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Estrogen and Brain Protection

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1. Introduction

In 1931, estrogen was originally discovered as a female sex hormone by Marrian and Butenandt (1931). Estrogen is responsible for maintaining female reproductive organs and functions. Beyond the effects on reproductive organs, the neuroprotective activities of estrogen have been identified by Simpkins et al. (1994) and thereafter by numerous other researchers (Viscoli et al., 2001). The simple classification of the mechanisms of estrogen is genomic and non-genomic processes. The genomic mechanisms of estrogen involve estrogen receptors located in DNA. Upon binding its receptors, estrogen stimulates the synthesis of a variety of neuro-modulatory proteins. A body of evidence indicates that estrogen receptors are not necessary for certain neuroprotective effects of estrogen. For example, estrogen scavenges harmful reactive free radical species (Dhandapani & Brann, 2002), inhibits apoptotic process (a certain type of cell death), and modulates signal transduction, all of which do not require nucleic estrogen receptors. Estrogen's neuroprotective properties may be the end result of well-orchestrated genomic and non-genomic processes.

There are three major forms of endogenous estrogens; 17β-estradiol, estrone, and estriol based on the hydroxyl or ketone ligand attached to the C17 position of the rightmost ring (D ring). Among these estrogens, 17β-estradiol (Figure 1) is the most potent, naturally occurring estrogen. Accordingly, 17β-estradiol has been the subject for neuroprotective properties in major neurodegenerative disorders such as stroke, Alzheimer's disease, Parkinson's disease, and ethanol withdrawal, and thus a topic of this book chapter.

Fig. 1. Chemical structures of 17β-estradiol, estriol, and estrone. Notice that 17β-estradiol has two hydroxyl (OH) groups, estriol has three hydroxyl groups, and estrone has one hydroxyl and one ketone group.

2. Estrogen and ischemia

2.1 Introduction

Stroke is the sudden loss of brain function that is attributed to ischemia which indicates a disturbance in the blood supply to the brain. The affected brain area is unable to function, resulting in an inability to move limbs, understand or formulate speech, or an inability to see the visual field. It is the leading cause of adult disability in the United States and Europe and the second leading cause of death worldwide (Feigin, 2005). Women have a higher risk, due to their longer lifespan and are also more likely to have fatal strokes than men (Bushnell, 2008). Especially women in the 45−54 age range (perimenopause) are reportedly at a higher risk for stroke (Towfighi et al., 2007). This study suggests that declining levels of ovarian hormones perpetuate the risk for this neurovascular disease. The depletion of ovarian hormones also alters stroke outcomes. In postmenopausal women, stroke-associated disability and fatality are worse compared to men (Niewada et al., 2005). If ovarian hormones influence stroke, it is not surprising to see sex differences in the severity of stroke. For instance, a smaller area of tissue death was found in young adult female mice (Park et al., 2006) compared to their age-matched males. Furthermore, the sex difference in stroke infarct (area of tissue death) was abolished when the female mice were ovariectomized, suggesting that ovarian steroids mediate the neuroprotection seen in younger females (Selvamani et al., 2010).

Among ovarian hormones, 17β-estradiol seems to possess greater protective properties than other ovarian hormones. 17β-estradiol mitigated brain inflammation (Suzuki et al., 2009) and blood-brain barrier dysfunction (R. Liu et al., 2005). 17β-estradiol increased the blood flow of the cerebrum (Pelligrino et al., 1998), the ability of neurons to transmit signals (synaptic plasticity), and cognitive function (Sherwin, 2007). By comparison to these protections in animal studies, human studies showed somewhat inconsistent results. In large clinical trials, such as the Women Estrogen Stroke Trial and the Women's Health Initiative, estrogen treatment failed to exert the beneficial effects on stroke incidence (Viscoli et al., 2001). Rather, the clinical study showed that estrogen treatment increased the stroke risk and worsened neurological outcomes in postmenopausal women (Viscoli et al., 2001). Similarly, the Women's Health Initiative study reported an increased risk for stroke following the treatment with estrogen or another female hormone progestin (synthetic progesterone) (Wassertheil-Smoller et al., 2003). Notably, many women in these clinical trials were postmenopausal for several years prior to the hormone treatment. The unexpected negative results might have been due to prolonged estrogen-withdrawal before estrogen was reintroduced (De et al., 2009). Other researchers suggested that differences in the duration of treatment, timing of administration, sex, age, and an ischemia model contributed to the inconsistent outcome of estrogen therapy (J. Li, 2011; Sherwin, 2009).

