

# **NEUROENDOCRINE CHANGES AND ALZHEIMER DISEASE IN POSTMENOPAUSAL WOMEN**

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## INTRODUCTION

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Recent experimental and clinical data indicate that ovarian hormones have essential functional effects on female neurobiology. They are important modulators of neuronal functions in the central and vegetative nervous system with influence on numerous physical and psychological processes. Estrogen deficiency in postmenopausal women causes severe neuroendocrine changes in the brain and autonomous nervous system and considerably influences numerous cellular and biochemical processes, with impact on mood, behaviour, vasomotor reactivity, memory, and other nervous functions. Recent epidemiological studies suggest that estrogen deficiency in the postmenopause represents an important factor in the pathogenesis of Alzheimer disease (AD) and that estrogen replacement therapy (ERT) may lead to reduced risk for and delayed onset of AD related dementia. It may have beneficial influences on memory, behaviour and mood as well as on cognitive dysfunctions. The role of ERT in the prevention and treatment of AD is one of the most important scientific and practical problems of current neuropsychiatry.

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## DEMENTIA AND ALZHEIMER DISEASE

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The term “dementia” includes acquired deficits of many areas of cognition and highest brain functions in fully conscient subjects; they present as dysfunctions of memory and of one or more cognitive facilities that cause deterioration of social, professional or other activities [1, 2]. AD is the most frequent cause of dementia in advanced age with a lifetime risk in the age group between 65 and 100 years of 33 % for men and 45 % for women or almost double prevalence in women than in men [3]. The prevalence for AD in women remains higher even after adjusting for their longer life-span compared to men [4, 5]. AD affects 3–10 % of all adults over age 65 years and shows an age-related increase with doubling of prevalence about every 5 years and a plateau after the 9<sup>th</sup> decade [6].

Except for rare genetically determined familial early-onset forms caused by gene mutations on chromosome 1 and 14 (presenilin 1 and 2) and 21 (amyloid precursor protein/APP/gene) accounting for 3–7 % of all AD cases [7, 8], the overwhelming majority are sporadic cases with disease-onset in the 7<sup>th</sup> decade and slowly progressive course over 5–10 years with an average of 8.5 years.

The initial clinical symptoms of AD are dysfunctions of short-term memory (difficulties in memory for names, telephone numbers, dates etc) with intact personality and social functions, frequently associated with depression. Later, slowing and difficulties of thinking, spatio-temporal orientation, abstract thinking, action performance, disturbances of constructive abilities, changes of behavior with apathy, anxiousness, paranoid ideas or confusion occur. In late stages of the disease, there are dysfunctions of speech, motor activities (apraxia) and progressive loss of higher brain functions with disorientation, confusion, aggressive behaviour towards the environment, incontinence, and other deficits progressing to full inactivity and necessity to be transferred to a nursing unit [9, 10]. Diagnosis of possible or probable AD can be made using current clinical consensus criteria [1, 2, 9–11] supported by neuropsychological examinations, neuroimaging techniques (magnetic resonance tomography/MRT), positron emission tomography/PET) as well as determination of biological disease markers (detection of apolipoprotein (Apo) E  $\epsilon$ 4 in serum and, eventually, of increased tau protein and reduced  $\beta$  amyloid ( $A\beta$ ) peptide in cerebrospinal fluid) with a sensitivity of about 90%, while around 10% of the patients suffer from other causes or forms of dementia. A definite diagnosis of AD is only possible by morphological examination of brain tissue [8].

The morphological hallmarks of AD are extracellular deposition of  $A\beta$  peptide in brain tissue as senile plaques and in cerebral vasculature (amyloid angiopathy), and changes of the neuronal cytoskeleton with deposition of hyperphosphorylated tau-protein forming paired helical filaments in neurons as neurofibrillary tangles, in nerve cell

processes as neuropil threads, and as neuritic plaques with dystrophic neurites. The changes start in the medio-temporal limbic cortex (transentorhinal and entorhinal region) and progress via the hippocampus to neocortical association areas and, later, also to subcortical nuclei. This distribution pattern of neuritic Alzheimer changes which causes dysfunction and loss of synapses (neuronal connections) and neurons as well as disruption of important connections between cortical areas and deeper brain regions with cerebral atrophy and dysfunction of important neurotransmitter systems, correlates well with the clinical course of early deficits of memory, followed by dysfunction and, finally, breakdown of higher brain activities [8, 12].

The causes of AD are still not clear, but a complex cascade of numerous pathogenic factors is suggested that leads to neurodegeneration: reduced cerebral energy and glucose metabolism, oxidative stress with deposition of cytotoxic free superoxid radicals, advanced glycation end products (AGE), of lipid peroxide products and pathologically oxidated cytoskeletal proteins, reduced activity of antioxidant enzymes, decreased calcium homeostasis, dysfunction of mitochondria, breakdown of neuronal cell membranes, all of which induce bioenergetic crises with damage to neuronal function and, finally, lead to neuronal cell death. These and other factors, in particular, abnormal proteolytic processing of APP with formation of neurotoxic  $A\beta$ -42 peptide, the major component of senile plaques, and abnormal hyperphosphorylation of cytoskeletal proteins induce dysfunction of microtubuli in the nerve cell which are important for signal transduction and axonal transport. These and other cytotoxic factors and immunologic-inflammatory processes

mediated by activated microglia finally induce neurodegeneration [8, 13, 14].

