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ESTROGEN AND BRAIN: SYNTHESIS, FUNCTION AND DISEASES

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1. ABSTRACT

This review summaries recent evidence from clinical and basic science studies on estrogen central nervous system. For decades, estrogen was thought of only as a "sex hormone" and plays a fundamental role in regulating behavioral and physiological events. In recent years, accumulated evidence shows that estrogen also plays very important roles in the brain. Recent basic science studies show that estrogen treatment decreases the neuronal response to various forms of insult through the regulation of both estrogen synthesis and estrogen receptor expression in the brain. Some clinical evidence also suggests that estrogen deprivation might be implicated as a risk factor in various neurodegenerative diseases. Estrogen may play a neuroprotective role through estrogen dependent alterations in cell survival, enhancement of synaptic transmission and neurogenesis. Some of the mechanisms underlying these effects are independent of the classical nuclear estrogen receptors and involve direct modulation of neurotransmitter receptor function, or anti-oxidant activities of estrogen. It is controversial whether estrogen is indicated in the prevention or treatment of various brain disorders such as Alzheimer's disease. The conflicting findings suggest that several variables, including age, estrogen dose and formulation, the length of treatment, may determine whether the potential benefits of estrogen treatment would outweigh the associated risks.

2. INTRODUCTION

Although clinical evidence has suggested for many years that estrogen affects mood, cognition, and mental state, the knowledge about estrogen action in central nervous system (CNS), especially in human brain, has been very limited. During the past 10 years, the discoveries of new estrogen receptor (ER), ER-β(1, 2) and new isoform of ERs (3-5), as well as characterization of brain isoform of estrogen synthase aromatase (6), opened new possibilities and interests in the diverse actions of estrogen in the brain The aim of this review is to give an overview of what is known about estrogen syntheses, ERs and their functions in the human brain and the influence of estrogen in neurodegenerative diseases are also reviewed.

3. SYNTHESIS OF ESTROGEN IN BRAIN

Estrogens are synthesized in a number of human cells and tissues, such as ovarian granulose cells, placental syncytiotrophoblast, adipose tissue and brain. Aromatase, the enzyme responsible for the conversion of testosterone to estradiol, is found in a wide variety of both male and female tissues and organs and is also present in the brain (7). As shown in Figure 1, in non-pregnant women, estrogens are primarily synthesized in the ovaries, using cholesterol as a precursor. Various enzymes are involved in the formation of estrogens, namely steroid sulfatase, 17β-hydroxysteroid dehydrogenases (17β-HSDs), 3β-hydroxysteroid dehydrogenases, and aromatase.

However, in both men and women, estrogen are also synthesized locally in non-endocrine tissue such as the brain by conversion androgens to 17β-estradiol (the most potent and dominant estrogen in human) due to the present of the aromatase cytochrome P450 enzyme (Figure 2) Estrogen is formed locally in neural tissue from precursor androgens by aromatase and might be only biologically active at the brain level in a paracrine or interacrine fashion (8). Before menopause, the ovaries are the principal source of systemic estrogen for non-pregnant women. After menopause, other sites of estrogen biosynthesis become the major source of estrogen and these sites include adipose tissue, skin, bone and brain (9, 10).

The long-term health consequences of estrogen decline after menopause involve bone loss, increased cardiovascular disease, and cognitive impairment (11). However, it is unclear if the occurrence of all of these diseases in postmenopausal women is directly due to the reduction of circulating estrogen levels, possible changes in local estrogen biosynthesis in some tissue, such as bone, heart and brain, or both.

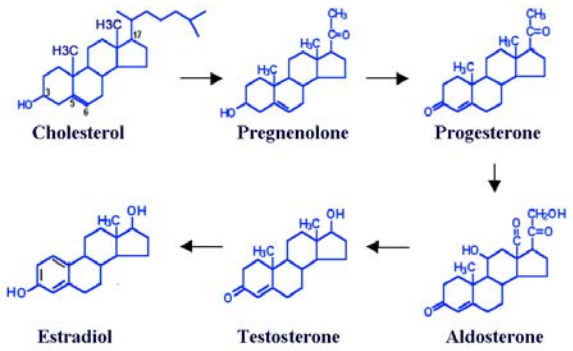

Figure 1. Estrogen synthesis in ovarian.

