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Review

Estrogens facilitate memory processing through membrane mediated mechanisms and alterations in spine density

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ABSTRACT

Estrogens exert sustained, genomically mediated effects on memory throughout the female life cycle, but here we review new studies documenting rapid effects of estradiol on memory, which are exerted through membrane-mediated mechanisms. Use of recognition memory tasks in rats shows that estrogens enhance memory consolidation within 1 h. 17α-Estradiol is more potent than 17β-estradiol, and the dose response relationship between estrogens and memory is an inverted U shape. Use of specific estrogen receptor (ER) agonists suggests mediation by an ERβ-like membrane receptor. Enhanced memory is associated with increased spine density and altered noradrenergic activity in the medial prefrontal cortex and hippocampus within 30 min of administration. The environmental chemical, bisphenol-A, rapidly antagonizes enhancements in memory in both sexes possibly through actions on spines. Thus, estradiol and related compounds exert rapid alterations in cognition through non-genomic mechanisms, a finding which may provide a basis for better understanding and treating memory impairments.

1. Introduction

Only 40 years have elapsed since the brain, specifically the hypothalamus, rather than the pituitary, was recognized as the site for estrogen's regulation of ovulation and sexual behavior (Everett, 1965; Gorski, 1971). An even shorter time, approximately 15 years, has passed since neuroendocrine research, driven by advances in molecular biology and technology, established that estradiol also impacts higher order brain functions such as mood and psychiatric disorders (Ostlund et al., 2003; Payne, 2003), bonding and affiliation (Carter et al., 1997), and the focus of this review, cognitive function (Luine and Harding, 1994; Dohanich, 2002). Cognitive effects of estradiol are mediated by actions of estrogens at sites and/or neural systems in the cerebral cortex, basal forebrain, hippocampus and striatum that are responsible for complex, higher order neural function. Thus, it is now recognized that estrogens not only regulate homeostatic/house-keeping functions of the CNS but also influence the intellectual/cognitive realms of life.

Estrogen's influence on learning and memory, similar to its reproductive effects occur through binding to classical nuclear receptors. These receptors, which were first isolated and characterized from the uterus, were subsequently found in many brain sites (see Fig. 1 and (Jensen and Jacobson (1962) for review). It is now known that there are two nuclear estrogen receptors, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) (Kuiper et al., 1997). Both receptors are ligand dependent transcription factors and through interactions at specific sites on DNA, initiate a cascade of intra-cellular reactions culminating in unique physiological responses within estrogen target tissues including the uterus, breast, osteoclasts and CNS (see McEwen and Alves (1999) for a detailed description of genomic mechanisms of estrogen action in the CNS and for information concerning some non-ligand-dependent actions). Genomic actions in the nucleus by hormones result in long lasting and sustained effects on neural function. Thus, it is likely that genomic alterations by estradiol sub-serve developmental hormone effects, which exert life-long actions in programming sex-dependent functions and sex differences in neural functions. In adults, genomic effects underlie changes in neural function that occur during the menstrual and estrous cycles, pregnancy, menopause and aging.

Another recent advance in understanding mechanism(s) for estradiol's mediation of physiological and neural function is that receptor(s) for estrogens are present outside of the cell nucleus in membranes of cells in the periphery and the CNS (see Fig. 2 and Blaustein (1992), Milner et al. (2001) and Towart et al. (2003)). Moreover, these receptors are present in the medial prefrontal cortex (PFC) and the hippocampus, areas which are

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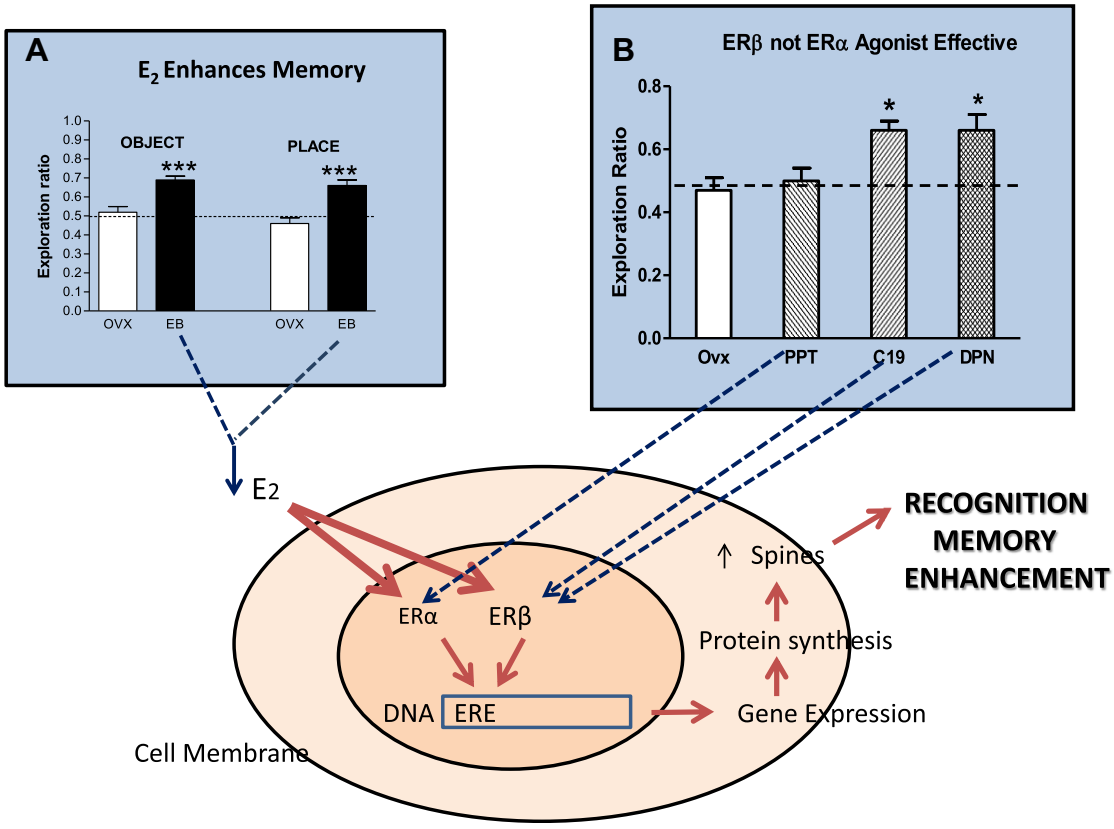

