the effects on permeability and transport of substances, synthesis of new proteins, cellular multiplication, cellular metabolism, and other effects (8).

Estrogen modulates cellular actions

The cerebrovascular stroke and neurodegenerative disorders are most frequently seen in males than females. Less occurrence of these disorders in females is attributed to the presence of estrogen or due to the lack of testosterone. Recently, it has been indicated that estrogen modulates variety of cellular reactions necessary for signal transduction to bring about the cellular protective actions (8, 11). The intracellular agents modulated by estrogen are as mentioned below.

1. Growth factors

   Insulin like growth factor (IGF-1)
   Transforming growth factor (TGF) α
   Transforming growth factor (TGF) β

2. Tyrosine kinase-A (Trk-A)

3. Nerve growth factor (NGF)

4. Factors that alter the synaptic activity

Estrogen modulates growth factors :

The estrogen regulates the cellular effects by modulating three different growth factors such as transforming growth factor α (TGF α), transforming growth factor β (TGF β) and insulin like growth factor (IGF). TGF α and IGF-1 are growth stimulatory and TGF β is growth inhibitory (8). IGF-1 is ubiquitously distributed and is an important factor for the cellular actions on diverse group of cells in the body.

Insulin like growth factor-1 is a pleotrophic factor with a wide spectrum of actions on the nervous tissue (11, 12). IGF-1 promotes division, differentiation, maturation, assures survival or reduces apoptosis of the neuronal cells in the olfactory bulb, septum, cerebral cortex, hypothalamus, hippocampus, mesencephalon, brainstem and cerebellum. It also possess similar actions on glial (Schwann cells, oligodendrocytes, astrocytes) cells. IGF-1 protects neurons against the toxicity–induced by iron, colchicine, Ca^{2+} destabilizers, H_2O_2, amyloid β protein, human amylin, cytokines, and pharmacological lesions (11, 12). It also modulates the release of neurotransmitters such as acetycholine, dopamine, serotonin, glutamate, neuropeptide Y etc.

Estrogen induces IGF-1 in the uterus and it is believed to be responsible for the uterotrophic response observed in stromal and epithelial cells (8). Further, it is shown that treatment with tamoxifen, anti-estrogen agent, decreased the circulating levels of IGF-1 (13–16). The reduction of IGF–1 (a potent mitogen) reduced the metastatic spread of the estrogen dependent cancer cells. Thus, IGF–1 plays a vital role for the action of estrogen on gonadal and non-gonadal cells.

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder of motoneurons and is mostly seen in males, almost in the ratio of 2 : 1 (17–19). In the experimental animals, it was shown that the excitatory actions of thyrotropin-releasing hormone (TRH) on spinal motoneurons was much lesser in female rats or in rats treated with estrogen than the male rats or from the castrated rats treated with testosterone. Thus, the involvement of testosterone for the aetiopathogenesis of this disorder has been postulated (20–21). This was further supported in the reviews elsewhere (19, 22, 23). Very recently, IGF-1 was shown to be useful in the treatment of ALS. It is further interesting to note that the IGF-1 modulates the transmitter release so did the the TRH. It is known that the TRH action is mediated directly on the motoneurons as well as by releasing the excitatory transmitters like glutamate and serotonin presynaptically (24–26). These observations indicate that the motor neuron activity is influenced by estrogen via IGF-1 mechanism which inturn decrease the amount of transmitter released at Ia-α motoneuron synapse as mentioned. Similar mechanisms may be operative in various neurological disorders such as multiple sclerosis, Alzheimer's disease, stroke and cerebrovascular disease where the role of estrogen-IGF-1 relation could be postulated. This is in addition to its protective action against toxic agents mentioned before.

TABLE II : Effect of IGF–1 on neuronal and glial functions.

1. Promotes neuronal/glial cell.
   Division, Differentiation, Maturation, Assures survival, Decreases apoptosis.
2. Protects against the toxicity from heavy metals Colchicine, Amyloid β protein, amylin, cytokines, H_2O_2 etc.
3. Modulates the release of neurotransmitters Acetycholine, glutamate, 5–HT, neuropeptide Y etc.
4. Induces expression of neurofilaments, tubulin, myelin basic protein.
5. Dendritic/motor neuronal sprouting.
6. Actions on glucose metabolism of the cells.
7. Increases myelination and inhibits demyelination.