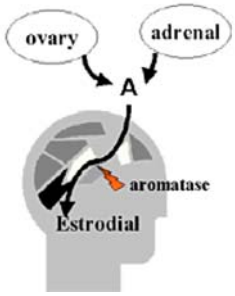

Figure 2. Extra-ovarian estrogen formation in women. Estradiol in women is either directly secreted by the ovary or produced in extra-ovarian sites (skin, adipose tissue and brain). The principal substrate for extra-ovarian aromatase activity in women is androstenedione (A). Androstenedione is converted by aromatase to estrone and further converted to estradiol by 17□-HSD type 1 activity in these peripheral tissues. Thus, extra-ovarian aromatization is the major source for circulating estrogen in the postmenopausal period or during ovarian suppression.

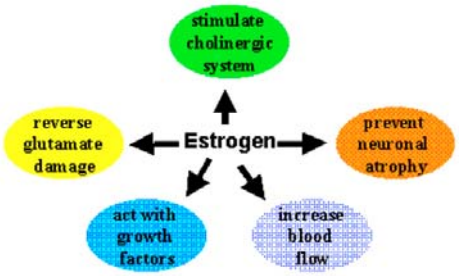

Figure 3. Estrogen actions in the brain.

Aromatase is the key enzyme of estrogen synthesis in the brain and distributed uniformly throughout the brain. It is detectable in neurons of discrete hypothalamic and limbic structures as well as hippocampus, mid-brain and different neocortical regions (12, 13). The mRNA expression of aromatase is higher in the temporal than in the frontal neocortex in human brain and higher aromatase activity was found in cerebral cortex than in subcortical white matter (12, 14). It is unclear that whether the specific brain regional expression of aromatase is related to the function of the brain. It has been reported a sex difference in the number of neurons which express both aromatase and ER (Ar-ER) indifferent regions of the musk shrew brain (15). Females have more Ar-ER neurons in the medial preoptic area and males have more in the bed nucleus of the stria terminalis the bed nucleus of the stria terminalis In addition, in the medial preoptic area of both sexes, a distinct nucleus of aromatase containing neurons which was devoid of ER immunoreactivity was noted. Taken together, these data suggest that estrogen produced in brain might act by binding to ER in neurons other than those that contain aromatase enzyme.

4. ESTROGEN FUNCTIONS IN BRAIN

For decades, estrogen was thought of only as a "sex hormone" and plays a fundamental role in regulating behavioral and physiological events. In recent years, increasing evidence indicates that estrogen also plays a critical role in the central nervous system. Recent researcher is showing that estrogen is not only affects hypothalamus in where reproductive actions were well controlled, but also affects structures like hippocampus and even cerebellum in where higher cognitive function, fine motor skills and mood are regulated.

As indicted in Figure 3, estrogen plays multi functions in the brain via various cellular and molecular mechanisms. These functions involve eliciting a selective enhancement of the growth and differentiation of axons and dendrites in the developing brain, modulating neurotransmitter production and release, enzyme activity, membrane potential, dendritic arborization, and synaptogenesis (16, 17). For example, estrogen affects the basal forebrain by regulating the cholinergic neurons that project to cerebral cortex and hippocampus, in where they play an important role in cognitive function. Studies of estrogen effects on cholinergic system indicate that estrogen depletion could induce a reduction of choline acetyltransferase (ChAT) activity, a decline in choline uptake in frontal cortex and hippocampus as well as a decline in learning performance in animals. Estrogen treatment could increase ChAT activity in the brain as well as prevent the estrogen deficiency-induced reduction of learning performance (18, 19). Furthermore, one of the most important actions of estrogen in the brain is regulation of synapses formation and act as neuronal trophic factor. There are numbers of studies indicate that estrogen treatments increase dendritic spine density on CA1 pyramidal neurons in hippocampus and numbers of synapses on multiple synaptic boutons between neurons not previously connected (20-22). As most of the molecules in the brain, estrogen does not act alone. Recent evidence indicates that estrogen-induced synapses formation in the CA1 pyramidal neurons might be N-methyl-D-aspartate (NMDA) receptor dependent. Estrogen treatments increase the density of NMDA receptor in the CA1 region of hippocampus and the activation of NMDA receptor by glutamate is an essential factor in causing new synapses formation (23, 24). In addition, estrogen is also reported to have neuroprotective effects in the brain. For example, estrogen depletion caused by ovariectomy or natural menopause leads to decline of declarative memory and motor coordination and that were prevented by estrogen therapy (25, 26). Furthermore, estrogen appears to be able