2.2 Apoptosis

Apoptosis is a type of cell death that normally occurs to replace aged or injured cells with newer cells. However, excessive or defective apoptosis is often present at regions affected by stroke (Dirnagl et al., 1999). Fas is a receptor protein that triggers apoptotic cell death upon the binding of its ligand (Fas ligand). The structure of Fas contains a particular region, called 'death domain'. There is a cytoplasmic protein that favors to associate with the death domain of Fas. Therefore, it is called Fas-associated death domain adaptor protein. When this adaptor protein binds to the death domain of Fas, it subsequently activates

another apoptotic protein, caspase-8. An increasing body of work has shown that Fas and Fas Ligand play an important role in the pathology of ischemic stroke (L. Liu et al., 2008; Rosenbaum et al., 2000). Both Fas and Fas ligand were upregulated by cerebral ischemia in brains of developing, as well as adult mice (Felderhoff-Mueser et al., 2000, 2003). Intriguingly, estrogen significantly reduced the level of Fas and the adaptor protein in mice undergoing post-ischemic stress (Jia et al., 2009). Furthermore, estrogen reduced the downstream apoptotic effectors such as caspase-8 and caspase-3. These findings suggest that estrogen protects against ischemia, in part, through its inhibitory effects on apoptosis associated with Fas (Jia et al., 2009).

Estrogen also protects neurons from ischemia (Petito et al., 1987). Estrogen administered at physiological levels for two weeks before ischemia rescued the hippocampal neurons and ameliorated ischemia-induced cognitive deficits in female rats (Lebesgue, 2009). This study provides direct evidence that estrogen is neuroprotective against ischemia. There are at least two estrogen receptors in the brain, estrogen receptor-α and -β (Shughrue, 2004). Estrogen receptors are intracellular proteins which activate genomic as well as nongenomic effectors in neural cells (Maggi et al., 2004). Selective agonists for estrogen receptor-α or estrogen receptor-β was to were able to spare hippocampal neurons following ischemia. In addition, ICI 182780, a competitive antagonist for both estrogen receptors-α and -β, completely blocked estrogen's protection against post-ischemic stress (Miller et al., 2005). On the other hand, Lebesgue et al. (2009) found that a single injection of estrogen into the brain ventricle immediately after an ischemic event reduced both neuronal death and cognitive deficits. The genomic mechanism of estrogen is typically a slow process because it involves estrogen's receptors in the nuclei, affecting protein synthesis. Therefore, the rapid protection achieved by acute estrogen in Lebesgue's study may indicate the non-genomic effects of estrogen.

Above studies suggest that estrogen exerts neuroprotection against ischemia through its anti-apoptotic property and the mechanisms associated with estrogen receptors.

2.3 Oxidative stress

When ischemic patients receive blood supply (reperfusion), the introducing blood itself can induce significant damage to the brain. The damage is largely attributable to very active harmful oxygen species such as the reactive superoxide anion (Peters et al., 1998; Sugawara et al., 2005). These oxygen species give rise to other damaging oxygen species, for example, hydroxyl ion and peroxynitrite (Mattson et al., 2000). Estrogen contains profound antioxidant properties that mediate its protective effects on neurons. Estrogen directly scavenges free radicals by oxidizing its hydroxyl group attached to the C3 position of A ring (left most ring) through an enzyme, NADPH. The A ring then becomes the phenoxyl radical ring, a certain type of a ring structure containing free radicals. The phenoxyl radical ring is converted to para-quinol ring by scavenging further free radicals like -OH. This para-quinol ring structure finally becomes the original A ring of 17β-estradiol through NADPH (Prokai et al., 2003; Prokai-Tatrai et al., 2008). The important point of this cyclic reaction is that 17β-estradiol is rejuvenated after it absorbs harmful free radicals (Figure 2). Indeed, estrogen attenuated superoxide production in hippocampal neurons after stroke (Q.G. Zhang et al., 2009). In addition to this directly scavenging of free radicals, estrogen upregulates antioxidant enzymes and chelates redox-active metal ions. In terms of estrogen receptor, Zhang et al. (2009) suggested that the antioxidant effect of estrogen is independent of estrogen receptor-α. They found that estrogen deprivation abolished the antioxidant and

neuroprotective effects on the hippocampus without affecting estrogen receptor-α mediated effect on the uterus. At the very least, these findings indicate that estrogen protects against ischemia through antioxidant properties.