Fig. 1. Schematic of genomic mechanism for estrogenic responses and effects of estradiol and receptor agonists on recognition memory. Circulating estrogens enter the cell nucleus where they bind to two types of receptors, ERα and ERβ, and the complex acts as a nuclear transcription factor by binding to an estrogen response element (ERE) on DNA and stimulating transcription of specific genes whose proteins then alter neural functions including the enhancement of memory. (A) Estradiol enhances memory. EB was given at 50 μg/kg for 2 days and object recognition and placement tested 48 h later, $P < 0.001$. (B) Effects of specific ER agonists on object recognition. ERα specific agonist, PPT, and ERβ specific agonists, C19 and DPN, were given as in Inset A. Only ERβ agonists enhanced memory, $P < 0.05$. Data from Jacome et al. (2010).

not directly involved in neuroendocrine regulation. In peripheral target tissues, the breasts, osteoclasts and epithelial cells of the cardiovascular system, the estrogen membrane receptors are similar or identical to classically identified ERα and β receptors, and they mediate rapid hormonal effects (sec to min) through signal transduction pathways (see Fig. 1 and Levin (2002) for review of early work on the topic). Thus, estrogen effects can be rapid and short-lived as well as delayed in onset and long lasting.

The focus of this review is to present results of current studies demonstrating that estradiol exerts rapid enhancements of memory that may be mediated through actions at membrane receptors. First we provide a short background on methods for assessing cognitive function, i.e. learning and memory. Then studies demonstrating estradiol's enhancements of cognition through classic, genomic mechanisms are provided in order to provide background for recent studies, which show rapid effects of various estrogens and specific estrogen agonists on recognition memory. Possible mechanisms underlying the cognitive changes are discussed, including the role of rapid increases in spine density in the medial PFC and hippocampus, as well as, a brief consideration of signaling cascades that may initiate the estradiol-dependent changes. We also provide evidence that the environmental estrogen, bisphenol-A, rapidly impairs memory consolidation through effects at the membrane and dendritic spines. We close with a consideration of how rapid signaling by estrogen may impact cognitive function in animals and humans. Thus, this review will provide evidence that both 17α- and 17β-estradiol initiate a rich repertoire of neural inter-actions that regulate physiology and cognition.

2. Assessing cognitive effects of estrogens

A substantial literature has demonstrated that gonadal hormones, mainly estradiol, influence cognition function during development, at adulthood and during aging (Frick, 2009; Luine, 2008). However, it is critical to note at the onset of this review that estradiol does not enhance all aspects of cognition (Dohanich, 2002; Frick, 2009; Luine, 2008). This observation is not surprising since cognition represents a complex, multidimensional set of intellectual functions whose component processes are subserved by specific, yet interrelated, brain regions. Moreover, cognition itself consists of several components. First, there is the process of learning or acquiring information. Then the information must be consolidated and stored. Finally, the memory or information must be retrieved when needed. This process can be illustrated through the playing of card games. First, the rules for playing Bridge or Poker must be learned or acquired (acquisition). Then cards played during a current game must consolidated and stored. Finally, memory of the played cards must be retrieved at the appropriate time during the game. Experimental rats undergo a similar process when they learn and then perform various cognitive tasks. An important point to emphasize is that estradiol may not enhance every aspect of this cognitive process.

Spatial memory tasks have been used in many learning and memory studies, including those utilizing estradiol, and these tasks have both learning and memory components. The radial arm maze and the water maze rely on rats making relationships between cues in the environment and a reinforcement site, hence their designation as spatial learning. The reinforcement site could be food