Important risk factors for AD are increasing age, positive family history (life-time risk of 20% in first degree relatives is three times higher than in the total population [15]), genetic factors, in particular the ApoE  $\epsilon 4$  allele on chromosome 19 is an essential risk factor which in AD patients is increased by 15–40% versus the general population. About 80% of all familial and 64% of sporadic AD patients carry at least one ApoE  $\epsilon 4$  allele as compared to 31% in controls [16]. Proband with one ApoE  $\epsilon 4$  allele have a three to four times increased risk, homozygotes with 2 ApoE  $\epsilon 4$  alleles a 10 to 13 fold increased disease risk with earlier disease onset [17]. Further risk factors are low educational level with reduced cerebral reserve function, and compensation capacity, history of craniocerebral injury, myocardial infarction or depression, lower socioeconomic status, nicotine abuse [1, 18], and female gender, probably due to behavioural and biologic factors, partially caused by estrogen deficiency [18]. In general, no connection between sporadic AD forms and menopause age of women has been confirmed, but women with positive family history and early natural menopausal age show significantly increased AD risk compared to controls. However, the inter-relationship between AD and early menopause (causative factor or consequence of AD) remains unclear [19]. Women with Down syndrome (DS) also have an earlier menopausal age than the general population with close relationship between the age at dementia onset and that of menopause [20]. The earlier-than-expected age at onset of menopause suggests that in general women with DS bear an increased risk of postmenopausal health disorders [21].

Women suffering from AD usually show more severe and more rapidly progressive cognitive decline, but better respond to antidementia drug treatment [22].

In the following, the current state of art of the relations between neuroendocrine changes and estrogen deficit in (post) menopause and AD as well as their consequences for prevention and treatment of the frequent form of dementias are reviewed.

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## ESTROGENS AND BRAIN FUNCTION

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The estrogen level strongly decreases in and after the menopause in women [23] which has important impact on neuroendocrine and other functions of the brain and vegetative nervous system [24]. Like other steroid hormones, estrogens in the CNS act either through genomic mechanisms via classical estrogen receptors on specific neuronal groups or directly on the neuronal membrane via rapid, non-genomic processes [25]. They interact with neurotrophic factors [26] and induce selective promotion of growth and differentiation of axons, nerve cell processes and of synaptic plasticity during brain development [27, 28]. Co-localization of estrogen and nerve growth factor receptors on neurons of cerebral cortex and in sensory ganglia promote their differentiation and reciprocal transcriptional regulation, but also induce a convergence of their signal pathways mainly in the area of mitogen-activated (MAP) kinases. This leads to influences on a broad cascade of cytoskeletal and growth-associated genes that participate in growth and differentiation of neuronal processes and circuits. Thus, the affects of estrogen in the brain are

not limited, as previously suggested, to sexual differentiation and reproductive neuroendocrine functions, but also exert important influences on the development, survival, plasticity, regeneration, and aging of the brain [28].

At present, two major estrogen receptor (ER) types, ER- $\alpha$  and ER- $\beta$ , are known that show different distribution in various organs and different signal mechanisms. This indicates specific functions and explains their distinct species-, cell- and promoter-specific affects, although the exact physiological importance of these receptor subtypes still awaits further elucidation [29]. ER- $\beta$  is expressed in high levels in neurons and glia cells of the CNS. Morphological abnormalities in the brains of ER- $\beta$  knockout (BERKO) mice showing neuronal deficits in the somatosensory cortex and proliferation of astroglia in the limbic system suggest that ER- $\beta$  is necessary for neuronal survival and that this gene could have an influence on the development of neurodegenerative diseases such as AD [30].

Estrogen receptors in human brain are found in the locus ceruleus of the brain stem which mediates the noradrenergic innervation of other brain regions as well as in the basal forebrain [27], the cholinergic neurons of which broadly project to hippocampus and neocortex and, thus, are essentially involved in cognitive and consciousness activities [31]. The ER- $\beta$  mRNA expression dominates in the hypothalamus and amygdala, indicating that this subtype may modulate neuronal cell populations involved in autonomic and reproductive neuroendocrine functions, emotional information and processing. In contrast, the hippocampal formation, entorhinal cortex, and thalamus are ER- $\beta$  dominated areas, suggesting their putative role in cognition, non-emotional

memory, and motor functions [32]. In the human nucleus basalis of Meynert (NBM), ER- $\beta$  is expressed to a higher degree than ER- $\alpha$ . A significantly positive correlation between the percentage of ER- $\beta$  nuclear positive neurons and age was found in men but not in women, whereas the proportion of ER- $\beta$  cytoplasm positive cells increased with aging in both sexes. In AD the proportion of neurons showing nuclear staining for both ER- $\alpha$  and ER- $\beta$  and cytoplasmic staining for ER- $\beta$  was markedly increased, with no effect of ApoE genotype on ER expression in AD. These data indicate a clear upregulation of both ER- $\alpha$  and ER- $\beta$  in human NBM in AD [33].

