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Estrogens, hormone therapy, and hippocampal volume in postmenopausal women

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Abstract

The brain atrophies in late life. However, there are many factors that either magnify or mitigate the rate of atrophy. Loss of estrogens during menopause and administration of hormone therapy have both been hypothesized as sources of individual variation in the prevalence of cortical and subcortical atrophy and loss of cognitive function in late adulthood. In this review we critically summarize and assess the extant rodent and human neuroimaging studies that examine the link between estrogens and hippocampal morphology and function and focus predominantly on human studies of the hippocampus in postmenopausal women. Several cross-sectional studies report that the size of the hippocampus is larger in women receiving hormone therapy while several other cross-sectional studies report either negligible effects or smaller volumes in women receiving hormone therapy. We suggest that these differences might be caused by the variation between studies in the age of the samples studied, the duration of therapy, and the age at which hormone therapy is initiated. Unfortunately, all of the human studies reviewed here are cross-sectional in nature. With the lack of well-controlled randomized trials with neuroimaging measures on postmenopausal women both before and after some exposure interval, the effect of hormone therapy on hippocampal atrophy will remain equivocal and poorly understood.

Keywords

Hormone therapy; Estrogen; Hippocampus; Volume; Brain

The hippocampus, a brain structure located in the medial temporal lobe, is vital to many functions including learning and memory, and is particularly vulnerable to age-related deterioration [1]. Hippocampal atrophy has been implicated in the development of Alzheimer's disease [2] with smaller volumes predicting more rapid conversion from mild cognitive impairment to dementia [3]. Yet, despite the link between the size of the

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hippocampus and Alzheimer's disease, it is clear that there is considerable variation in the trajectory of hippocampal loss over time. Such individual variation has prompted the investigation of factors that might explain the variation. If, for example, a reduction in circulating hormones (e.g. estrogens) during the climacteric and after menopause is partly responsible for this individual variation, then treatments such as hormone therapy might attenuate or amplify the rate of decline. Many women begin hormone therapy to alleviate the symptoms of perimenopause and to aid in the prevention of health problems such as osteoporosis. However, hormone therapy has its disadvantages with long-term treatment, or treatment initiated many years after menopause, associated with a greater risk of breast and ovarian cancer [4,5]. Given the manifold effects of hormone therapy on risk for disease, it has been a challenge for researchers to predict whether hormone therapy would have a beneficial or disadvantageous effect on hippocampal volume and function in late life.

In this review we attempt to summarize and assess the studies that examine whether hormone therapy has any appreciable effect on the size and morphology of the hippocampus in humans. Several prior reviews have described the association between hormone therapy and cognition in post-menopausal women [6,7]. Therefore, to avoid redundancy, we will limit our discussion to neuroimaging studies, focusing on the associations between hormone therapy and the size of the hippocampus. Although we focus this review on the hippocampus in postmenopausal women, it is clear that hormones and hormone therapy affect many other brain areas throughout the lifespan. The absence of a discussion of other brain areas or other ages or populations is not one of negligence, but simply stems from a need to focus this review on the most frequently studied structure (i.e. hippocampus) and population (i.e. postmenopausal women) in human neuroimaging studies of estrogen effects. Similarly, although we primarily focus on human research, we will first discuss the well-established links between estrogens and hippocampal function in rodents since it is essential to understand this work before attempting to understand the findings in humans.

1. Effects of estrogen administration on hippocampal morphology and function in rodents

Some of the earliest indications that estrogens modulate the structure and function of the limbic system came from demonstrations that seizure thresholds vary across the menstrual cycle in women and estrous cycle in rodents, with increased hippocampal excitability, synaptic transmission, and tendency for seizures at times of high levels of estrogens (for review see [8–10]). The search for neural mechanisms of this shift in excitability state led to the discovery in rodents that endogenous or exogenous elevations in estradiol produce striking increases in the density of dendritic spines and synapses in subregions of the hippocampus that wane with decreases in estradiol [11–13]. Estradiol treatment to ovariectomized rats also promotes neurogenesis and protects against ischemic damage in the hippocampus of both young and old rats [14,15]. Furthermore, estrogens stimulate angiogenesis and may do so in the hippocampus through upregulation of vascular endothelial growth factor (VEGF) in astrocytes [16]; new capillaries may provide metabolic support for newly formed neurons and for regenerative processes. Taken together, these findings suggest that the loss of hormones with reproductive senescence may place the aging female at greater risk for brain atrophy and that hormone therapy might protect against age-related volumetric decreases in hippocampus and related structures.

