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Review

Estradiol: Mediator of memories, spine density and cognitive resilience to stress in female rodents

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ABSTRACT

Estradiol rapidly activates, within minutes, various physiological functions and behaviors including cognition in rodents. This review describes rapid effects of estradiol on hippocampal dependent learning and memory tasks in rodents. Mechanisms underlying the memory enhancements including the activation of signaling molecules and the enhancement of dendritic spinogenesis are briefly reviewed. In addition, the role of estradiol in the cognitive resilience to chronic stress exhibited only in females is discussed including contributions of ovarian as well as intra-hippocampally derived estrogens to this sex difference. Finally, speculations on possible physiologic functions for rapid mnemonic changes mediated by estrogens are made. Overall, the emergence of a novel and powerful mechanism for regulation of cognition by estradiol is described.

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Contents

1. Introduction

Estradiol was first demonstrated to regulate learning and memory through alterations in neural morphology, physiology and chemistry approximately twenty years ago [see Luine, [1] for review]. Estrogen dependent increases in spine density and synapse number in the hippocampus, as well as increased activity of monoaminergic and cholinergic terminals, were similar to earlier descriptions of estrogen dependent modulations in pre-optic-hypothalamic area neurons that regulate sexual behavior, ovulation and also food ingestion [2]. The mechanism for effects in both the hypothalamus and hippocampus depend on binding of estrogen to classical receptors (ERs) which subsequently act as ligand dependent transcription factors. Interactions of the receptor-ligand complexes at estrogen response elements (ERE) on DNA stimulate transcription of specific genes whose proteins then

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determine the unique physiological responses of estrogen target tissues such as the uterus, breasts, osteoclasts as well as the CNS. These genomic alterations by estradiol are delayed in onset (several hours to days) but result in long lasting and sustained effects on neural function and most likely underlie physiological, behavioral and cognitive changes that occur in females during the menstrual and estrous cycles, pregnancy, menopause and aging. For a description of the major neuronal systems altered and specific proteins changed by genomic actions of estrogens, see Ref. [2].

More recently, estradiol has been demonstrated to rapidly, within minutes, activate various physiological functions and behaviors in rodents, birds and possibly humans. These behaviors include female rodent sexual behavior [3], avian male sexual displays [4], nutrient ingestion [5], social learning [6] and cognition [7,8]. The expression of these behaviors is dependent upon activation of different, but often, inter-related areas in the brain through estrogen's interaction with membrane ERs. Rapid effects of estrogens were reported in the 70s and 80s (1–5), but it is only recently that they have been widely explored in behavioral paradigms; nonetheless, some consistent patterns of action are emerging. This review will describe rapid effects of estradiol on hippocampal dependent learning and memory tasks in rodents, and the contribution of signaling molecules and dendritic spines in rapidly mediating memory enhancements will be briefly reviewed. The ecological advantages and usefulness for rapid mnemonic changes are currently unknown, but speculations are made. Finally, the contribution of this mechanism, combined with intra-hippocampal synthesis of estradiol, for mediating cognitive resilience to chronic stress demonstrated by females, but not males, is considered. Overall, the emergence of a novel and powerful mechanism for regulation of cognition by estradiol is described.

2. Estradiol rapidly enhances recognition memory

My laboratory and others have utilized a number of hippocampal dependent spatial memory tasks to show that chronic treatments with estradiol, several days to several weeks, enhance learning and memory. Ovariectomized (OVX) rats injected daily with estradiol benzoate (long acting form of estradiol) or implanted with Silastic capsules containing estradiol (release constant amounts of hormone for weeks) for 2–10 days show improved performance on the radial arm maze (RAM) [9], water maze [10] and novel object recognition and novel object placement [11–13]. For RAM and water maze studies, many trials over several days are required to learn the tasks, and these tasks are therefore ideal for assessing effects of chronic estradiol. However, for evaluating potential rapid effects of hormones or drugs, tasks with a shorter time course are necessary, and one-trial learning and memory tasks have recently been adopted [12,13]. Fig. 1 depicts such tasks showing assessment of recognition memory using either a spatial configuration, novel object placement (NOP) or a non-spatial configuration, novel object recognition (NOR). As indicated, estradiol or other hormones/drugs can be given for days before the learning or sampling trial (T1) to assess chronic treatments, or minutes before T1 or immediately following T1 (known as post-training injections) in order to assess rapid hormonal effects. The retention trial (T2) is typically given from 1 to 48 h after T1. If a subject, rat or mouse, remembers the old object or the old location, then the new object or the object in the new location is explored more than the old object or object in old location because rats are exploratory and novelty seekers. Data is usually expressed as the exploration ratio (time exploring new object or location/total exploration time) where values over

