Hormones and Behavior xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Hormones and Behavior

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

Review

The evolving role of dendritic spines and memory: Interaction(s) with estradiol

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ARTICLE INFO

Available online xxxx

Keywords:
Estrogen
Estradiol
Dendritic spines
Memory
Hippocampus
Prefrontal cortex
Synaptic plasticity

ABSTRACT

This article is part of a Special Issue "Estradiol and Cognition".
Memory processing is presumed to depend on synaptic plasticity, which appears to have a role in mediating the acquisition, consolidation, and retention of memory. We have studied the relationship between estrogen, recognition memory, and dendritic spine density in the hippocampus and medial prefrontal cortex, areas critical for memory, across the lifespan in female rodents. The present paper reviews the literature on dendritic spine plasticity in mediating both short and long term memory, as well as the decreased memory that occurs with aging and Alzheimer's disease. It also addresses the role of acute and chronic estrogen treatments in these processes.

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Introduction

The complex mechanisms underlying the formation and retention of memories are assumed to involve synaptic plasticity in the hippocampus and cerebral cortex. Although dendritic spines are sites of synaptic contact and turnover of dendritic spines is an important aspect of synaptic plasticity, the precise role that dendritic spines play in immediate memory formation and long-term storage remains unclear. Given that the focus of our studies has been the relationship between estradiol, memory, and dendritic spines in rodents, this paper will review the literature on dendritic spines and memory function and highlight the association(s) between estradiol, spines, and memory.

Dendritic spines

First described by Ramon Y Cajal, using Golgi impregnation in Purkinje cells of the bird cerebellum (reviewed by García-López et al., 2007), most dendrites are covered with dendritic spines, which were initially assumed to increase the surface area for neurotransmission (Nimchinsky et al., 2002). Spine density varies from extremely spiny

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http://dx.doi.org/10.1016/j.yhbeh.2015.05.004

Please cite this article as: Frankfurt, M., Luine, V., The evolving role of dendritic spines and memory: Interaction(s) with estradiol, Horm. Behav. (2015), http://dx.doi.org/10.1016/j.yhbeh.2015.05.004

pyramidal neurons in the cortex and hippocampus (Nimchinsky et al., 2002; von Bohlen und Halbach, 2009) to the relatively sparse spine density of neurons in the hypothalamus (Frankfurt et al., 1990). In addition to identifying spines on many different neurons, Ramon Y Cajal also described subtypes of spines and noted that the density of dendritic spines increased with increased innervation. Although spine subtype classification varies, dendritic spines generally consist of a protrusion and may have a bulbous termination (in the case of mushroom spines). One may also distinguish between thin spines with a smaller head and stubby spines, which lack any terminal enlargement and have extremely thin filopodia. This latter type are presumed to be the precursors to mature spines (Bourne and Harris, 2008; von Bohlen Und Halbach, 2009; Urbanska et al., 2012).

The cytoskeleton of dendritic spines consists mostly of filamentous actin, which extends from the base of the spine to the postsynaptic density (Bosch and Hayashi, 2012; Penzes and Rafalovich, 2012; Koleske, 2013). The vast majority of dendritic spines have an excitatory synapse at their termination suggesting that their role is to increase the surface area for synaptic contact. However, the observation that adjacent dendritic shafts are devoid of excitatory synapses combined with studies that have demonstrated that Ca^{++} is concentrated in spines has led to the hypothesis that dendritic spines play a critical role in the formation and plasticity of specific functional neuronal circuits rather than increasing the surface area for synaptic contact (Yuste, 2010, 2011). Filopodia, which lack a bulbous termination, also seem to lack synapses, promoting the idea that filopodia may be an immature/transient spine species. The synapse localized to most dendritic spines is an excitatory, glutamatergic one and modulation of that excitatory input by other neurotransmitters, especially inhibitory GABA, is assumed to be indirect. However, recent studies have shown that GABA neurons synapse directly on a subset of dendritic spines adjacent to a glutamatergic synapse (Higley, 2014) demonstrating a more direct relationship between inhibitory and excitatory inputs.

Dendritic spine plasticity

It has become increasingly clear that the nervous system is capable of plasticity and that the dendritic spine is poised to be the major site of this activity (Bourne and Harris, 2008; Bosch and Hayashi, 2012; Penzes and Rafalovich, 2012; Urbanska et al., 2012). There exists a developmental increase in the number of dendritic spines followed by pruning, which appears to depend on many factors (Urbanska et al., 2012). Perhaps more importantly, it is clear that after the connectivity is initially established in the brain, dendritic spine turnover continues (reviewed by Koleske, 2013). As part of the process of establishing neural networks, dendrites and dendritic spines develop, mature, and are retracted as needed. In the adult brain, however, plasticity appears to involve primarily the dendritic spine rather than the dendritic tree. In addition, alterations in dendritic spines are now known to accompany brain trauma, underlie addiction and are implicated in neurological and psychiatric disease (see below) as well as learning and memory.