Given the robust effects of estrogens on hippocampal morphology, it is not surprising that estradiol modulates neurophysiological output of hippocampal neurons. Induction of long-term potentiation of synaptic efficacy (LTP) in the hippocampus fluctuates with ovarian hormone levels (for review see [17]). Application of estradiol to hippocampal slices from ovariectomized rats facilitates LTP, which is highest in female rats at proestrus when

circulating estrogens are at their zenith and lowest when hormones are at their nadir. While much of the evidence of estrogenic effects on hippocampal function comes from paradigms using young adults, recent tests have been made across aging [17,18]. Even after long periods of hormone deprivation, within minutes of exposure, estradiol rapidly facilitates synaptic transmission measured by in vitro recordings of field potentials in CA1 pyramidal neurons, corroborating earlier reports in young adult females and males [15]. Modes of synaptic plasticity in the hippocampus appear to shift with aging making increases in synaptic strength such as LTP less likely and decreases in synaptic strength, such as long-term depression (LTD) more likely [19]. Interestingly, chronic estradiol treatment to old, ovariectomized female rats blocked the LTD that is typical of old rats [18]. Thus, estrogens increase synaptic transmission and strength and attenuate synaptic weakening, potentially increasing information flow through the hippocampus. Viewed in this way, hormone therapies that contain estrogens might be expected to enhance cognitive abilities that rely on intact hippocampal function.

There is now considerable evidence in rodent models that changes in estrogen status can alter performance on learning and memory tasks that tap hippocampus function (for review see [20]). In general, moderate elevations in estrogens promote hippocampus-sensitive functions such as spatial navigation that requires place learning, object placement recognition, and working memory in spontaneous and food-motivated tasks. However, the same treatments impair other abilities that require sensorimotor integration, cued learning, and the use of egocentric response strategies known to tap the striatum [20–22]. These bidirectional effects are not limited to young adults, and can be found in middle-aged and old female rodents as well [23–25]. The opposing actions of estrogens point to a memory systems view that hormone therapy may up- and down-regulate different neural systems thereby producing enhancements in cognitive functions that may engage only certain structures or that may even come with a cost to other functions.

2. The effects of hormone therapy on hippocampal volume

The extant animal research described above along with evidence that administration of hormone therapy to postmenopausal women was associated with improvements in verbal memory [26–29] led to the hypothesis that hormone therapy might have some positive effect on brain health in humans. To test this hypothesis investigators have used magnetic resonance imaging (MRI) to acquire high-resolution brain images in either a cross-sectional sample of postmenopausal women or both before and after some period of administration of hormone therapy. One of the most frequently employed, and validated, measure of “brain health” in older adults is hippocampal volume. Studies have found that the size of the hippocampus in late life (after normalization by overall brain size or intracranial cavity) is a predictor of memory performance [30] and conversion to dementia [3] with smaller structures associated with poorer memory and greater risk of conversion to dementia.

Several cross-sectional studies found that postmenopausal women currently receiving or who had previously received hormone therapy had larger hippocampal volumes compared to women who had never received hormone therapy [31–36]. For example, volume of the hippocampus and other brain structures were examined in a sample of 43 postmenopausal women at an average age of 67.8 years, who retrospectively recalled whether they had received hormone therapy during menopause. Voxel-based morphometry was used to examine differences in hippocampal volume between the groups, while education and socio-economic status were considered covariates of no interest [33]. Women who had reported receiving hormone therapy during menopause had significantly greater hippocampal volumes than their peers not receiving hormone therapy. Similar results have emerged from studies using manual tracing or automated segmentation of the hippocampus [32] even after

controlling for variation due to age, years of education, socio-economic status, and other potentially confounding variables. Thus, from cross-sectional studies, there is evidence that hormone therapy might have protective or proliferative effects on hippocampal volume.

On the other hand, several studies have found that women receiving hormone therapy have smaller hippocampal volumes compared to women either not receiving hormone therapy or receiving a placebo [37–39]. One study compared the size of the hippocampus in women who had completed the Women's Health Initiative Memory Study (WHIMS), a randomized, clinical trial where post-menopausal women received either estrogen alone, estrogen with progesterone, or placebo. MRI scans conducted 1–3 years post-trial in a subset of 1403 women aged 71–89 revealed that women in either of the hormone therapy groups had significantly smaller hippocampi than women who had been assigned to the placebo group. The authors concluded that the use of conjugated equine estrogens in older women was associated with greater hippocampal atrophy [38].

In contrast, there have been other studies reporting no significant differences in hippocampal volume when comparing women receiving hormone therapy and those not receiving hormone therapy [40–43]. For example, one study compared global and regional brain volumes of 213 women aged 60–64 who were currently or formerly taking hormone therapy to women that had never taken hormone therapy. They found negligible differences in whole and regional brain volumes, including the hippocampus, between these groups [42]. Other cross-sectional studies in postmenopausal women have also reported little variation in hippocampal volume as a function of hormone therapy usage [40,41].

3. Moderators of the effect of hormone therapy

Clearly, there is significant variation between studies with some finding greater hippocampal volumes in women receiving hormone therapy and others reporting either smaller volumes or negligible differences between groups. This variation begs the following questions: (1) What factors explain the differences between studies? (2) Are there moderating factors that are either augmenting beneficial effects or offsetting deleterious effects on hippocampal volume?

There are many factors that vary between studies that could explain these different results. In fact, since the majority of previous studies have been cross-sectional in nature, there is the potential for many unknown third variables to be influencing the pattern and direction of results. For example, the age of the women selected to participate in the studies described above varies considerably. Lord et al. [36] included postmenopausal women aged 50–74 while Resnick et al. [38] included women 71–89. Given the significant and non-linear hippocampal atrophy within this age range along with an increase in age-related comorbidities (e.g. cardiovascular disease), it is possible that age is an important confounding variable that is contributing to the differences between studies.