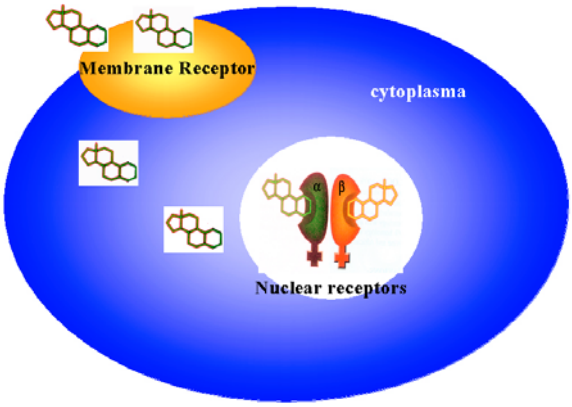

Figure 4. Estrogen and estrogen receptors.

to protect neurotoxic agents-induced brain damage. Recent *in vitro* experimental evidence shows that of estrogen can protect against cytotoxicity caused by glutamate, free redicals, β-amyloid protein and HIV coat protein (27-31). In brain, cerebral blood flow is enhanced by estrogen through various mechanisms, such as vasodilation mediated by production of nitric oxide synthase (32, 33), regulation of coagulation and thrombolysis (34, 35), and reduction of blood total cholesterol and low-density of lipoprotein (36, 37). Furthermore, *in vivo* studies of estrogen-mediated neuroprotection have also reported successful reduction of lesion size by estrogen in rats subjected to meddle cerebral artery occlusion (38).

5. ESTROGEN AND ESTROGEN RECEPTORS

As a classical steroid hormone, estrogen regulates gene expression through interaction with its two nuclear receptors: ERα and ERβ. In brain, both receptors are expressed in neurons, astrocytes, microglia and oligodendrocytes. These two receptors share 97% homology in the DNA domains, 60% homology in the ligand binding domains and no homology in their N-terminal regions (39). These two receptors also are different in expression pattern and ligand specificities (1, 40). It has been suggested that these two receptors are complementary functionally located. For example, most of neurons in the arcuate nucleus, cortical amygdaloid nuclei and ventromedial nucleus, only express one estrogen receptor, while neurons from other brain regions, including bed nucleus of the stria terminalis, medial amygdala and preoptic area contain both receptors (40-43). Furthermore, the major ER located in bone, the immune system and the brain is ERβ while ERα seems to be the major ER in the uterus and liver (44). The differential function of ERα and ERβ is also supported by gene knockout studies (45-47). Most interesting, recent study suggested that a physiological role of ERβ is to modulate ERα-mediated gene transcription, supporting a "Ying Yang" relationship between ERα and ERβ in mice (48). In light of overlap in expression for both estrogen receptors in brain, it is unlikely that the protective effects of estrogen on neuronal cell death are mediated though one estrogen receptor alone. This issue is further supported by the observation that ERα and ERβ can exist and act not only as homodimers but also as heterodimers (4, 49), suggesting a functional interaction between ERα and ERβ.

Although the traditional view of estrogen action is mediated by nuclear receptors, some estrogenic effects cannot be attributed to either ERα or ERβ. Recently, using electron microscope technology and gene transfection method, studies suggest that estrogen receptors also express in non-nuclear locations (50, 51). Extensive new membrane-associated estrogen receptors have been reported during past few years. For example, an estrogen binding protein, pER, is identified from mouse liver, with a distinct binding moiety from classical steroid hormone receptors (52). ERγ, a new estrogen receptor, is also cloned from a teleost fish, has not found in other species (53). A novel and unique plasma-membrane-associated estrogen receptor, ER-x, is also identified in mouse recently (54).

Along with this discovery, studies also demonstrate the non-nuclear ERs (membrane-associated ERs) can couple to second messenger system and generate rapid actions in the nervous system (55-57). For example, estrogen has been shown to rapidly active adenylate cyclase, increase intracellular calcium, activate phospholipase C to generate inositol 1,4,5-trisphosphate and diacyglycerol, stimulate nitric-oxide synthase to generate nitric oxide, and activate the extracellular regulated mitrogen-activated protein kinase (MAPK) pathway (58). These rapid actions of estrogen have also been shown to play an important role in neuronal differentiation, which is very important during neurodevelopment.