Estrogens are important modulators of neurotransmission in the cholinergic, serotonergic, noradrenergic and dopaminergic systems which are mediated via sexual steroid receptor genes and their receptors as well as by ligand independent mechanisms [34]. Estrogens alter the concentration of norepinephrin and serotonin, probably by inhibition of monoamine oxidase activity, the key enzyme of catecholamine synthesis. It further acts as serotonin agonist, increases the serotonin synthesis and uptake, the number of serotonin receptors and of serotonin transporters in brainstem and forebrain, and the bioavailability of the serotonin-precursor tryptophan. Furthermore, estrogens and testosterone (by transformation to estrogen) stimulate the expression of the arginin-vasopressin gene in the bed nucleus of stria terminalis of the cholinergic forebrain which plays an important role for olfactory memory [35]. By contrast, estrogen deficiency activates norepinephrin and dopamine synthesis which can lead to dysfunctions of vasomotor and blood pressure control. Castration of rats causes reduction of  $\beta$ -endorphins which is also observed

in surgically induced or spontaneous menopause, while steroid replacement induces an increase of these components [36]. Since aminergic and opioid neurons are involved in brain functions, such as mood, behaviour, cognition and pain recognition, estrogen deficiency in this period of the woman has severe influences on mood, behaviour, nociceptive perception (pain sensitivity) and other psychophysiological processes [36–40].

Experimental studies displayed neuroprotective effects of estrogens against neurotoxically induced neuronal damage. They protect against the noxious effect of MPTP, a neurotoxin that, via selective damage of the dopaminergic nigrostriatal system in human and many animal species induces a Parkinson-like syndrome and currently represents its most frequently used animal model [41, 42]. This neuroprotective effect is probably caused by the antioxidant effect of estrogens, e.g. 17 $\beta$ -estradiol [13, 43], which protects neurons against oxidative stress and production of toxic oxygen radicals as important pathogenic factors of cell damage in neurodegenerative disorders. Estradiol has been shown to protect against ATP depletion, mitochondrial membrane potential decline and the generation of reactive oxygen species induced by 3-nitropropionic acid in human neuroblastoma cells; 17 $\beta$ -E2 can preserve mitochondrial function in the face of inhibition of oxidative phosphorylation [44, 45]. Recent studies, however, suggest that the effect of estrogens as neuroprotective antioxidants is independent from their estrogenic capacity [43]. Chronic estrogen treatment replaces striatal dopaminergic function in ovariectomized rats and reverses spontaneous locomotor activity which suggests that ERT may be beneficial in the

treatment of female menopause patients with Parkinson's disease [46]. The experimentally induced neuroprotective or symptomatic effect of estrogens on the dopaminergic system, before recommendation as a hormone replacement therapy for women with movement disorders, however, needs further clarification [47]. Neuroprotection by estrogens has been shown via extracellular signal-regulated kinase (ERK) against quinolinic acid-induced cell death in the rat hippocampus [48].

Further effects of estrogens important for AD are:

- Activity on the metabolism of the amyloid precursor protein (APP) by modulation of the processing and secretion of soluble APP with stimulation of its non-amyloidogenic transformation by activation of APP-processing enzymes in vitro [49]. Estrogen, like testosterone, reduces the neuronal secretion of A $\beta$  peptides in neuronal cultures [50]. This causes reduced formation of the fibrillary non-soluble A $\beta$ , a principal pathogenic factor of AD, and reduction of plaque formation in brain [51, 52]. While ovariectomy is associated with a 1.5 fold average increase in total A $\beta$  brain levels as compared to control animals, 17 $\beta$ -estradiol (E2) treatment significantly reverses this increase [53]. This suggests that cessation of ovarian estrogen production in postmenopausal women might facilitate A $\beta$  deposition by increasing the local concentrations of A $\beta$ -40 and -42 peptides and that modulation of A $\beta$  metabolism may be one of the ways by which ERT prevents and/or delays the onset of AD in postmenopausal women. Estrogens protect neurons from the neurotoxic effect of acetylcholinesterase-amyloid complexes and other



cytotoxic substances, like glutamate and oxygen superoxide. Some of the mechanisms underlying these effects are independent of the classically defined nuclear estrogen receptors and involved unidentified membrane receptors, direct modulation of neurotransmitter receptor function and second messenger pathways, or the known anti-oxidant activities of estrogen [28, 45]. Further neuroprotective effects of estrogen depend on the classical nuclear estrogen receptor, through which estrogen alters the expression and transcription of estrogen responsive genes that play a role in apoptosis, axonal regeneration or general trophic transport [54–56]. Yet other possibilities are that estrogen receptors in the membrane or cytoplasm alter phosphorylation cascades through direct interaction with protein kinases or that estrogen receptor signaling may converge with signaling by other trophic molecules to confer resistance to injury [28]. Further neuroprotective effects are mediated by a significant increase of expression of the antiapoptotic protein Bcl-xL in neuronal tissue cultures which appears to be related to a neuronal colocalization of the estrogen receptor and Bcl-xL immunoreactivity in the hippocampus. This induces inhibition of proteolysis mediated by the enzyme caspase and of A $\beta$  induced apoptosis, a specific form of programmed cell death [57]. Estrogen-mediated neuroprotection has been described in several neuronal culture model systems with toxicities including serum-deprivation, A $\beta$  induced toxicity, excitotoxicity, and oxidative stress [57]. Estrogen has been shown to protect neuronal cells in culture from amyloid  $\beta$  induced apoptotic cell death, probably