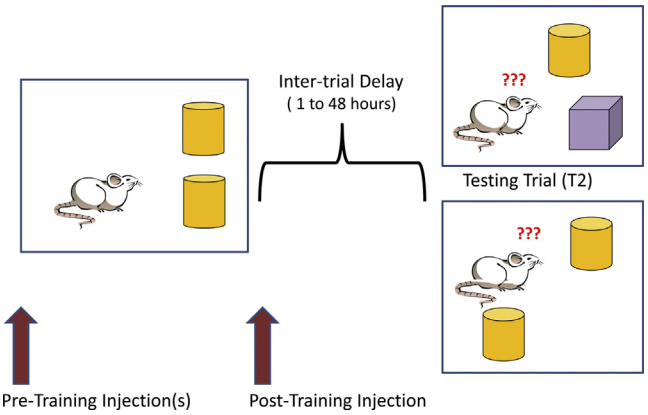

Fig. 1. Schematic of recognition memory task protocols.
On the left side of the figure, a rat is depicted during the training or sampling Trial (T1) where two identical objects are explored, typically for 3–5 min or until a set amount of exploration is obtained. An inter-trial delay is given, and then, shown on the right side, the retention or testing trial is given (usually for 3–5 min). If one identical object is replaced with a new object, this is the novel object recognition (NOR) protocol. If one of the objects is moved to a new location, this is the novel object placement (NOP) protocol, a spatial memory task. Hormones or drugs can be given pre-training (hours or days) to assess genomic changes or immediately post-training or up to two hours later in order to asses rapid changes. Post-training injections test effects of agents on memory consolidation.

0.5 indicate better than chance memory or the actual exploration times for old vs new can be compared.

As shown in Fig. 2A, chronic treatment with estradiol benzoate for two days results in significant enhancements in both NOR and NOP in the retention trial [11], a result similar to chronic treatment effects on the radial arm or water maze. These effects are mediated through classical ERs and genomic mechanisms and appear to involve enhancements of both learning and long term memory [12]. Fig. 2B shows effects of estradiol treatment on NOR and NOP when one estradiol injection is given immediately after the training trial. [14] Significant enhancements are seen 4 h later in the retention trial, and further investigations of this effect by varying time of treatments after T1 indicate that estradiol is enhancing memory retention by increasing memory consolidation (see Ref. [15] for details). Further studies show that these effects are consistent with estradiol acting at membrane receptors [14]. Overall, Fig. 2 illustrates that chronic (multiple treatments given over days) or acute (one treatment given for a few hours) estrogen treatments enhance recognition memory in rats, an effect reported in many studies [12].

3. Mechanisms for rapid enhancements of memory

3.1. Activation of cell signaling

Estrogens exert rapid effects on neural function by activating numerous cell-signaling cascades and epigenetic processes within 5–30 min of treatment in the hippocampus [8,16] and also in the prefrontal cortex, although less evidence is extant for cortical areas [17]. These actions form the bases for estrogen's ability to enhance the consolidation of hippocampal memories. The initial event responsible for memory consolidation appears to be the activation of glutamate receptors (mGluR), primarily MGluR1. These events trigger long term potentiation (LTP) induction, spine formation and memory formation [see Sweat, [18], for review]. Estradiol rapidly activates mGLuR signaling *in vivo* in both the PFC and the hippocampus, and ERs are found on membranes of dendrites and spines, in presynaptic terminals and near post-synaptic receptors where estrogen binding to the ERs initiates rapid activation of

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