6. ESTROGEN AND NEURODEGENERATIVE DISEASES

6.1. Estrogen and Alzheimer's disease

Alzheimer's disease (AD) is the most common type of progressive dementia in the elderly. The pathological characterizations of AD are the deposition of extracellular Aβ plaques, accumulation of intracellular neurofibrillary tangles, and neuronal cell loss (28). The prevalence of AD after age 65 is roughly 2-3 times higher in women than in men (59, 60). Early clinical and experimental studies have demonstrated that estrogen replacement therapy in postmenopausal women decreases the probability of developing AD (61-68, 8).

After menopause, a declining estrogenic stimulus, either from dramatically reduced levels of circulating estrogen or from decreased aromatizable androgen levels in the female, might make estrogen target neurons in the brain which are more susceptible to age- or disease-related processes such as AD. In fact, recent evidence strongly suggests that estrogen deficiency may be a risk factor that contributes to the etiology of AD in women (68, 69). The relationship between serum estrogen level and AD is unclear. Women with AD show reduced or elevated serum estrogen concentration (70, 71). Regardless the controversial findings in serum estrogen level in AD, our recent study found for the first time, a reduction of brain estrogen concentration in 9 female AD patients compared to 10 aged

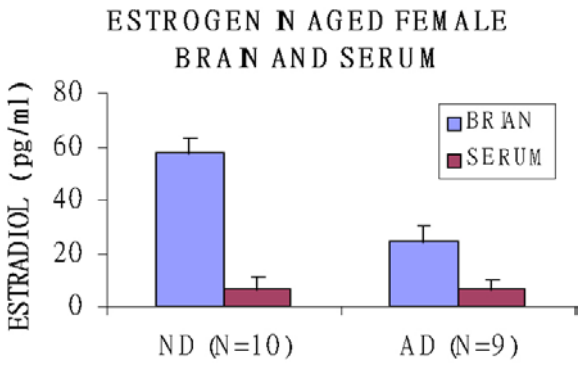

Figure 5. Estrogen level in serum and brain from female AD patients and age-matched female non-dementia controls.

matched non-dementia female controls (Figure 5). In addition to the brain estrogen deficiency in AD, we also found a low expression of ERβ in the AD patients. Our data suggest that an impairment of estrogen in the brain might contribute the high risk of AD development in menopausal women. In addition to women having a higher prevalence of AD, women with a history of myocardial infarction are five times more likely to develop AD than those without such a history (59). In contrast, myocardial infarction is not a risk factor for the development of AD in men, suggesting that the greater risk observed in women is not due to the underlying vascular disease.

Women have higher risk of developing AD. A community-based study by Fratiglioni on aging and dementia (72), which is part of the Kungsholmen project on a Stockholm population of 1500 women, has shown that incidence of AD continues to increase with age, but only among women after the age of 79. In this group, older women have the higher incidence rates of AD. The risk of AD increases in this group by 60% for each five-year increment in age. The age-adjusted relative risk for women is 1.9 for dementia and 3.1 for AD. Being a woman increases the relative risk of AD by a factor of almost 3. Preliminary data from the Stockholm study suggest that early menopause may also represent a risk factor of incidence in women. Similar results have been reported from other epidemiological studies in the United Kingdom and The Netherlands. These results answer positively to the question of a gender-related risk of developing AD, and ask a new question of whether or not early menopause and estrogen replacement therapy (ERT) could influence the disease process itself.

Despite of the current report from the Women's Health Initiative Studies, numerous studies from humans and animal models suggest that estrogen exert a beneficial action in preserving cognitive function. In either surgically induced or natural postmenopause, estrogen has been shown to help improve specific aspects of cognitive function (73). Similarly, from studies in ovariectomized rodents, estrogen has also been shown to have significant beneficial effects on learning and memory (74).

In addition, reduced estrogen levels in such animals are also accompanied by morphological, neurochemical, and molecular deficits such as structural alterations in hippocampal dendritic spines, decrease in NGF and BDNF mRNA expression (75, 76), and reduced cholinergic function (77). These changes have been implicated in the etiology or progression of AD. The specific pharmacological effects of estrogen that may protect the brain against AD pathology are reported. As shown in Figure 3, estrogens have multiple and selective cellular targets in the CNS such as cholinergic synapses, hippocampal neurons, or generally, neurons endowed with estrogen receptors. Theoretically, their effects could be extend from protecting neurons from glucocorticoid damage under stress, to increasing cerebral blood flow and preventing vascular dementia, to promoting secretion of the amyloid precursor protein (APP), which might result into an anti-amyloidogenic effect, to increasing expression of nerve growth factors that may regenerate nerve processes (78).