not by direct interaction with A $\beta$ , but via blocking the mitochondrial apoptotic pathway induced by A $\beta$  [58]. Estrogens also have been shown to attenuate neuronal death in rodent models of cerebral injury, traumatic injury, and overexpression of APP-mitochondrial ribonucleic acid (mRNA) following experimental cerebral focal ischemia, an additional risk factor of late-onset forms of AD [62]. Some of these neuroprotective effects include activities of the nuclear estrogen receptor, altered expression of bcl-2 and related antiapoptotic proteins, activation of the MAP pathway, of cAMP signal transduction, modulation of intracellular calcium homeostasis, and direct antioxidant activity [28, 45, 57, 58]. For recent reviews of the neuroprotective activities of estrogen and sex hormones in general see [28, 59–61].

- Promotion of growth of cholinergic neurons and their dendrites in hippocampus, of the expression of acetyl transferase and nerve growth factor receptors in cholinergic neurons of the basal forebrain [62] as well of the synthesis of cholin acetyltransferase (ChAT), the enzyme responsible for synthesis of acetylcholine, in the CA 1 sector of hippocampal formation, a region important for memory processes. The distribution of the estrogen binding sites in the basal forebrain which are important for the function of cholinergic neurons shows close relationship to the pattern of AD pathology. Dysfunctions of the cholinergic system are the most important neurochemical deficit of AD [31, 63]. After experimental ovariectomy in female rats, there is a significant reduction of the marker enzyme ChAT and of its mRNA in the cholinergic

forebrain as an indicator of reduced function of the neurons projecting to hippocampus and neocortex. These data suggest that estrogen deficiency increases the sensitivity of the cholinergic system towards aging processes. This appears to contribute to the risk of cognitive dysfunctions in women related to aging and AD [64], but recent studies in ovariectomized rats and after unilateral injection of ibotenic acid or unilateral transection of the fimbria fornix showed that neither short-term (3 weeks) nor long-term (13 weeks) of continuous estrogen administration prevented the loss of ChAT-containing cells in the medial septum and nucleus basalis. Notably, increased numbers of ChAT-positive cells were detected in the contralateral nucleus basalis and in the medial septum of both sides, at 2 weeks following unilateral injection of ibotenic acid into the nucleus basalis, which effects were not related to hormone treatment [64]. Studies of ovariectomized rats have further shown that estrogen stimulates acetylcholine release in the hippocampus and overlying cortex [65]. While these data suggest that ERT does not protect cholinergic neurons in the medial septum and nucleus basalis from the effects of excitotoxic or mechanical injury, both estrogen and estrogen plus progesterone have been demonstrated to show neuroprotective effects when administered before or immediately after intrahippocampal colchicin infusion and to reduce the damage to hippocampal neurons and the related loss of acetylcholine [66]. This could indicate a delayed effect on brain aging and on the risk and severity of dementia of the AD type in postmenopausal women [64].

- An increase of the density of estrogen receptors in the choroid plexus following estrogen administration was observed in post-mortem brain of AD patients using immunohistochemical methods which probably represents an important factor in the defense mechanisms by regulation of CSF formation and filtration [67].
- Modulation of ApoE in plasma and brain tissue with reduced progression of atherosclerosis, cardioprotective effects by influencing the lipoprotein metabolism as well as reduction of AD risk mainly in ApoE  $\epsilon$ 4 negative women [40]. Estrogens enhance the synaptic sprouting via ApoE-dependent mechanisms [68], and they also reduce the cholesterol level in serum and the risk for coronary heart disease [69] by decreasing serum low-density lipoproteins and increasing high-density lipoproteins. They further reduce the progression of atherosclerosis in ApoE-deficient, ovariectomized mice [70] and increase the concentration of ApoE in brain [71]. Since ApoE appears to be important for repair mechanisms and growth of neurites [68], it may have potential neuroprotective effects. In higher concentrations, estrogens also influence cholesterol synthesis and, thus, may show inhibitory effects on the amyloidogenic APP metabolism [72].
- Inhibitory effects on immune mediated inflammatory processes in the pathogenesis and progression of AD pathology which appear to be related to dysregulation of natural killer cells by increased exposition to cytokines and their cytotoxic effects and/or to reduced sensitivity towards immunosuppressive effects of glucocorticoids [40, 73]. Estrogens, like non-

steroidal anti-inflammatory substances (NSAID), induce a reduction of killer cell activities during cytokine activation [74] and, via reduced plaque formation and other neuroimmunological components, may contribute to reduction of AD risk [40, 75].