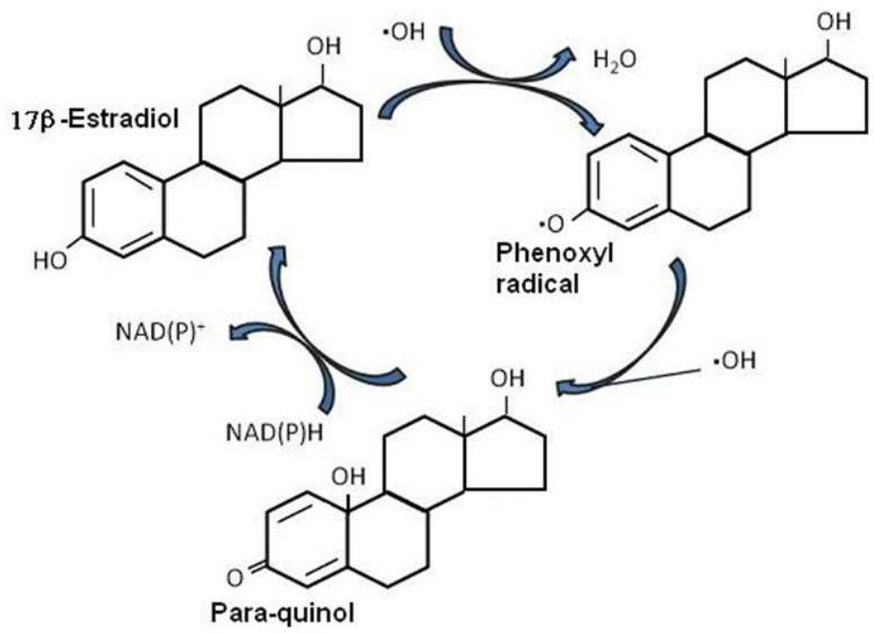

Fig. 2. Schematic illustration of the free radical scavenging antioxidant activity of 17β-estradiol. 17β-estradiol captures •OH, producing the phenoxyl radical and then bioreversible quinol. The quinol is rapidly converted to the parent estrogen via a NAD(P)H-dependent reductive aromatization to perpetuate the antioxidant action. During this process, •OH is detoxified to H_2O (Prokai et al., 2003; Prokai-Tatrai et al., 2008).

2.4 Inflammation\Immune response

Inflammation is a critical event that occurs upon ischemic insults. Post-stroke events include the stimulation and subsequent degeneration of lymphoid organs such as the spleen and thymus (Offner et al., 2009). The activation of these lymphoid organs likely leads to immunocyte translocation into brain, exacerbating the evolving brain ischemia (Ajmo et al., 2008). Proinflammatory genes are rapidly induced in brain after ischemic injury, including genes synthesizing TNF-α (X. Wang et al., 1994), IL-6 (X. Wang et al., 1995), IL-1β (X. Wang et al., 1994), and interferon inducible protein-10 (IP-10) (X. Wang et al., 1998). The subsequent degeneration of lymphoid organs leads to immunodepression. Humans who survive the initial brain insult, may succumb to fatal infection due to the immunodepression (Dirnagl et al., 2007; Meisel et al., 2005).

Estrogen deficiency during menopause is associated with a proinflammatory phenotype, namely 'T cell expansion' in bone marrow that secretes inflammatory proteins such as IL-1, TNF-α, and IL-6 (Pfeilschifter et al., 2002). In a study done by Zhang et al. (2010), estrogen partially restored immune reactivity in ovariectomized females by increasing spleen cell population and cytokine responses (B. Zhang et al., 2010). In agreement, estrogen induced anti-inflammatory cytokines in the spleen after traumatic brain injury (Bruce-Keller et al.,

2007). In lipopolysaccharide-induced brain inflammation, estrogen suppressed both resident microglial activation and the recruitment of peripheral T and B cells (Vegeto et al., 2001). These studies provide empirical evidence that the anti-inflammatory effect of estrogen plays a protective role in immune responses to stroke.

Collectively, cumulative evidence indicates that the convergence of endocrine changes, especially estrogen, impacts the pathophysiology of stroke and ischemic injury. It appears that estrogen protects against ischemia through multiple factors associated with apoptosis, inflammation, redox, and estrogen receptors. Understanding these mechanisms may ultimately contribute to better research and therapeutic strategies for stroke therapy.

3. Estrogen and Alzheimer's disease

3.1 Introduction

Alzheimer's disease is characterized as a gradual failure of memory, cognition, and bodily functions, ultimately leading to death. Although the exact etiology and mechanisms are unknown, the abnormal accumulation of a particular protein, called Amyloid β, has long been proposed as the most likely culprit in the pathogenesis of this disease (Hardy & Selkoe, 2002; Tanzi & Bertram, 2005). In a healthy brain, Amyloid β remains at a steady-state level as a result of the metabolic balance between production of Amyloid β from amyloid precursor protein and removal by cellular uptake and proteolytic degradation (Saido, 1998; Selkoe, 2000). Such a dynamic equilibrium, however, could be altered by genetic or environmental factors that may lead to Alzheimer's disease. It has been hypothesized that Amyloid β is folded into a oligomeric form or a fibrillar (cable-like strings) form (Yamin et al., 2008), both of which are more neurotoxic than Amyloid β itself. Of several different Amyloid β peptides produced, products of Amyloid β-40 and Amyloid β-42 residues are the most common constituents of amyloid plaques, and are widely accepted as the primary trigger for Alzheimer's disease (St George-Hyslop, 2000). In brains with early onset Alzheimer's disease, Amyloid β excessively accumulates. This may be due to the mutations of presenelin genes, which provoke the overproduction of Amyloid β from amyloid precursor protein (Hardy, 2004). In late-onset Alzheimer's disease, which constitutes more than 90% of the disease, the excess accumulation of Amyloid β has been associated with abnormal Amyloid β degrading proteases (Nalivaeva et al., 2008).

