Behavioural Brain Research 285 (2015) 140–157

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review article

Regulation of object recognition and object placement by ovarian sex steroid hormones

Jennifer J. Tuscher, Ashley M. Fortress, Jaekyoon Kim, Karyn M. Frick*

Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI 53211, United States

HIGHLIGHTS

- 17β-Estradiol (E_2) and progesterone (P_4) potently regulate hippocampal memory.
- Object recognition (OR) and object placement (OP) are enhanced by E_2 and P_4.
- E_2 and P_4 rapidly activate the molecular processes underlying object memory.
- Both endogenous and exogenous E_2 and P_4 affect object memory across the lifespan.
- This review discusses regulation of object memory by E_2 and P_4 in female rodents.

ARTICLE INFO

Article history:
Received 19 June 2014
Received in revised form 29 July 2014
Accepted 1 August 2014
Available online 15 August 2014

Keywords:
Estradiol
Progesterone
Hippocampus
Object location
Rat
Mouse

ABSTRACT

The ovarian hormones 17β-estradiol (E_2) and progesterone (P_4) are potent modulators of hippocampal memory formation. Both hormones have been demonstrated to enhance hippocampal memory by regulating the cellular and molecular mechanisms thought to underlie memory formation. Behavioral neuroendocrinologists have increasingly used the object recognition and object placement (object location) tasks to investigate the role of E_2 and P_4 in regulating hippocampal memory formation in rodents. These one-trial learning tasks are ideal for studying acute effects of hormone treatments on different phases of memory because they can be administered during acquisition (pre-training), consolidation (post-training), or retrieval (pre-testing). This review synthesizes the rodent literature testing the effects of E_2 and P_4 on object recognition (OR) and object placement (OP), and the molecular mechanisms in the hippocampus supporting memory formation in these tasks. Some general trends emerge from the data. Among gonadally intact females, object memory tends to be best when E_2 and P_4 levels are elevated during the estrous cycle, pregnancy, and in middle age. In ovariectomized females, E_2 given before or immediately after testing generally enhances OR and OP in young and middle-aged rats and mice, although effects are mixed in aged rodents. Effects of E_2 treatment on OR and OP memory consolidation can be mediated by both classical estrogen receptors (ERα and ERβ), and depend on glutamate receptors (NMDA, mGluR1) and activation of numerous cell signaling cascades (e.g., ERK, PI3K/Akt, mTOR) and epigenetic processes (e.g., histone acetylation, DNA methylation). Acute P_4 treatment given immediately after training also enhances OR and OP in young and middle-aged ovariectomized females by activating similar cell signaling pathways as E_2 (e.g., ERK, mTOR). The few studies that have administered both hormones in combination suggest that treatment can enhance OR and OP, but that effects are highly dependent on factors such as dose and timing of administration. In addition to providing more detail on these general conclusions, this review will discuss directions for future avenues of research into the hormonal regulation of object memory.

* Corresponding author. Tel.: +1 414 229 6615; fax: +1 414 229 5219.
E-mail address: frickk@uwm.edu (K.M. Frick).

http://dx.doi.org/10.1016/j.bbr.2014.08.001
0166-4328/

Contents

1. Introduction

The object recognition (OR) task was first introduced in 1988 to provide a method of testing episodic memory in rodents that was similar to methods used in clinical neuropsychology [1]. The task capitalizes on rodent's inherent predilection for novelty. In the most common version of the task, rodents explore two identical objects during a single training session. During the single test session, subjects are then allowed to explore an object identical to the training objects and a novel object. More time spent exploring the novel object indicates memory for the familiar object. In the years since its introduction, OR has become prevalent in rodent learning and memory studies, where it is used alone or as part of a test battery to investigate the effects of lesion, genetic, or pharmacological manipulations. The task has also evolved to assess spatial memory in rodents via a modified version referred to as object placement or object location (referred to herein as object placement) [2]. As such, OR is used to assess memory for the identity of objects (i.e., "what") and object placement (OP) is used to assess memory for the location of objects (i.e., "where"). To this end, OR in rodents is generally considered a non-spatial memory task involving the hippocampus, perirhinal, entorhinal, and parahippocampal cortices [3–5], whereas OP in rodents is considered a spatial memory task that relies primarily on the hippocampus [6]. However, the brain regions involved in OR in rodents and other species have been the subject of intense debate, particularly the role of the hippocampus in mediating OR. Although this issue is not the primary focus of this review, rodent data from our laboratory and others do support a role for the hippocampus in OR, as will be discussed below. Therefore, this review is written from the perspective that the hippocampus is essential for memory formation in both OR and OP. Because the amount of data collected on hormonal regulation of object memory in rodents far outnumbers the amount of data collected in other species, this review will limit discussion to studies employing rats or mice as subjects.

OR and OP are particularly well suited for investigating the molecular processes underlying the formation of hippocampal-dependent memories in rodents. First, they take advantage of a rodent's natural tendency to explore novel stimuli, while avoiding other potentially confounding variables. For example, no rule learning is required, nor are any rewarding or punishing stimuli involved that may influence motivational, rather than mnemonic, aspects of task performance [1,7]. Therefore, memory can be measured in the absence of confounds due to the stress of nutrient restriction (as commonly used in the radial arm maze and T-maze), shock (as used in fear conditioning), or submersion in water (as used in the Morris water maze). Second, OR and OP are true one-trial learning tasks. This quality makes them ideal for studying the effects of acute drug or hormone treatments, which may be given pre- or post-training to investigate effects on different phases of learning and memory such as encoding, consolidation, and retrieval.

This unique combination of one-trial learning in a relatively stress-free environment has appealed in recent years to behavioral neuroendocrinologists seeking to identify the molecular mechanisms through which sex steroid hormones, such as 17β-estradiol (E_2) and progesterone (P_4), influence memory across the rodent lifespan. The low stress associated with OR and OP testing is advantageous for behavioral endocrinologists because corticosteroids released in response to more stressful tasks may interact with ovarian hormones and could confound the interpretation of results [8,9]. Tasks like OR and OP that do not provoke a strong stress response allow for effects of ovarian hormones on memory to be more clearly identified in rodents. Furthermore, behavioral endocrinologists have found that E_2 and P_4 can very rapidly impact hippocampal function [10–13], and therefore, the one-trial nature of OR and OP makes these tasks particularly useful for identifying the molecular mechanisms underlying hormonal regulation of memory consolidation. As such, both OR and OP have been widely used in the past decade to study the effects of sex steroid hormones on hippocampal learning and memory in rats and mice.

However, as will be seen below, investigators have taken very different approaches to studying hormonal regulation of object memory in rodents. Both rats and mice of various strains have been used, with studies employing mice generally outnumbering those using rats. Although species differences could influence the effects of hormones on OR, OR does not appear to differ between