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Frontiers in Neuroendocrinology 26 (2005) 51–64
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Interaction of rapid signal transduction cascades and gene expression in mediating estrogen effects on memory over the life span

Thomas C. Foster *

Department of Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, FL 32610-0244, USA

Available online 14 July 2005

Abstract

Estrogen treatment during middle-age postpones memory impairments, which depend on the hippocampus. However, estrogen responsiveness diminishes with advanced age. The challenge remains to determine, which processes are important for delaying brain aging and the mechanisms for decreased sensitivity. Estrogen can influence transcription through estrogen receptors (e.g., ERα and ERβ) and membrane effects on rapid signal transduction cascades ultimately influencing the phosphorylation state of transcription factors. In middle-aged animals, the membrane effects involve Ca^{2+} and G-protein cascades, which rapidly counteract senescent physiology. Moreover, estrogen induces transcription for elements of signal transduction cascades that decline with age. Together, the rapid and genomic influences promote synaptic transmission and cell growth. Thus, interruption of genomic/membrane interactions due to loss of ERs, disruption of the hormone cycle, or uncoupling of the hormone/receptor system associated with extended exposure to estrogen could contribute to a decline in these biological pathways during aging.

Keywords: Estrogen; Aging; Memory; Ligand-independent; Synaptic; Hippocampus; Signal transduction cascade; Estrogen receptor

1. Introduction

The incidence of Alzheimer's disease (AD) is projected to increase dramatically in the next several decades with the greatest prevalence in women (68%) [26]. Mounting evidence suggests that estrogen influences memory processes which depend on the hippocampus and can delay the onset of age-related memory impairments. As such, estrogen treatment could have a major impact on public health by delaying the progression of memory loss associated with normal aging and AD [20]. However, estrogen use is also associated with risks and controversies have arisen due to reports that suggest estrogen can increase the possibility of dementia [165,198]. To develop therapies based on estrogen mechanisms, the challenge remains to determine which biological processes are important for estrogen effects on cognition. The discovery of several different nuclear estrogen receptors and emerging evidence for rapid non-genomic influences on signal transduction cascades makes this challenge more formidable. Finally, the efficacy of hormone replacement therapy (HRT) may be greatly reduced or nonexistent if therapy is not set in motion until several years after the onset of menopause or after the symptoms of AD are manifest. Thus, in addition to distinguishing the mechanism for estrogen effects on memory, it is important to determine how estrogen responsiveness interacts with brain aging.

2. Estrogen effects on memory over the life span

2.1. Humans and primates

Interest in estrogen effects on memory mechanisms has increased due to evidence indicating that HRT delivered near the onset of menopause can delay the progression of

* Fax: +1 352 392 8347.
E-mail address: Foster@mbi.ufl.edu.

0091-3022/$ - see front matter © 2005 Published by Elsevier Inc.
doi:10.1016/j.yfrne.2005.04.004

AD [102,150,207,223] and age-related cognitive decline [40,53,97,170]. Moreover, estrogen amelioration of memory impairments has been reported following surgical and naturally occurring menopause [189,237]. Accordingly, it has been suggested that estrogen treatment acts to increase "brain reserve," delaying the progression of memory loss associated with normal aging and AD [20,102,208].

The enthusiasm for estrogen as a cognitive enhancer needs to be tempered by important limits on treatment. First, while HRT may be beneficial in postmenopausal women, preventing osteoporosis, cardiovascular disease, age-related memory decline, and AD; estrogen use is also associated with an increased risk of cancer [44]. A second consideration relates to the treatment paradigm. One particularly relevant factor is the age at which HRT is initiated. The evidence suggests that beneficial effects may be limited to middle-aged, perimenopausal women [190]. In contrast to perimenopausal women, higher estrogen levels have been associated with impaired spatial memory in younger women [84,155,191]. A similar pattern of interaction between estrogen and age is observed in monkeys such that estrogen replacement is associated with impaired [111,112,218] and improved cognition [113,164] in young and middle-aged animals, respectively. Finally, the beneficial effects of estrogen on memory in elderly postmenopausal women [10,52,127,157] or women previously diagnosed with AD [25,140] is controversial with several reports indicating no effect. Indeed, for women over 65 years of age, HRT with an estrogen–progestin combination may be associated with an increased incidence of dementia [165,198].

In those cases in which estrogen facilitated memory in older postmenopausal women, better performance was associated with higher plasma estrogen levels, suggesting the possibility that higher estrogen levels were required to overcome a reduction in estrogen responsiveness [6,46,228,229,233]; however, see [45,51], or reduced bioavailability [92]. Alternatively, it is possible that in these cases, estrogen was acting through nonreceptor mechanisms including antioxidant activities [138]. The upshot of this work indicates that estrogen delivered at about the time of menopause provides a reserve capacity or protective factor against brain aging and memory decline [80,169,236]. However, the efficacy of HRT, at least for physiological levels of hormone, may be greatly reduced or nonexistent if therapy is not set in motion until several years after the onset of menopause or after the symptoms of AD are manifest [19,140].

2.2. Rodents

The extensive literature concerning estrogen effects on cognition in rodents provides an opportunity for examination of differences, which may illuminate important variables for understanding hormonal modulation of memory processes. In addition, much research has focused on the hippocampus due to its role in memory function. This body of work has demonstrated that estrogen influences hippocampal anatomy, physiology, and biochemistry [230]. In rodents, aging is associated with deficits in memory retention/consolidation and has been extensively characterized using the Morris water maze (for a review see [55]). The impairment on this hippocampal-dependent task is sexually dimorphic, emerging at a time when alterations in the estrous cycle regularity are observed [57,60,124]. As with humans, the literature concerning estrogen effects on the water escape tasks in young rodents is complex with studies showing improved memory [105,146,148,172,177,216,234], impaired memory [36,57,61,62,65–67,224], and no effect [13,202]. For example, in young intact animals, impaired learning has been reported for the Morris water task during times when plasma estrogen is rising or near peak levels [61,65–67,224]. Studies that attempt to mimic the estrous cycle confirm that rising estrogen levels or the fluctuating levels of both ovarian hormones are associated with impairments in learning [36,61,62,106]. These spatial learning deficits maybe reduced when estrogen is delivered chronically [57,173,202]. Interestingly, acute subcutaneous or intrahippocampal injection of estrogen, within 2 h after water maze training significantly improves retention in young rats [148]. Moreover, memory enhancing effects are observed with acute estrogen administration delivered several days prior to training [177]. Taken together the results indicate that, in young animals, there is an important temporal component for estrogen effects such that hormone treatment during training can impair learning/memory and beneficial effects are observed when estrogen is delivered several days prior to or shortly after learning.

One possibility for the impaired learning is that the level of estrogen during training may interact with training associated stress to influence acquisition or retention [29,43,85,193,215]. In this regard, chronically elevated hormone is associated with impaired memory for tasks with a prominent stress or emotional component [68,77] and the interaction of estrogen and stress can be reduced by habituation to stressful aspects of the procedure [24,57] or using less stressful tasks, such as a delayed matching-to-position [73]. In addition, it is possible that there is a therapeutic window for positive effects on memory, such that estrogen improves memory only under conditions of memory impairment. For example, estrogen can act as an extrinsic modulator of synaptic plasticity effectively blocking some forms of neural plasticity or driving other plasticity processes to some maximum limit, in effect removing the potential range of modulation [57]. Similar, effects on memory and synaptic plasticity are observed for genetic manipulations, which modify the G-protein signaling cascade [156].