- Increase of regional cerebrovascular perfusion and glucose utilization with improvement of cerebral energy metabolism that is severely reduced in AD [76]. In women with cerebrovascular disorders, estrogen induces improvement of the mental state by increase of cerebral blood flow [77]. A randomized study of estrogen and placebo administration in postmenopausal women under estrogen displayed a specific pattern of brain activation in the inferior parietal lobe and superior gyrus during verbal storage [78]. Estrogens, via increase of sensitivity of insulin receptors in the hippocampus cause potentiation of cholinergic effects on cognition, whereas insulin inhibits the neurotoxic effects of A $\beta$  on cultured hippocampal neurons and, thus, might improve the insulin sensitivity and glucose homeostasis in dementia [40]. Following dysfunction of neuronal glucose and energy metabolism caused by intraventricular application of streptococin, estradiol 17 $\beta$  improves disorders of learning and memory also in male rats via normalization of cerebral energy metabolism [79].

no serious negative effects on the spatial reference memory but on the spatial working memory [80], while long-term estrogen deficiency considerably increases dysfunctions of spatial learning and memory caused by intraventricular infusion of A $\beta$ -42 peptide [81]. Estrogen replacement in animal experiments (in ovariectomized rats) causes increase of cholinergic activity in the basal forebrain and its projection areas with improvement of sensomotor and learning capacities [82].

In addition, it induces an increase of gene expression of the 5-HT<sub>2A</sub> receptors and serotonin transporter in the dorsal raphe of the brainstem and in basal forebrain [40]. Estrogen also reduces the negative effects of scopolamin and lorazepam on learning and memory functions [83].

Studies were performed on healthy women during different stages of their menstruation cycle [84, 85], on women with surgically induced natural menopause [86, 87], on those with inhibition of their ovarian functions by gonadotropin releasing hormone antagonists [88] and after crossed sexual hormone therapy in transsexual men and women [89]. In these trials, the best documented effect of estrogen was improvement in tests examining verbal memory and other cognitive functions, although this effect, in general, was rather mild [37]. Whereas older studies did not show any influence of estrogens on memory processes [84], and in others, its effects were limited to verbal and visual short and long-term memory and reaction time without influence on the visuo-spatial memory or other cognitive functions [83, 85], more recent studies indicate that the effects of ERT are not limited to memory but also involve both abstract thinking and speech [90–92]. Most recent studies in a cohort of nondemented, elderly Cau-

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## ESTROGENS, MOOD, AND COGNITION

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Short-term estrogen deficiency and administration of NMDA receptor antagonists in ovariectomized animals have



casian women with high educational level showed that high serum levels of estrogen correlated with better protracted verbal memory, and low estrogen levels with improved visual memory, whereas testosterone levels correlated positively with word fluency. Plasma levels of progesterone and androstendion showed no correlations with cognitive activities. Since hormone levels in CSF, in general, closely correlate with those in serum, from these data complex relations between circulating sexual hormones and cognition can be assumed [93]. Some studies suggest an indirect improvement of cognitive and memory functions via improvement of mood and wellness feeling in postmenopausal women [94], while others did not show such correlations. Women with surgical menopause displayed improvement of memory even without relationship to affective or other postmenopausally caused dysfunctions [84, 86], whereas in asymptomatic women no definite improvement of cognitive functions were observed [95]. A recent study of the effects of 9 months of ERT in a small sample of asymptomatic women aged 75 years and older suggests that short-term estrogen replacement in combination with trimonthly progestin administration does not improve cognitive performance in women 75 years of age or older [96]. A systematic review and meta-analysis of ERT and cognition revealed that in women with menopausal symptoms ERT may have specific cognitive effects but further studies should target these effects. The meta-analysis found a decreased risk of dementia in ERT users but most studies had distinct methodological biases, and no benefits were observed in asymptomatic women [97].

There are close relationships between circulating estrogen levels and mood

[98]. Estrogen deficiency in the menopause, probably via changes of central serotonin, norepinephrin and  $\beta$ -endorphin systems, may induce depression, anxiousness and changes of mood. Many studies showed positive effects of ERT in depressed postmenopausal women [94, 95, 99], while others could not confirm these effects [100]. This might be caused by different estrogen doses or progesterone component of combined hormone preparations. In general, the conventionally used estrogen doses show no influence on mood of women with endomorphic depression [98] but have strong effects on mood and the feeling of wellness in healthy, non depressed postmenopausal women [36, 94, 99]. The positive effects of estrogens on mood are possibly related to its effects as serotonin antagonists. In addition, they influence the concentration and bioavailability of serotonin via increased degradation by monoamine oxidase A, the key enzyme of serotonin metabolism [101]. According to experimental studies, estrogen replaces tryptophan from its binding sites on plasma albumin and increases the bioavailability of this serotonin precursor in brain.

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## ESTROGEN AND RISK OF ALZHEIMER DISEASE

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With regard to the possible importance of estrogens in AD, preventive strategies in cognitively intact and demented individuals are to be distinguished; data are predominantly available for women but hardly for men.

A relationship between long-term exposure to endogenous estrogens and incident dementia has been hypothesized but not studied. Recent data are

from the Rotterdam study, a population-based prospective cohort study of 3601 women aged 55 years and older who did not have dementia at baseline and had information on age at menarche and menopause, and type of menopause. During 21046 person-years of follow-up (median 6.3 years), 199 women developed dementia including 159 cases of AD. After adjusting for multiple covariates, women with natural menopause and more reproductive years exhibited an increased risk of dementia, which was most pronounced in ApoE  $\epsilon$ 4 carriers, whereas in noncarriers no clear association with dementia or AD was observed. These findings do not support the hypothesis that a longer reproductive period reduces risk of dementia in women who have natural menopause [102].

