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Review

Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after menopause

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ABSTRACT

Hormonal changes associated with the menopausal transition and postmenopause have the potential to influence processes linked to Alzheimer's disease symptoms and pathogenesis, but effects of menopause on Alzheimer risk can be addressed only indirectly. Nine randomized clinical trials of estrogen-containing hormone therapy in Alzheimer's disease patients were identified by a systematic literature search. Findings suggest that hormone therapy does not improve cognitive symptoms of women with Alzheimer's disease. No clinical trials of hormone therapy address Alzheimer prevention, but one clinical trial provides moderate evidence that continuous, combined estrogen plus progestogen initiated at age 65 years or older increases the risk of dementia. The timing, or critical window, hypothesis suggests that hormone therapy initiated at a younger age in closer temporal proximity to menopause may reduce the risk of Alzheimer's disease. This hypothesis is supported by observational research but is not addressed by clinical trial data. Unrecognized confounding is of concern in interpreting observational results, and research that helps resolve this issue will have important public health implications. Well-designed cohort studies, convergent evidence from appropriate laboratory models, and long-term clinical trials using surrogate biomarkers of brain function and neural pathology could provide relevant answers. Other estrogenic compounds are of theoretical interest with respect to Alzheimer treatment and risk. Effects of selective estrogen receptor modulators such as raloxifene may differ from those of estrogens; potential effects of phytoestrogens are not well studied.

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1. Introduction

Estrogens and progesterone are produced cyclically by the ovaries during a woman's reproductive years. The perimenopause is associated with fluctuations in the hormonal milieu. After menopause, the depletion in ovarian follicles culminates in permanent reductions in circulating levels of these sex steroids. In the postmenopause, low concentrations of estrone are derived from androstenedione, which is made in adipose tissue and from other peripheral sources [1]. Estradiol is derived in turn from estrone. Estradiol is the predominant estrogen before menopause, but in the postmenopause circulating concentrations of estrone exceed those of estradiol. Circulating levels of testosterone are largely unchanged after the natural menopause [2], derived from androgen precursors produced by the adrenal glands and stromal cells of the involuted ovary. The hormonal changes associated with the menopausal transition and postmenopause affect the brain and may modulate neural processes concerned with cognition and pathological processes linked to Alzheimer's disease. Effects of menopause on Alzheimer risk, however, cannot be assessed directly; it is obvious that menopause cannot be randomly allocated as an experimental intervention. The preponderance of research pertaining to Alzheimer's disease has therefore focused on potential therapeutic roles of estrogen-containing hormone therapy during the postmenopause. Androgen effects have also been explored, but particularly in men [3].

Estrogen receptors are part of a nuclear receptor superfamily whose main function is the regulation of the expression of genes involved in growth, differentiation, and sexual development. Other members include receptors for androgen, progesterone, glucocorticoids, and mineralocorticoids. Estrogen effects on the brain are mediated in part through two estrogen receptor isoforms, estrogen receptor alpha and estrogen receptor beta. Within the brain, human estrogen receptors are distributed in a topographic pattern unique to each isoform. Estrogen receptor beta is more abundantly expressed in the cerebral cortex and the hippocampus [4,5]. For widely projecting magnocellular cholinergic neurons in the basal forebrain region, estrogen receptor alpha is the predominant subtype. Estrogen binding to the ligand-binding domain of the receptor induces receptor dimerization, which in turn enables binding to hormone response elements on the genome. Binding of the receptor complex stimulates or inhibits expression of nearby target genes. Putative G-protein-coupled estrogen receptors are associated with the plasma membrane and are likely involved in regulating intracellular signaling cascades and mediating rapid actions that do not involve genomic activation [6,7].

The brain is affected secondarily by estrogens acting on nonneural tissues. Estrogen effects on the vascular endothelium and on inflammation may be especially germane to disorders such as Alzheimer's disease [8,9].