In addition to the difficulties in interpreting the aforementioned results with respect to age, there are several other factors that could moderate the effects of hormone therapy on hippocampal volume. For example, the duration of exposure to hormone therapy might influence the direction and magnitude of the effects. Some studies have observed that longer treatment durations are associated with smaller hippocampi [36,39,44], while others have either failed to find an association or found a positive association between treatment duration and hippocampal volume [33,42]. For example, Lord et al. [39] included women who had used hormone therapy from six months to 26 years, while other studies have included a more narrow range of treatment duration. In addition, the association between the duration of hormone therapy and hippocampal volume might not be linear in nature such that shorter durations might be protective while longer durations might be harmful. For

example, Erickson et al. [44] found that hippocampal volume was greater in women receiving hormone therapy for 1–10 years, but women receiving hormone therapy for more than 10 years had smaller hippocampal volumes. Hence, studies that categorize short-term or long-term use without reference to the meaning of those categories might be examining only part of the association.

Another explanation for the differences between studies is that there is an ideal window after menopause to initiate hormone therapy, a likelihood supported by a growing body of evidence in non-human animal models [45], with greater intervals between onset of menopause and initiation of treatment being associated with greater impairments and hippocampal atrophy. For example, one study found that women who started hormone therapy during the onset of menopause had significantly larger hippocampi than women who had never used hormone therapy. Furthermore, hippocampal volumes in women who began treatment at least one year after the onset of menopause were comparable to women who had never used hormone therapy, suggesting that the possible protective effects of a hormone regimen on hippocampal volume could be negated by late treatment initiation [34]. In concordance with this result, an ancillary study of the Women's Health Initiative (WHI) found that women who had initiated hormone therapy close to the onset of menopause had a trend for a reduced risk of coronary heart disease compared to women who initiated hormone therapy long after the onset of menopause [46]. However, in retrospective studies it can be difficult to separate the effects of duration and timing of initiation of hormone therapy. For example, some studies examining the effects of hormone therapy on verbal and visual memory have only included those who had initiated therapy early in menopause and who had continued therapy for several years [47,48]. While these studies have found positive effects of hormone therapy on memory performance, they are unable to determine whether early initiation or long-term use is more important for improved cognitive performance.

Of course there are other factors that might also be moderating the effect of hormone therapy on hippocampal volume. For example, higher cardiorespiratory fitness levels are associated with larger hippocampal volumes [34], and studies with a greater percentage of postmenopausal women tend to show larger effect sizes on cognitive outcomes in interventions that administer aerobic exercise [49]. Because of this it has been speculated that aerobic exercise moderates the effect of hormone therapy on brain and cognition. In support of this hypothesis, rodent research has reported that the combination of estrogen administration and exercise promotes the expression of brain-derived neurotrophic factor (BDNF) more than either treatment by itself [50]. Some comparable results have been reported in humans. That is, a graded treadmill test was conducted to assess cardiovascular health in post-menopausal women. Women with higher cardiorespiratory fitness levels, regardless of hormone status, had larger parahippocampal gyri than their less fit counterparts. While there was a decline in hippocampal volume with increasing hormone treatment duration, fitness modified this relationship markedly. Women with higher fitness levels who were also receiving hormone therapy showed a much smaller decline in hippocampal volume with increasing treatment duration [44].

The moderating effects of age, duration of hormone treatment, timing of treatment initiation, and cardiovascular fitness are factors that many studies overlook in data collection or fail to examine in cross-sectional research. Randomized clinical trials of hormone therapy are necessary to tease these associations, and their moderators, apart to more formally conclude whether hormone therapy has any appreciable effect on hippocampal volume, or the volume of any other brain region. Unfortunately, the largest trial to date, the WHIMS trial, did not have MRI scans conducted at baseline before randomization. However, if we assume that volumes were equivalent between groups at baseline, it would appear that the initiation of

hormone treatment is associated with a reduction in volume. However, as the authors of these studies point out [37,38], the initiation of hormone treatment occurred many years after menopause, likely after any window-of-opportunity that could have had a protective effect on volume.

4. Summary

Unfortunately, the association between hormone therapy and hippocampal volume in humans remains equivocal. About half of the studies have reported that women receiving hormone therapy have larger volumes than their peers not receiving hormone therapy. Yet, the largest studies to date have found that women randomly assigned to receive hormone therapy have smaller volumes than do women not receiving hormone therapy. There are clear discrepancies and so much variation in factors (e.g. age) that could be explaining this variation, that it is impossible to make any firm conclusion about the effects of hormone therapy in postmenopausal women. This, however, is in stark contrast with the results from rodent studies that clearly and unequivocally assign an important role for estrogen in many aspects of hippocampal function including gene expression, spatial learning and memory, dendritic spine density, and long-term potentiation. Rodent studies, however, have their own limitations that impair direct translation to studies of human postmenopausal women. In short, there remains much to learn about whether hormone therapy, estrogen and/or progesterone administration has any detectable effects on hippocampal volume in postmenopausal women.

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