Until more sophisticated techniques were developed, fluctuations of dendritic spine number and type had been demonstrated in response to many different types of stimuli at different developmental stages and over different periods of time using Golgi impregnation to label spines (see Figs. 1 and 2). Early experiments demonstrated the importance of afferent input to the maintenance of spine density. In 1967, Valverde (Valverde, 1967) demonstrated that mice raised in total darkness had significantly fewer dendritic spines on apical dendrites of pyramidal cells in layer V of the striate cortex compared to control animals. In the hippocampus, deafferentation of granule cells, following lesions of the entorhinal cortex, resulted in a decrease in the number of dendritic spines present on the granule cells, an effect that was reversed with reinnervation (Parnavelas et al., 1974). As described below, many different types of stimuli have been demonstrated to influence dendritic spine plasticity since these early studies.

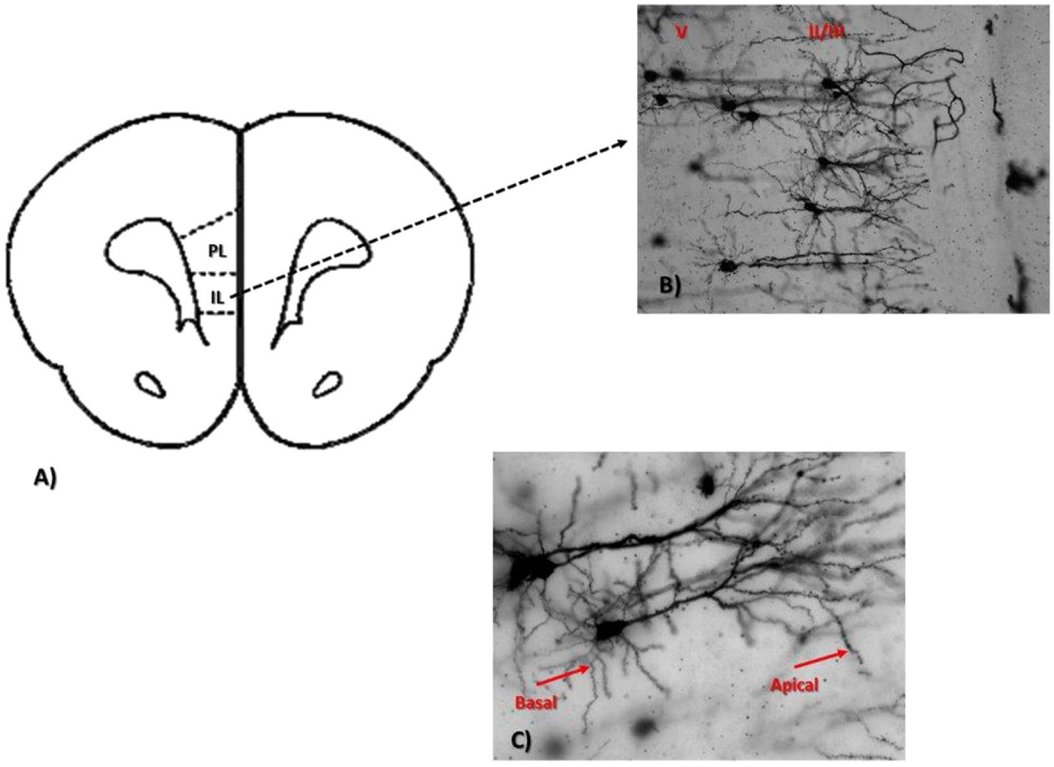

Fig. 1. A. Schematic coronal section illustrating the region of the medial prefrontal cortex of the rat examined in Golgi preparations. B. Golgi impregnated pyramidal neurons from layer III/III and V of the medial prefrontal cortex (10×). C. Representative pyramidal cells from medial prefrontal cortex. Arrows denote the secondary basal and tertiary apical dendrites used for analysis (20×).

Please cite this article as: Frankfurt, M., Luine, V., The evolving role of dendritic spines and memory: Interaction(s) with estradiol, Horm. Behav. (2015), http://dx.doi.org/10.1016/j.yhbeh.2015.05.004