Up to date, there are controversial data about the effects of ERT on the risk

for AD. Older case control studies did not show significant correlations, but were often methodologically incorrect [37, 95, 103]. More recent epidemiological studies suggest protective effects of estrogen substitution in postmenopause with reduced risk and delayed onset of AD, but some studies are limited to current estrogen administration or showed demographic differences between AD patients and controls.

Up to present, 13 studies of estrogen administration and risk of dementia in late-onset AD have been published; four suggested an increased, and seven a reduced risk of dementia [95, 104]. A meta-analysis of 10 such studies showed reduced development of dementia in 29% [95] with an odds ratio (OD) of 0.71 (confidence interval /CI/ 0.53–0.96). However, these studies vary considerably in methodology (cohort

Table 1. Epidemiologic trials on ERT and risk of Alzheimer's disease (AD) with informations on administration of estrogens in the postmenopause before onset of dementia.

| Authors                                       | Study design     | Location              | N (AD-cases) | N (controls) | Information about estrogen intake | Type of estrogen compound | Relative Risk <sup>a)</sup> |
|---|------------------|-----------------------|--------------|--------------|-----------------------------------|---------------------------|-----------------------------|
| Paganini-Hill & Henderson [19]                | case-control     | Leisure World CA, USA | 138          | 550          | Proband                           | All                       | 0.69                        |
| Brenner et al. [138]                          | case-control     | Seattle WA, USA       | 107          | 120          | Pharmacy                          | All Oral <sup>b)</sup>    | 1.1<br>0.7                  |
| Tang et al. [108]                             | cohort           | New York, USA         | 167          | 957          | Proband                           | Oral                      | 0.5                         |
| Morrison et al. [139]                         | cohort           | Baltimore MD, USA     | 38           | 434          | Proband                           | Oral or transdermal       | 0.44                        |
| Paganini-Hill & Henderson [107] <sup>c)</sup> | case-control     | Leisure World CA, USA | 248          | 1198         | Proband                           | All Oral                  | 0.65<br>0.7                 |
| Kawas et al. [103]                            | cohort           | Baltimore MD, USA     | 230          | 242          | Proband                           | Oral and transdermal      | 0.46                        |
| Waring et al. [105]                           | case-control     | Rochester MN, USA     | 222          | 222          | Case record                       | All                       | 0.4                         |
| Slooter et al. [106] <sup>d)</sup>            | Population based | Rotterdam, NL         | 109          | 119          | Proband                           | All                       | 0.34                        |

a) relative risk of 1 indicates no estrogen effect on AD risk, < 1 protective effect, > 1 increased risk; b) retrospective analysis limited to comparison of oral versus no estrogen; c) some probands of earlier trials included; d) presenile AD

or case-control studies, different diagnostic criteria); other studies indicating a reduced AD risk, due to differences in the educational and social levels and estrogen-doses are not representative [37]. In prospective studies, however, a reduced risk was observed (Table 1).

One study in 306 postmenopausal women (83 with AD, 65 with vascular dementia (VaD), and 148 age-matched controls), only few of them having taken estrogen (29 controls and seven each with AD and VaD) suggested that lack of ERT in postmenopausal women may increase the risk of both AD and VaD [104]. A representative, population relevant study in Rochester, MN, on the development of AD between 1980 and 1985 in 222 women each with and without ERT (same age at menarche and menopause) revealed more frequent estrogen intake in controls versus AD patients (19% versus 5%). These inverse relations between estrogen replacement and AD remained constant even after adaption to education and menopausal age [105]. Similar results were found in a recent population-based study of the Rotterdam group on estrogen use and early onset AD with an OR of 0.34 and 95 % CI of 0.12–0.94 [106]. These data suggest that estrogen substitution in postmenopause is correlated with reduced risk of both presenile and late forms of AD. Other studies also provided significantly reduced frequency of ERT in demented versus non demented women. Population-based epidemiological studies from South California and New York in women after estrogen administration (minimal duration 6 months) provided a 35–50 % reduced AD risk than in those without estrogen use. Here, a relationship between duration and dosage and the reduced risk of dementia has been suggested [107, 108]. The Baltimore study identified 34 cases of probable AD in a

cohort of 472 community-dwelling women, followed up to 16 years, and reported a reduced relative risk of 0.46, indicating again a protective effect of ERT [103]. This study was unable to detect any increase in protection depending on the duration of ERT. These results were replicated in a 3-year longitudinal study of 1,568 Italian women who were included in the risk factor analysis [109]. This investigation also reported that the risk of AD for ERT was reduced three quarters below that of women who had never used estrogen (summary odds ratio 0.24). Daily estrogen doses of 1.25 mg and more appear to have a higher protective effect than lower doses, and the protective effect might be increased by addition of progesterone. A retrospective long-term study in California on 3,128 elderly women with and without estrogen use, in those with ERT, displayed a significantly lower incidence of possible or probable AD and a significantly higher incidence of the diagnosis “mild cognitive dysfunction”. ERT at trial onset and following one year ( $n = 358$ ) was significantly associated with higher cognitive functions, while women without estrogen during the observation time of one year showed significant deterioration [110]. From these data can be concluded that the protective effect of estrogen against cognitive deterioration may increasingly act in early stages of illness. The protective effect of estrogen in all studies remained after adjusting for other covariates (usually age and education).