Estrogen replacement therapy exerts a neuroprotective effect against various toxic insults (28-30, 79). Recent studies indicate that estrogen is neuroprotective against NMDA-mediated neurotoxicity in the rat hippocampus (80) and prevents apoptosis in cardiac myocytes and U937 cells (74, 81) via reduction of caspase-3 and NF-□β transcription factor activities. Furthermore, estrogen is found to reduce neuronal generation of Aβ in cultured neuronal cells (27), attenuate Aβ-induced energy impairment in rat brain (82), protect against Aβ-induced cytotoxicity *in vitro* (83), and enhance the Aβ clearance in AD microglia (84). Furthermore, clinical data suggested that estrogen replacement might also facilitate other treatments used or being developed for the treatment of AD. For example, in clinical trials with Tacrine, an anticholinesterase drug currently in use for the treatment of Alzheimer's disease, a greater efficacy of this drug was seen in women receiving estrogen replacement therapy relative to women who were not (84). These observations further emphasize the importance of estrogen in the brain and underscore its ability to affect a wide variety of systems in the central nervous system.

Several studies have shown that neurons in the central nervous system are endowed with high affinity intranuclear estrogen receptors (86). Therefore, the effect of estrogens on the brain may reflect a direct action of the hormone on nerve cells. In addition, testosterone can be converted intraneurally in the brain to 17-β-estradiol, thus providing an additional source of the hormone.

Although several early case– control studies did not detect an effect of ERT in reducing the risk of dementia, more recent studies (both case control and cohort) seem to indicate a reduced risk of AD. Effects of estrogens on behavior, cognition, and mood have also been observed in cognitively normal young women treated with ERT after hysterectomy and oophorectomy. The literature on ERT treatment consists mainly of epidemiological studies and case series, with very few and small-randomized placebo-controlled pilot studies; therefore, one

has to be cautious to infer specific therapeutic effects from current data. The longest study (almost 40 years) on the process of aging in humans is the Baltimore Longitudinal Study Aging of the National Institute of Aging (NIA) including 2000 subjects who had taken nonsteroidal anti-inflammatory drugs as well as estrogens (Data not shown). Recent results derived from this NIA study indicate that estrogens may be as effective as nonsteroidal anti-inflammatory drugs in reducing the risk of AD in women (68). The estrogen study involved nearly 500 women who taken ERT during a 16-year period. Only 4% of these subjects developed AD compared with 10% of those who had not taken ERT, a risk reduction of more than 50%. The women of the NIA study used a wide variety of oral and transdermal estrogens at different dosages. Only randomized prevention trials with different estrogens different dosages and duration of treatment could provide more precise information on therapeutic applications of these hormones. Two multi-center studies are now in progress in the United States on 120 and 8000 women, respectively, treated with estrogens. These trials might provide more definite information on specific effects of estrogens on dementia and possible neuroprotective effects (87), in the most recent study of estrogen therapy in postmenopausal women, have reviewed a 10-year period of literature (1986 –1997) and 10 major studies. This analysis includes methods, sources of bias, and outcomes. Based on these data, the authors performed a meta-analysis addressing the effect of estrogens on cognitive function and dementia. They conclude that these retrospective studies have substantial methodological problems (small number of subjects, short duration, being nonrandomized and uncontrolled) and have produced conflicting results. Therefore, new and large placebo-controlled trials are required before drawing conclusions about roles of estrogens in AD prevention. The same authors, given the known risks of estrogen therapy, do not recommend using estrogens for the prevention of AD until adequate trials have been completed. In conclusion, retrospective studies suggest that taking estrogens for a number of years after menopause may reduce the risk for women to develop AD. If this effect of hormones on AD will be definitely demonstrated, the interesting perspective of synergistic action and the possibility of co-administering estrogens with anti-AD drugs such as cholinesterase inhibitors may become a therapeutic reality.