Women are more likely to develop Alzheimer's disease after adjusting for age (Andersen et al., 1999). After menopause, the decline of estrogen levels in the brain may render neurons more susceptible to age-related neurodegenerative processes (Coffey et al., 1998). Estrogen therapy, when initiated at the onset of menopause, has reduced the risk or delayed the onset of Alzheimer's disease in women (LeBlanc et al., 2001; Zandi et al., 2002). A recent randomized control trial indicated that estrogen treatment had a beneficial effect on verbal memory in men with mild cognitive impairment (Sherwin et al., 2011 in press). However, clinical studies of estrogen therapy in non-demented and menopausal women have yielded inconclusive results (Craig & Murphy, 2010; Sano et al., 2008). In addition, estrogen administration induced beneficial effects on neuronal function and survival through improving mitochondrial function in healthy neurons (Brinton, 2008). When neurons became unhealthy, estrogen exposure had a detrimental effect (Brinton, 2008). This discrepancy may be due to differences in neurological health, age, hormonal status, the severity of symptoms, the type of menopause (surgical vs. natural), and the type of estrogen compound used (Brinton, 2009). Also, the age when estrogen therapy is initiated, may in part determine the

outcome of estrogen therapy and probably estrogen treatment during the peri-menopause has the highest efficacy (Craig & Murphy, 2010; Genazzani et al., 2007).

In diverse animal models of Alzheimer's disease, estrogen has prevented or delayed the development of Alzheimer's disease pathology in particular Amyloid β accumulation and plaque formation (Carroll et al., 2007; Zheng et al., 2002). Mechanistically, estrogen may regulate the production of Amyloid β and in turn, sustain an improved Amyloid β homeostasis by increasing the metabolism of amyloid precursor protein and destabilization of Amyloid β fibrils (Greenfield et al., 2002; Morinaga et al., 2007). Estrogen's bioenergetic protection may also influence Alzheimer's disease. For instance, estrogen prevented the brain from using alternative fuel sources, such as the ketones (Brinton, 2008, 2009). Aromatase catalyzes the conversion of testosterone to estrogen. Not surprisingly, mice lacking aromatase genes (low estrogen production) showed the loss of hippocampal neurons in response to neurotoxins more severely than wild type mice (Azcoitia et al., 2001), suggesting that estrogen spared those neurons. Indeed, the levels of estrogen and aromatase were significantly reduced in the brains of Alzheimer's disease women (Yue et al., 2005). The view of brain estrogen deficiency as a risk factor for developing Alzheimer's disease pathology is consistent with genetic studies showing an association between the aberration of aromatase gene and the risk for Alzheimer's disease (Iivonen et al., 2004). All these studies suggest that estrogen may have the capacity to interfere with the pathways mediating Alzheimer's disease.

3.2 Estrogen synthesis in Alzheimer's disease

Since estrogen has a potential capacity to control Alzheimer's disease, one therapeutic strategy might be to target the biosynthesis of estrogen. Indeed, numerous studies have tested whether Alzheimer's disease alters the endogenous synthesis of estrogen. While the levels of estrogens were unchanged in the prefrontal cortex of Alzheimer's disease patients (Rosario et al., 2011), the estrogen biosynthetic enzymes such as aromatase and 17β-hydroxysteroid dehydrogenase type 1 were upregulated in the late stages of Alzheimer's disease (Luchetti et al., 2011). Studies using immunohistochemistry showed that aromatase expression was upregulated in astrocytes in later stages of Alzheimer's disease (Azcoitia et al., 2003). Another immunochemistry study also detected an increase in the level of aromatase in the hypothalamic neurons of Alzheimer's patients (Ishunina et al., 2005). The increase was especially profound in the Nucleus basalis of Meynert, a nucleus that is strongly affected in Alzheimer's disease (Ishunina et al., 2005). These findings suggest that during Alzheimer's disease, there is an attempt to increase the biosynthesis of estrogen. The aromatase upregulation may be a defense mechanism of brain areas that undergo neurodegeneration. In support of this notion, the reduced levels of testosterone were found in the aging brain of male and female Alzheimer's patients (Rosario et al., 2011; Weill-Engerer et al., 2002). This seems in line with the idea of a compensatory mechanism, since testosterone is used up after it is locally metabolized into neuroprotective estrogen.