Estrogen modulates Tyrosine kinase A (Trk–A) :

Tyrosine kinase A is an enzyme necessary for the signal transduction mechanism involving second messenger systems (1). The binding of neurotrophins to Trk receptors leads to dimerization and autophosphorylation. The tyrosine phosphorylated Trk-A activates Ras replacing GDP to GTP. Activated Ras interacts directly with the serine threonine kinase Raf. The activated Raf leads to sequential activation of mitogen activated protein (MAP) kinase system. MAP kinase translocates to the nucleus where it phosphorylates the transcription factors. A second pathway emanates from Ras-MAP kinase pathway where it transcripts the cyclic AMP/Ca^{2+} response elements. These intracellular cascade of events bring about the cellular changes. Activation of Trk-A results in various reactions leading to the activation of mRNA for various neurotrophic actions. Further, it is a regulator for generating the signals for cell apoptosis. Thus, is an indicator of the sustainability of the cell in a system. Estrogen is shown to increase the expression of mRNA for Trk-A synthesis (27), brain-derived neurotrophic factor (BDNF) mRNA and NGF receptor RNA (28).

Huntington's disease is a neurodegenerative disease where the selective loss of nigrostriatal dopaminergic pathway is demonstrated (2, 29). The rats treated with 3-nitropropionic acid (3-NPA), an irreversible inhibitor of succinate dehydrogenase, exhibits lesions similiar to

Huntington's disease. It was observed that the female rats were resistant to the toxic neurodegenerative effects of 3-NPA (30). Taking clue from this finding Nishino et al (2) examined the role of estrogen in 3-NPA-induced toxicity. The gonadectomized female rats were sensitive the toxic effects of 3-NPA as the male ones. Further, treatment of healthy female rats with tamoxifen, estrogen receptor antagonist, became more vulnerable to the toxic effects of 3-NPA. Thus, providing the evidence for the attenuating effect of estrogen for the neurotoxicity produced by 3-NPA. Although the direct evidences are still lacking, the attenuating effect may be due to the activation of tyrosine kinase (Trk) system and the NGF or BDNF or lowering action of estrogen on oxidative stress resulting from free radicals as 3-NPA is shown to increase the NO activity (31–33).

Estrogen modulates the neurotrophic factors :

Of the neurtrophins, nerve growth factor is the first trophic factor to be reported, later on several other factors have been described like Brain-derived neurotrophic factor, (BDNF), neurotrophin-3 (NT3) etc. These neurotrophic substances are responsible for the complex connectivity and functions of the neuronal cells of the nervous system. NGF is secreted by glia. NGF is necessary for the survival of neuronal cells *in vitro* and also the survival and proper growth of the neuronal cells *in vivo*. Increased dendritic arborization of the hippocampal regions by estrogen is the indicator of this activity (27). Estrogen stimulates the growth of glial processes and also the synthesis of NGF from glia (34). Further, the NGF or other growth factor stimulation is also governed by the activation of signal transduction mechanism.

Estrogen alter the synaptic activity :

The increase of dendritic spine formation and arborization in hippocampal area and increased axonal sprouting of α-motoneurons is reported after the estrogen treatment (27). At the hippocampal regions the dendritic spines provide larger area for the synaptic contacts. The increase in memory observed elsewhere is suggestive of the synaptic actions of estrogen (27). Many inflammatory cytokines are involved in the successive stages of development of the central and peripheral nervous systems. Unlike the neurotrophins and other classical growth factors, these cytokines signal through receptors that frequently lack intrinsic Trk activity. They are involved in virtually all stages of neurogenesis including the formation of neural tube, differentiation, expression of neurotransmitters, receptors and formation of synapses (35). The regulation of these cytokines by estrogen is suggested.

CONCLUSIONS

The estrogen stimulate/upregulates the expression of mRNA required for Trk-A, NGF, IGF-1a, BDNF etc which in turn regulate the cellular differentiation, proliferation and permeability changes. The Trk-A plays greater role for the signal transduction mechanisms and can directly activate the cellular activity or through the involvement of growth factors such as NGF/ BDNF. Thus the estrogen is a hormone which prevents/slows down the process of degenerative disorders and cerebrovascular diseases and might be the reason for greater longevity of life in females.

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