This estrogen effect could be caused by cholinergic mechanisms and other „neuroprotective“ effects [37], but causal relations will only be confirmed from statistical data of larger randomized studies [111, 112]. However, a recent population-based nested case-control study in the UK based on General

Practice Research database of 112,481 recipients of ERT and of 108,923 women who did not use estrogen, revealed no association of ERT use by women after menopause onset with a reduced risk of developing AD, thus highlighting the need for restraint in advocating postmenopausal ERT for this purpose. Among the 59 newly diagnosed cases of AD, 15 (25 %) were current ERT users, while among controls 53 (24 %) were current users. Odds ratios were similar for estrogen recipients who received ERT alone, and for recipients who had a combined estrogen-progesterone treatment [113]. At present, two clinical trials to determine the possibility whether estrogen may delay AD are in progress [114]: one addition to the Women's Health Initiative (WHI) sponsored by the National Institutes of Health, USA, a 12 year study to investigate the course of cardiac disease, cancer and osteoporosis in 8,300 women aged over 65 years, where in the sub-study WHI Memory Study (WHIMS) yearly controls of the psychiatric state with testing of cognitive dysfunctions is performed; this study will be finished by 2005 [115]. Another study sponsored by the National Institute for Aging (NIA) to determine whether estrogens may reduce memory loss and prohibit AD in elderly women with positive family history, as a double blind trial between premarin and placebo is in progress. It recruits healthy women with normal cognition with first degree relatives with AD or severe dementia who yearly will undergo extensive psychological tests to determine dementia or memory loss. A description of this study is available in the internet ([www.delay-ad.org](http://www.delay-ad.org)). The final results of this and of two other ongoing randomized trials of ERT for preventing dementia [115, 116] are unlikely to be available for the next few

years. In the interim, evaluation of the question in valid observational studies can serve as a guidepost to the value of ERT in preventing AD [113].

A preliminary case-control study in 50 postmenopausal women with AD and 93 age-matched controls in Washington showed that the AD patients had lower estradiol levels than controls which, however, did not reach significance. Compared to estradiol levels >20 pg/ml, women with AD were four to six times likely to have levels of <20 pg/ml, after adjusting for age, years of education, presence of an ApoE  $\epsilon$ 4 allele, ethnicity, and body mass index. Since there were no significant differences in frequency of AD among women with different quartiles of estrogen after adjusting for potential confounds, these data suggest that estradiol levels may decline significantly in women in whom AD develops and that factors that may put an individual at risk of developing AD may also contribute to lower endogenous estrogen levels after menopause [117]. A recent cross-sectional study revealed no correlation between sex hormone levels and cognitive scores in community dwelling postmenopausal women with AD and healthy controls. Although the failure to detect estradiol in one third of cases limits the conclusions that can be drawn for this hormone, the possibility that AD is associated with certain serum sex hormone levels should definitely be considered and warrants further research [118]. Another study dealing with the knowledge of informants of reproductive history and estrogen replacement of AD patients revealed this information to be accurate for some but not all aspects of reproductive history. Of concern for such studies, however, will be the 30 % of patients who have no informant with personal knowledge of them [119].

About the effects of female sexual hormones on Parkinson's disease the following results are available: While a small randomized double-blind study revealed no significant dopaminergic motor effects of estradiol (E2), according to an open study, progesterone shows a rather antidopaminergic effect [120]. In a randomized placebo-controlled trial, standard ERT (transdermal 17 $\beta$  estradiol) was well tolerated and showed a mild dopaminergic effect without essential motor improvement or any changes of the dyskinesia scores [121]. A community study of 80 female Parkinsonian patients with and without dementia each and 989 nondemented controls in New York revealed a protective effect of estrogen in the Parkinsonian group (OR 0.22; 95% CI 0.05–1.0) as well as versus controls (OR 0.24; 95% CI 0.07–0.78), without influence on the risk of Parkinson's disease [122]. These data, however, have to be confirmed by randomized studies.

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## ESTROGEN IN AD THERAPY

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Studies on the effects of long-term low-dosage estrogen substitution in women with AD suggest a mild improvement of cognitive and daily activity scores, most significant in name (semantic) memory tests. These effects probably cannot be explained by mood differences [123]. They were particularly observed with mild to moderate dementia [124], but they were generally derived from small cohorts with short duration of ERT without placebo-controlled double-blind studies. A critical review of these studies was given by Henderson [37].