3.3 Amyloid β

Cumulative evidence indicates that estrogen protects against Amyloid β and its toxicity through mechanisms involving Amyloid β degradation and signaling changes. Estrogen deficiency accelerated the formation of Amyloid β plaque in mice (Yue et al., 2005). Estrogen treatment reduced the level of Amyloid β (Jaffe et al., 1994; Xu et al., 1998) and its

availability through enhancing the uptake of Amyloid β by microglia (R. Li et al., 2000). In vitro estrogen treatment inhibited the formation of toxic Amyloid β oligomers (Morinaga et al., 2007). Finally, estrogen activated Neprilysin, the primary enzyme that degrades Amyloid β, thereby facilitating Amyloid β degradation in human neuroblastoma cells (Liang et al., 2010). It is possible that this effect of estrogen is preceded by estrogen's action on amyloid precursor protein. Several studies support this notion that estrogen treatment profoundly decreased the levels of amyloid precursor protein by enhancing the degradation of this precursor through the α- and β-secretase pathways (Amtul et al., 2010). Alternatively, estrogen may reduce available amyloid precursor protein by stimulating the formation of vesicles that uptake this precursor-protein, thereby precluding maximal generation of Amyloid β (Greenfield et al., 2002). These findings suggest another mechanism underlying estrogen's protection against Alzheimer's disease involving Amyloid β degredation (Liang et al., 2010). Estrogen may also protect the signaling function of protein kinases from Amyloid β. For example, Amyloid β oligomer inhibited the activity of calcium/calmodulin-dependent protein kinase II and extracellular signal-regulated kinase in a manner ameliorated by estrogen treatment (Logan et al., 2011). In agreement with the protective effect of estrogen on protein kinase, Szego et al. (2011) reported that the function of protein kinases correlated with avoidance learning behavior. In that study, the treatment with Amyloid β oligomers impeded the learning in a manner that was protected by estrogen. These studies suggest a diverse mechanism by which estrogen protects against Amyloid β as an attempt to cope with Alzheimer's disease.

3.4 Neuroinflammation

The neurotoxicity of Alzheimer's disease is in part mediated by inflammatory processes (McGeer et al., 2006). Glial cells (non neuronal cells) are involved in this process such that Amyloid β activates glial cells to produce pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α. Activated glial cells have the potential to produce large amounts of reactive oxygen species/nitrogen species by various mechanisms (Zhu et al., 2007). Activated astrocytes produced excessive nitric oxide, which reacted with superoxide to form harmful peroxynitrite (Smith et al., 1997). Excess nitric oxide synthetase was also detected in astrocytes surrounding plaques in Alzheimer's disease (Luth et al., 2001). Estrogen interfered with this process by limiting astroglial cells and inhibiting chronic inflammation associated with Alzheimer's disease (Vegeto et al., 2003). The anti-inflammatory effects of estrogen were shown in a primary culture study; estrogen treatment decreased the expression of pro-inflammatory molecules, such as TNF-α and IL-1β, as well as nitric oxide synthase and cyclooxygenase-2 in astrocytes (Valles et al., 2010).

Vegeto et al. (2006) conducted a study further supporting the protective effects of estrogen on inflammation associated with Alzheimer's disease. They used the APP23 mouse model, a model of Alzheimer's disease that creates chronic neuroinflammation resembling that in Alzheimer's disease. They found that the number of plaques associated with reactive microglia was increased with age (Vegeto et al., 2006). Interestingly, ovariectomy accelerated microglial activation surrounding Amyloid β plaques, whereas estrogen replacement delayed this process. In parallel, they showed that estrogen reduced the expression of inflammatory mediators, such as monocyte chemoattractant protein-1, macrophage inflammatory protein-2, and TNF-α. That study indicates that microglia is a direct target of estrogen action in the brain. All of these findings reinforce the hypothesis

that inflammatory mechanisms significantly contribute to the pathogenesis of Alzheimer's disease and support the use of estrogen in the fight against Alzheimer's disease.
Collectively, animal studies on Alzheimer's disease have shown beneficial effects of estrogen through inhibiting the synthesis of amyloid β, facilitating its metabolisms, modulating protein kinases, and inhibiting inflammatory pathways. Human studies on the effects of estrogen on Alzheimer's disease have resulted in both positive and negative effects. It is unclear what causes the inconsistent results. Nevertheless, it seems clear that estrogen influences Alzheimer's disease pathology, if not etiology. How to identify and adjust factors underlying the discrepancies seems to be an essential task.

4. Estrogen and Parkinson's disease

4.1 Introduction

Parkinson's disease is the second most common neurodegenerative movement disorder. It is mainly characterized by the slow and gradual emergence of motor disorders such as tremor, rigidity, bradykinesia, and postural instability (Lang, 2007). Parkinson's disease is less prevalent in women than in men by an approximate 2:3 ratio and evidence suggests that estrogen influences the onset and severity of disease-associated symptoms (Currie, 2004; Shulman, 2006). Women with Parkinson's disease tend to have an earlier menopause, are more likely to have undergone hysterectomy, and used estrogen therapy less frequently than control subjects (Benedetti et al., 2001). Ragonese et al. (2004) suggested that factors reducing estrogen contribute to the development of Parkinson's disease (Ragonese et al., 2004). This was recently supported by the Observational Study of the Women's Health Initiative (WHI-OS) that employed 83,482 women. The study showed association between the number of women with longer fertile lifespan and a reduced risk of Parkinson's disease (Saunders-Pullman et al., 2009). In another human study, women with Parkinson's disease were less likely to have used postmenopausal estrogen therapy (Currie et al., 2004), suggesting that estrogen produces a beneficial effect on Parkinson's disease.