2. Alzheimer's disease

Dementia represents major cognitive impairment, which substantially affects social or occupational function and interferes with independence. Dementia implies a decline from some premorbid level of independent functioning due to an underlying pathological substrate. In most regions of the world, Alzheimer's disease is by far the most common cause of dementia [10]. It is rare before age 60 years, and both incidence and prevalence increase well into late old age.

The cognitive symptoms of Alzheimer's disease begin insidiously and progress gradually over a period of years. A consistent early symptom is a deficit in episodic memory, manifest by impaired recollection of recent events or poor recall of recently encountered information [11]. Other cognitive skills are also affected but typically less so early in the disease course. Women with Alzheimer's disease may have relatively greater difficulty with cognitive skills viewed as female-advantaged, for example, verbal fluency, naming, and verbal episodic memory [12,13].

The microscopic hallmarks of Alzheimer's disease are neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles are located within cell bodies of affected neurons in the cerebral hemisphere and brainstem. They consist largely of paired helical filaments whose main constituent is tau, a cytoskeletal protein, which has been excessively phosphorylated.

The principal component of plaques is amyloid-beta, or Aβ, a peptide derived from the amyloid precursor protein. When strands of Aβ line up next to one another, they assume a beta-pleated structure, which aggregate to form insoluble amyloid sheets. These accumulate within extracellular spaces between nerve cell bodies. Over time, these diffuse plaques become associated with microglia, reactive astrocytes, and the deposition of complement, together with distended neurites (usually axons), which may contain paired helical filaments. At the center of these neuritic plaques is a dense amyloid core. The amyloid hypothesis suggests that Aβ formation or Aβ deposition is the central initiating event in Alzheimer's disease pathogenesis. However, the relation between amyloid burden and cognitive symptoms by no means clear, and therapeutic approaches to reduce Aβ production or Aβ aggregation have thus far been disappointing. Aggregates of hyperphosphorylated tau may precede amyloid accumulation. The relation between tangles and plaques has yet to be fully elucidated, but Aβ fibrils can promote tangle formation [14].

The onset of Alzheimer symptoms before about age 60 years is associated with autosomal dominant mutations that lead to excessive accumulations of Aβ in the brain. The late onset of Alzheimer's disease is much more common, and the incidence increases with age [15,16]. Dominantly inherited mutations do not play an important role in this older age group, but a common polymorphism in the gene that encodes apolipoprotein E (the $\varepsilon 4$ allele) increases risk, more so for women than men [17,18]. Estrogen influences apolipoprotein E expression in the brain in a regionally specific manner [19]. Apolipoprotein E is a lipid carrier protein that regulates the transport of lipids during dendritic growth, synaptogenesis, and neuronal repair [20]. It forms complexes with Aβ and may be involved in amyloid trafficking [21,22]. In Alzheimer's disease the $\varepsilon 4$ allele is associated with greater Aβ deposition in the brain [23,24].

The hippocampus and adjacent structures of the medial temporal lobes are affected early by pathological changes of Alzheimer's disease, as are cholinergic neurons of the basal forebrain. Cholinergic deficits are prominent in Alzheimer's disease [25], and the current mainstay of treatment is directed toward increasing brain levels of acetylcholine. Association areas of the cerebral cortex are increasingly involved as the illness progresses. Pathological features of Alzheimer's disease may be found decades before clinical manifestations emerge [26]. Increasingly, it is appreciated that Alzheimer pathology usually does not occur in isolation. Often, there is coexisting evidence for vascular changes and other abnormalities. Not surprisingly, multiple pathologies appear to reduce the threshold at which Alzheimer changes are clinically manifest as cognitive impairment [27]. Improving vascular health might, for example, reduce the likelihood of later developing symptoms of Alzheimer's disease.

Estradiol reduces the formation of Aβ [28] and reduces tau hyperphosphorylation [29]. It can enhance neurogenesis within the dentate gyrus of the hippocampus [30]. Further, estradiol facilitates long-term potentiation in the hippocampus [31]. This physiological process is believed to be important in the formation of episodic memories. Estradiol has other attractive properties. It is