Having known that estrogen replacement therapy may play a preventive role in AD development, it has not been clear if estrogen treatment could be used as a treatment of AD. Recently, Mulnard *et al.* (2000) (88), in the Alzheimer's Disease Cooperative study (ADCS), reported the results of a randomized, double-blind, placebo-controlled clinical trial, including a total of 120 women with mild to moderate AD, who had had a hysterectomy. They reported that estrogen replacement therapy for 1 year did not slow the disease progression; nor did it improve global, cognitive, or functional outcomes. Henderson *et al.* (2000) (89) also performed a randomized, double-blind, placebo-controlled trial. Their results suggested that short-term estrogen therapy did not improve the symptoms of most women with AD. These clinical results suggested that estrogen might not useful in the treatment of AD. However, both studies were performed on different baselines of serum estrogen levels. For example, the mean baseline levels of serum estradiol were 5.4 pg/ml in the placebo group (n=35). The serum estrogen levels were 48.0 pg/ml and 58.4 pg/ml in the low-dosage estrogen group (n=42, 0.625 mg of Premarin per day) and the high-dosage estrogen group (n=39, 1.25 mg of Premarin per day), respectively. In addition, some of these studies involved usage of Donepezil, an inhibitor of acethylcholinesterase (AChE) in combination with estrogen. Research data suggested that Donepezil might interact with estrogen directly (90). At this point, we conclude that more studies will definitely be needed to evaluate the therapeutic effects of estrogen on AD.

6.2. Estrogen and Parkinson's disease

Parkinson's disease (PD) is characterized by the progressive degeneration of dopamine (DA) neurons within the substantia nigra in the brain. Although the mechanism which initiates this selective neurodegeneration is unknown, increases in lipid peroxidation and free iron, decreased glutathione content, altered expression of antioxidant enzymes, and impaired mitochondrial function have been observed in postmortem PD brains.

Interestingly, there is a gender difference associated with PD. Epidemiological studies indicate that the incidence and prevalence of PD is greater in men than in women (91, 92). The higher risk of PD in men has been confirmed by others (93). These findings are consistent with a possible effect of hormonal factors, in particular estrogen, on the risk of PD. For example, a neuroprotective effect of estrogen has been demonstrated in animal models of PD employing the neurotoxins, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (94-96). In addition, estrogen was found to modulate nigrostriatal dopaminergic activity and this could provide the substrate for any such neuroprotective effect (97, 98). Estrogen administration lowers the severity of symptoms of PD in postmenopausal women with early onset of the disease, such as improvement in certain types of memory impairment and motor disability (73, 100-101). As PD is characterized by the mesencephalic dopaminergic neuronal loss, at least partly, with apoptotic cell death (102), the strategy of estrogen might play a role in slowing and even preventing dopaminergic neuronal loss becomes very important impact on PD. Indeed, there is recent but still somewhat controversial evidence that estrogen treatment is beneficial for PD symptoms as well as other neurological disorders (103-104, 99). With respect to Parkinsonism, the reduction of estrogen supplementation in postmenopausal women causes a worsening of PD-related symptoms (99) and the symptom severity in women with early PD is lowered by estrogen application (100). However, other studies failed to show a clear-cut positive effect of estrogen on PD but rather found progesterone application to be helpful (105). Despite this conflicting data from human studies, experimental investigations in rodents strongly support the idea that estrogen may play a protective role in PD. Estrogen exposure yields a reduction of the degree of dopamine depletion resulting from treatment with the

neurotoxin 6-hydroxydopamine, which serves as a model for PD (106, 97).

While the mechanisms of estrogen protection in dopaminergic neuronal apoptotic death is still unclear, several lines of evidence in different experimental animal models suggest that estrogen produce functional change in striatal dopamine metabolism and receptor levels. Estrogen administration reportedly causes striatal dopamine receptor supersensitivity resulting in increased agonist-induced stereotypic behavior in rats (106, 107), although a biphasic effect has also been reported (108). Despite this large body of literature about the biochemical and behavioral impact of estrogenic stimulation on the dopaminergic system, the effect of this hormone on the transcriptional control of dopamine receptor genes has also been investigated. There has been evidence for the transcriptional activation of the human D1A dopamine receptor gene by estrogen. Transient co-transfection experiments in the D1A expressing human neuroblastoma cell line SK-N-MC using reporter CAT constructs along with an estrogen receptor expression vector revealed a 1.7-fold induction of the D1A gene following 17β-estradiol treatment. On the other hand, no such transcriptional regulation was detected with either progesterone or glucocorticoid receptors. Thus, these observations suggest molecular regulation of the D1A gene specifically by estrogen but not by the other steroid hormones tested (109). Furthermore, the molecular basis for the estrogen-induced up-regulation of D1A has been found through binding estrogen-response-element (ERE) located in the upstream region of the D1 promoter (109). In addition, recent studies also indicate that estrogen treatment could also cause a down-regulation of dopamine D2 receptor through an unknown mechanism and inhibits D2-induced dopamine uptake (110).