4.2 Dopamine neurotransmission

Dopamine is a neurotransmitter that has multiple functions in the brain such as cognition, reward, mood, and voluntary movement. The substantia nigra is a brain area that governs these functions. So far, this neurotransmitter has been the major player in Parkinson's disease such that dopamine synthesizing neurons are progressively depleted in the substantia nigra of Parkinson's patients (Emborg, 2004). Aberrant dopamine transmission is implicated in Parkinson's disease, particularly because the symptoms are ameliorated by a drug which increases dopamine signaling. Dopamine is actively eliminated from the extracellular space by astrocytes and neurons through dopamine transporters. Afterwards, dopamine is either recycled into vesicles or metabolized. In previous studies, estrogen increased the availability of dopamine by inhibiting uptake and by decreasing the affinity of the transporter for dopamine (Disshon et al., 1998). Estrogen also increases the synthesis of dopamine in the substantia nigra and the release of dopamine from axon terminals. In rodents and in neuronal cell culture studies, estrogen protected dopaminergic neurons from injury (B. Liu & Dluzen, 2006; Arvin et al., 2000). Given this, the beneficial effect of estrogen on Parkinson's disease may be mediated through estrogen's action on dopamine.
Studies have further identified how estrogen acts on the dopamine system. Estrogen modulates the development of dopaminergic neurons and neurotransmission (Bourque,

2009) by promoting neurite plasticity (Beyer et al., 2000). These effects are either mediated through a direct action on dopaminergic neurons or interactions with local astroglia (Ivanova et al., 2001, 2002). Alternatively, estrogen may act on genetic levels to modulate dopamine. For instance, estrogen regulates dopamine gene expression by activating transcriptional factors (DonCarlos et al., 2009). Estrogen also exerts non-genomic membrane effects, interaction with neurotransmitter receptors, and ionic channel regulation (Garcia-Segura et al., 2009). These studies suggest that estrogen protects against Parkinson's disease through genomic and non-genomic effects on the dopamine system.

Dopamine transporters mediate the uptake of dopamine from synapses to presynaptic vesicles, thereby restoring depleted vesicular dopamine levels (Jourdain et al., 2005). Estrogen stimulated dopamine uptake by nerve cells through neuronal dopamine transporter (D'Astous et al., 2004). On the other hand, estrogen decreased astroglial dopamine uptake, increasing the available levels of synaptic dopamine. This allowed more synaptic dopamine to be taken up by neurons. These studies suggest a few important points: first, not only dopamine neurons but also nigrostriatal astroglia contribute to the metabolic processes of dopamine (Karakaya et al., 2007); second, astroglia are implicated in estrogen-transmitted neuroprotection during dopamine neuro-degeneration (Morale et al, 2006), and finally, as the complementary action of estrogen on neurons, astrocyte and microglia may represent a potential pharmacological target for Parkinson's disease management (Vegeto et al., 2008).

4.3 Oxidative stress

In the process of dopamine being catalyzed by monoamine oxidase, a large amount of reactive oxygen species is produced, resulting in cell death (Hastings et al., 1996; Luo et al., 1998). In addition, dopamine aldehyde generated in the oxidative deamination reaction is 1000-fold more toxic than dopamine (Burke, 2003). Dopamine neurons in Parkinson's disease become vulnerable to oxidative stress (Dexter et al., 1989; Sian et al., 1994) perhaps due to lower levels of glutathione (endogenous antioxidant) than other cell types.

The brain has a predominant defense mechanism against superoxide radicals through antioxidant enzymes such as superoxide dismutase. Studies have demonstrated that superoxide dismutase is implicated in dopamine and Parkinson's disease. Mutant mice that over-expressed or lacked superoxide dismutase were more resistant to (Przedborski et al., 1992) or vulnerable to (Andreassen et al., 2001; J. Zhang et al., 2000) dopamine neurotoxin than wild type mice, respectively. The expression of superoxide dismutase was upregulated in the substantia nigra following the dopamine neurotoxin insult, yet the loss of dopaminergic neurons still occurred (Tripanichkul et al., 2007). These results suggest that there is an attempt to combat the oxidative stress in nigral neurons but not sufficient to spare neurons. The implication of superoxide dismutase in the antioxidant effect of estrogen has been shown in a study done by Tripanichkul et al. (2007). In that study, estrogen treatment increased the expression of superoxide dismutase in the substantia nigra of animals that were treated with the dopamine neurotoxin. This study suggests that estrogen up-regulates superoxide dismutase in critical brain areas, thereby exerting protection against dopamine neurotoxin or Parkinson's disease.