The effects of ERT in patients with active AD appear to be mild. A retrospective study from California did not

show significant differences in the progression rate of cognitive dysfunction between AD patients with and without estrogen substitution [125]. It was surprising that estrogen substitution was associated with early onset of AD, mainly in women without ApoE  $\epsilon$ 4 allele but not in those with  $\epsilon$ 4 allele. This could be explained by the fact that women with estrogen substitution in general were younger and that a subgroup of AD patients may be resistant against ERT, in particular those with early hysterectomy and familial forms of early AD. A comparison between chronic and late estrogen substitution showed no different effects on the progression of cognitive deficits. By contrast, the Cardiovascular Health Study in the USA revealed a correlation between estrogen substitution and milder disease progression in ApoE  $\epsilon$ 4-negative but not in  $\epsilon$ 4-positive women following long-term ERT [126]. A recently finished randomized, placebo-controlled, double-blind short-term trial on women with mild to moderate dementia in California (daily estrogen dose 1.25 mg for 16 weeks) did not show any significant differences in the clinical and cognitive test results [127]. Likewise, a controlled, double-blind one-year study with ERT in 120 hysterectomized women with mild to moderate AD (Mini-Mental Scores 12–28) in California did neither show a slowing of disease progression nor an improvement of global, cognitive or functional scores [128]. A third double-blind, placebo-controlled 12-week trial of conjugated estrogen (Premarin 1.25 mg/day) administration in 50 female AD patients from Vancouver, Canada, also did not produce a meaningful effect on cognitive performance, dementia severity, behaviour, mood, and cerebral perfusion [129]. However, poor recall of ERT use by patients and altered physician behaviour may have



confounded some of the effects. Surprisingly, both healthy and demented women with low education seem to benefit most from ERT, and duration of treatment seems to play an important role, with beneficial effects declining – and even reversing – with longer treatment in women with AD [130]. In a recent study 20 postmenopausal women with AD randomized to receive either 0.01 mg/day of 17  $\beta$ -estradiol or a placebo by skin patch for 8 weeks, were evaluated cognitively at baseline, at weeks 3, 5 and 8 during, and again 8 weeks after treatment. Significant effects of ERT were observed on attention, verbal, visual and semantic memory, supporting a cognitive benefit of estrogen for women with AD [131].

These discrepant findings need clarification by future randomized trials of the cognitive effect of different ERT preparations, serum estrogen levels, and the interaction of ERT with age, menopausal status and existing protective (e.g. education) and risk factors (e.g. smoking and ApoE genotypes) for cognitive decline in AD [132].

Single case observations in elderly male AD patients showed that administration of conjugated estrogens (daily doses of 0.625–1.875 mg) had a positive effect on psychical and sexual aggression that had not been influenced by antipsychotic drugs [133].

Since the positive estrogen effect in AD may be caused by cholinergic mechanisms [37], there might be an additive or potentiated effect with current symptomatic treatment by cholinesterase inhibitors, e.g. tacrin, donepezil, rivastigmin or galantamin [8, 63]. In a large retrospective study with tacrine, women with oral ERT at the time of study inclusion showed significantly better results than those under placebo, while women in the tacrine treatment arm without estrogen showed similar

results as the placebo group [134]. Most recent studies in the USA showed that a combination of estrogen (alone or with progesterone) with cholinesterase inhibitors, e.g. donepezil, revealed better cognitive results than those who received donepezil alone. The addition of progesterone might have potentiated the beneficial effect of estrogen [135].

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## CONCLUSIONS

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Experimental, epidemiological, and clinical studies suggest a possible, but not definite, reduction of AD risk in postmenopausal women under ERT but questionable or only very mild treatment effects of estrogen or its combination with anticholinergic drugs in female AD patients with mild to moderate dementia. However, many questions about the causal relationship and possible effects of estrogen on disease progression remain unclarified. According to available data, daily estrogen doses of 1.25 mg or more appear to have a stronger protective effect than small doses. This effect could be shown for estrogens with and without progesterone [107]. The same applies for therapeutically active doses of estrogen in mild to moderate AD [37]. Obviously, ERT, in addition to reduction of cardiovascular disorders, osteoporosis and mortality, in view of increasing longevity and the increasing incidence of AD and other dementias will have a high importance for risk reduction and treatment in elderly women. They clearly surmount the risks of ERT (endometrial cancer, breast cancer, thromboembolic complications etc). However, in view of many still open questions about the

role of estrogens in AD, very careful strategies in the application of hormone replacement therapies in cognitively healthy postmenopausal women and those with early symptoms of AD are advisable. This particularly concerns women with persistent uterus, while these precautions appear not necessary in those after hysterectomy. Recently, the estrogen receptor (ER-) gene was detected as new susceptibility gene of AD [136]. The P- and X-alleles were significantly more frequent in AD patients than in controls. Likewise, in demented Parkinsonian patients, an increased incidence of the P-allele versus controls was found, but not in patients without dementia. These data suggest that the ER-gene represents a common susceptibility factor for dementia in AD and Parkinson's disease [137].

Exciting and important avenues for future investigation into the protective effects of estrogen include the optimal ligand and doses that can be used clinically to confer benefit without undue risk, modulation of neurotrophin and neurotrophin receptor expression, interaction of estrogen with regulated co-factors and co-activators that couple estrogen receptors to basal transcriptional machinery, interactions of estrogens with other survival and regeneration promoting factors, potential estrogenic effects on neuronal replenishment, and modulation of phenotypic choices by neural stem cells. Hence, extensive experimental and clinical studies to identify specific estrogen receptors in the CNS and the possibility of their selective activation without involuntary side effects on other biological systems as well as concerning the relevance of estrogen substitution for the prevention and treatment of AD and other dementias are necessary in order to provide future

prevention and treatment strategies to improve the quality of life of the patients.

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