Apart from estrogen regulation on dopamine receptors, evidence indicates that the neuroprotection provided by estrogen in dopaminergic neurons is partially mediated by the ER because some protective actions of estrogen could be antagonized by ICI, a pure antagonist for ER. Estrogen has similar affinity for both subtypes of ER (111) ERα and ERβ. It has been suggested that the neuroprotection of nigral dopaminergic neurons is probably mediated by ERβ activation since the exclusive distribution of ERβ subtype in the substantia nigra of the mesencephalon (40,111). Furthermore, neuronal deficit and degeneration of neuronal cell bodies have been found throughout the brain, but in particularly, much more within the substantia nigra in the ER β knockout mice (112). Gene expression as result of ligand-bound ER includes both primary and secondary responses, with the former directly regulated by the ER and the latter regulated by products of the primary response. The primary response to ligand-bound ER is mediated in two ways, through the ERE and through the AP-1 element. ER activated by estrogen binds to DNA as a homodimer and enhances gene transcription through the ERE. However, it also suppresses gene transcription from the AP-1 element by coupling with the AP-1 proteins c-Fos and c-Jun (113). Tamoxifen acts as a pure antagonist for ERβ (114) and, when bound to ERβ, regulates transcription through either the ERE or the AP-1 element in a reverse manner: it suppresses transcription through ERE and enhances it through the AP-1 site (113).

Interestingly, estrogen can also protect cells independently from binding to ER. There are have been several reports indicating that estrogen provides antioxidant neuroprotection against glutamate- or radical-induced neurotoxicity in vitro (28, 29, 87), including in nigral dopaminergic neurons (115). Recent investigations reported that the neuroprotection by estrogen is at least partially mediated by conjugation of estradiol with glutathione (87). Interestingly, the antioxidant protective effect of estrogen against the toxicity of glutamate is not ER dependent. Both 17 β-estradiol and 17 α-estradiol showed equal antioxidant neuroprotective activity (29). This pure free radical scavenging activity is independent of the activation of ERs and the only prerequisite is the chemical phenolic structure of the molecule (29, 116). Modifications of this particular moiety by etherization (e.g. mestranol, methylether of ethinyl estradiol) or removal of the phenolic group blocks the antioxidant activity of the molecule.

Finally, the protective effect of estrogen is also involved in regulation of the Bcl-2 family and other anti-apoptotic molecules. Recent reports show that one mechanism by which estrogen may affect apoptosis is through the increased expression of Bcl-2, a member of a family of apoptosis regulating proteins (117,118). Bcl-2 is a survival factor that can block apoptotic cell death. Bcl-2 acts upstream to prevent the activation of caspases, inhibits free radical formation, regulates calcium sequestration (119) and blocks the pro-apoptotic actions of other members of the Bcl-2 family such as Bax and Bad (120).

7. CONCLUSION

Gondola hormones have been suggested to influence mood, cognition, and psychiatric disorders for many decades, though the mechanism and sites of action in the human brain have been fairly unknown. During recent years, the number of publications regarding estrogen synthesis, ER distribution and function in the CNS has increased tremendously. New discoveries and more sensitive techniques have helped one to increase knowledge about where the brain estrogen synthesis, different ER subtypes, and which neurotransmitter systems they may interact with. However, one is only in initial stages of understanding the estrogenic effects in the brain and possible roles in AD and PD, the knowledge that has been accumulated to date indicates the system to be not simple.

Tasks for the future will be to delineate which genes are regulated by the ERs in different neuronal populations and how this transcriptional-control correlates with human behavior and mental state. By understanding the differences in distribution and actions between the ER

subtypes, future subtype-selective ligands may be useful for treatment of various neurodegenerative disorders and HRT.

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