4.4 Neuroinflammation

Neuroinflammation and microglial activation are often seen in Parkinson's disease (McGeer et al., 1988; Hunot et al., 2003) and anti-inflammatory drugs reduce the risk of this disease

(H. Chen et al., 2003; Wahner et al., 2007). A positive correlation was found between antecedent brain injuries, such as trauma or exposure to infectious agents and the development of Parkinson's disease (B. Liu et al., 2003). This correlation implies that the brain inflammatory response to these noxious events, and specifically microglial activation, plays a critical role in Parkinson's disease. In support of this view, researchers have detected pro-inflammatory molecules (e.g. TNF-α) and excessive reactive oxygen species in the nervous system of Parkinson's disease patients (Hunot et al., 1996; Knott et al., 2000). The inflammatory molecules seem to amplify neuroinflammation as well as neuro-toxicity, ultimately leading to a slow and irreversible destruction of dopaminergic neurons. Using estrogen receptor-null mice, several studies have demonstrated that estrogen receptor-α is involved in the anti-inflammatory activity of estrogen (Dubal et al., 2001; Vegeto et al., 2003). Although estrogen receptor-β is expressed widely in brain, it does not seem to mediate the protective effect of estrogen. Or the effects of estrogen receptors on inflammation depend on the brain area (Harris et al., 2003). Whether or which receptor mediates estrogen's protection against inflammatory response still remains unclear.

Collectively, the protective effects of estrogen on Parkinson's disease appear to involve dopaminergic neuroprotection, anti-oxidant activities, anti-inflammatory activities, and estrogen receptors. Considering that Parkinson's disease is more prevalent in male than female patients, how these effects of estrogen can be implemented to clinical usages is an open question. At the very least, estrogen can be used as an interventional tool for a new mechanistic insight into this neurodegenerative disease.

5. Estrogen and ethanol withdrawal

5.1 Introduction

The distress of alcohol (ethanol) withdrawal is initiated by abruptly removing the inhibitory stimulus of ethanol and thus, is associated with rebound hyper-excitatory stimuli. In general, the overt initial signs of ethanol withdrawal include anxiety, ataxia, muscle incoordination, seizures, coma, and even death (American Psychiatric Association, 2000). While repeating unsuccessful attempts to quit heavy drinking, the brain undergoes random exposure to ethanol and withdrawal, damaging cellular and neuronal integrity (Wober et al., 1998).

The neuronal activity of the brain tends to be hyper-excitable during ethanol withdrawal due to an increase in the level of glutamate, a major excitatory neurotransmitter (Rossetti & Carboni, 1995). This can result in neuronal damage to vulnerable brain areas such as the cortex, hippocampus, and cerebellum. In addition to this well known glutamate neurotransmission, ethanol withdrawal perturbs the homeostasis of redox balance and signaling mechanisms. For instance, ethanol withdrawal provokes the intense generation of reactive oxygen species and activates stress-responding protein kinases (Jung et al., 2009). In addition, ethanol withdrawal inflicts mitochondrial membranes/membrane potential and suppresses mitochondrial enzymes such as cytochrome c oxidase, all of which impair fundamental functions of mitochondria (Jung et al., 2007, 2009). In our recent study, brain aging occurred earlier in ethanol withdrawn animals than in control-diet animals (Jung et al., 2010). These studies indicate that mal-managed ethanol withdrawal can clearly provoke neurodegenerative disorders.

5.2 Oxidative stress

Chronic ethanol consumption and ethanol withdrawal both generate oxidative free radicals and subsequent lipid peroxidation (Nordmann et al., 1990; Montoliu et al., 1994). Lipid peroxidation reflects the interaction between oxygen and the polyunsaturated fatty acids of membrane lipids, generating deteriorating breakdown products. Since the brain consists of a high content of unsaturated membrane lipids, it is a preferred target of both reactive oxygen species and ethanol (Hernandez-Munoz et al., 2000). Ethanol withdrawal-induced oxidative stress was associated with an increase in glutamatergic neurotransmission (Rossetti & Carboni, 1995), the upregulation of calcium channels, and the accumulation of intracellular calcium (Rewal et al., 2005). The functional consequence of prooxidant ethanol withdrawal is shown in several animal and human studies. For instance, enhanced reactive oxygen species concurred with ethanol withdrawal-induced seizure activity in rats (Vallett et al., 1997). The cerebrospinal fluid of patients who underwent ethanol withdrawal showed higher concentrations of excitatory neurotransmitters and oxidative markers (Marotta et al., 1997; Tsai et al., 1998) than control subjects. Higher levels of lipid peroxide and lower levels of superoxide dismutase (antioxidant enzyme) activity were also seen in those patients (Tsai et al., 1998). These studies indicate that the redox imbalance has a causative relationship with ethanol withdrawal insults.

If ethanol withdrawal is a prooxidant stimulus, estrogen treatment should be able to mitigate the stress through its antioxidant property. Our recent findings essentially confirmed the hypothesis using the in vivo and in vitro model of ethanol withdrawal. Estrogen treatment mitigated reactive oxygen species generation, lipid peroxidation, and protein oxidation (Jung et al. 2004, 2006). Estrogen protection against the prooxidant effect of ethanol withdrawal may involve glutamate transmission because glutamate-induced oxidative stress is attenuated by estrogen (Behl & Manthey, 2000) and the quinol derived from estrogen (Prokai et al., 2003). It is also possible that estrogen elevates the levels of endogenous antioxidants, such as glutathione, so that a favorable redox potential for an antioxidant environment is created (Prokai et al., 2003). Since oxidative molecules are generated mainly from mitochondria, these studies suggest that the antioxidant protection of estrogen against ethanol withdrawal is linked to the mitoprotective activity of estrogen.

5.3 Mitochondria

Indeed, the mitoprotective effects of estrogen are interactive with the antioxidant effect by virtue of the fact that mitochondria are the major source and target of oxidative free radicals. The mitoprotective effect of estrogen has been extended to the ethanol withdrawal model in our recent study in which ethanol withdrawal provokes the oxidation of mitochondrial proteins in rats, in a manner mitigated by estrogen. Since cellular energy ATP is mainly generated in mitochondria, it is not surprising that estrogen protects against mitochondrial respiratory deficit during ethanol withdrawal (Jung et al., 2011). Presumably, estrogen plays a role in alleviating the oxidative burden in mitochondria, thus increasing mitochondrial respiration efficiency (J.Q. Chen & Yager 2004; Jung et al., 2011).

5.4 Signaling pathways

P38 is referred to as a stress-activated protein kinase because it is often activated in response to a variety of stress. A transient, moderate activation of P38 normally occurs in association

with cell survival or differentiation. However, excess activation generally correlates with pathological conditions (Barca et al., 2008). P38 is activated upon phosphorylation (Moriguchi et al., 1996) and thus, pP38 is often measured as an indicator of P38 activation. A previous study reported that the P38 inhibitor SB203580 attenuated ethanol-induced cell death (Ku et al., 2007), suggesting that P38 activation mediates cytotoxic ethanol. Acute ethanol treatment led to P38 activation (Norkina et al., 2007) and augmented endotoxin-induced pP38 levels in a manner attenuated by P38 inhibitor in human monocytes (Drechsler et al., 2006). Recently, we have demonstrated that estrogen protected against ethanol withdrawal-induced hyperactivation of P38, suggesting that there is a crucial link between estrogen, P38, and ethanol withdrawal (Jung et al., 2010). In that study, middle-age female rats (12-15 month old) were more vulnerable to the ethanol withdrawal-induced P38 activation than young or older rats (Jung et al., 2010). Importantly, chronic estrogen treatment abolished the age difference in P38 activation. These studies indicate that ethanol withdrawal interferes with signaling pathways, including P38, in a manner that depends on age and that is protected by estrogen.

In conclusion, findings from our and others' laboratories suggest that ethanol withdrawal distress is more than a neurotransmitter disorder. It is attributed to the perturbation of redox balance, protein kinase signaling, and mitochondria, all of which can be mitigated by estrogen treatment. Understanding the interaction between ethanol withdrawal and estrogen may contribute to the improvement of the pharmacological treatment of ethanol withdrawal.

6. Conclusion

There are some lingering controversies in the neuroprotective effects and underlying mechanisms of estrogen. Nevertheless, numerous studies indicate the profound neuroprotective effects of 17β-estradiol on neurodegenerative diseases including ischemia, Alzheimer's disease, Parkinson's disease, and ethanol withdrawal syndromes. Diverse mechanisms mediate estrogen's protection through neurotrophic, neuroprotective, antiapoptotic, and antioxidant activities. Furthermore, estrogen exerts its neuroprotection through inhibiting inflammation and preserving the homeostasis of neurotransmitters. Estrogen receptors appear to mediate some of estrogen's protection, although it is not yet entirely clear whether it is estrogen receptor-α, estrogen receptor-β, or membrane estrogen receptors. At the mitochondrial level, estrogen inhibits peroxidation, eliminates reactive oxygen species, and maintains the homeostasis of mitochondrial membranes/respiration.

The extent to which estrogen can actually ameliorate neurodegenerative diseases in clinical settings may depend on well controlled systematic clinical studies that are largely absent in current situations. Nevertheless, it may be a matter of time that this amazing molecule alleviates the human burden of devastating brain diseases.

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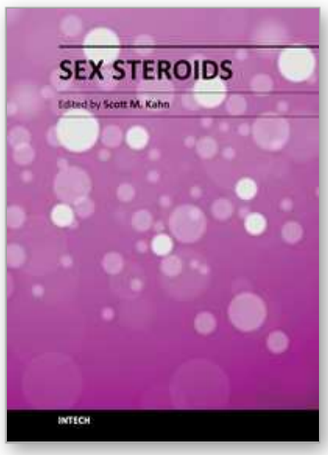

Sex Steroids

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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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