REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN REVIEW ARTICLE

Some actions of the ovarian hormones estradiol and progesterone on cognition

Ofir Picazo, Antonio Vega-Rosales and Judith Espinosa-Raya*

Escuela Superior de Medicina, IPN, México, D.F., México

ABSTRACT

Experience is understood as a sequence of events that occurred in the past, while memory allows recalling the information derived from such experience to face similar events in the present. Currently, great efforts are being made to classify the different expressions of memory. Simultaneously, new animal models are continuously being proposed to explore the complex learning-memory. One of the main factors modifying learning and memory consolidation are the ovarian hormones estradiol and progesterone. This document offers a general memory classification together with a brief review of the recent literature about the role of these hormones on cognition. (REV MEX ENDOCRINOL METAB NUTR. 2015;2:80-4)

Corresponding author: Ofir Picazo, rifo99mx@gmail.com; rifo99@hotmail.com

Key words: Cognition. Ovariectomy. Estradiol. Progesterone. Window opportunity.

RESUMEN

La experiencia es entendida como la secuencia de eventos que ocurrieron en el pasado, mientras que la memoria permite recobrar la información, derivada de esa experiencia, para encarar eventos similares en el presente. Actualmente, se están haciendo grandes esfuerzos para clasificar las diferentes expresiones de la memoria. Simultáneamente, se proponen nuevos modelos animales para explorar el complejo aprendizaje-memoria. Uno de los principales factores que modifican la consolidación de la memoria lo constituyen las hormonas ováricas estradiol y progesterona. Este escrito ofrece una clasificación general de la memoria junto con una breve revisión de la literatura reciente en relación al papel de estas hormonas sobre la cognición.

Palabras clave: Cognición. Ovariectomía. Estradiol. Progesterona. Ventana de oportunidad.

Correspondence to:
*Ofir Picazo
Escuela Superior de Medicina, IPN
Plan de San Luis y Díaz Mirón
Col. Sto. Tomás, C.P. 11340, México, D.F., México
E-mail: rifo99mx@gmail.com; rifo99@hotmail.com

Received for publication: 04-03-2015
Accepted for publication: 26-04-2015

DEFINING MEMORY

Basically, memory, used here as synonymous with cognitive function, is defined as the ability to learn, retain, save, and recall information resulting from exposure to new experiences. This information implies new physical and psychological skills to face similar environmental conditions to those giving rise to such knowledge. Thus, learning the sequential order of events that are commonly encountered allows us to form predictions about the impending future and plan upcoming actions accordingly.

Some attempts to classify memory involve two major systems: declarative and non-declarative memory. Although only the first type remains available to multiple response systems and is responsible for learning and remembering of events, facts, and experiences[1], both types of memory are considered as long-term memory. Declarative memory allows remembered material to be compared and contrasted and therefore is a representational entity, which is generally classified as episodic and semantic memory[2]. While episodic memory involves information consolidated or learnt under specific contextual conditions and has to be evoked when similar circumstances are faced[3], semantic memory is available all the time and includes all information that an individual possesses regarding their internal and external environment[4]. Nevertheless, episodic memory eventually can be translated into semantic memory due to the repetition of evocation[5]. In general, it is well accepted that the hippocampal region together with adjacent structures constituting the medial temporal lobe are responsible for regulating declarative memory[6]. Both spatial memory and the novel object recognition test are two animal models broadly used to explore this kind of memory.

On the other hand, non-declarative memory involves the ability to gradually extract the common elements from a series of separate events, evoking multiple sensory systems that regulate distinct functions. This kind of memory includes motor skills and development of habits, specific emotional and reflex responses in whose regulation several neural regions participate (Fig. 1). Non-declarative memory also can be divided in associative (classical conditioning and instrumental conditioning) and non-associative (habituation, motor, and skill learning) memory. Animal models used for studying the associated memory include fear conditioning, conditioned taste aversion, Skinner box, etc., while non-associative memory can be explored by means of rotarod apparatus, beam walking devices, water mazes, and the start reflex test[7].

OVARIAN HORMONES AND MEMORY

Overall, natural or surgical menopause induced by oophorectomy results in a reduction of both 17β-estradiol (E2) and progesterone (P) secretion because of the failing of ovarian function[8]. These hormones modulate neural plasticity in the hippocampus, the amygdala, and the prefrontal cortex, which are involved in both declarative and non-declarative memory. Absence of ovarian hormones is accompanied by a major incidence of stroke, hot flashes, anxiety, osteoporosis, depression, and cognitive deterioration, etc.[9-12]. Regarding the latter, some basic studies have found that removal of ovaries in rodents alters one of the main neurotransmitters involved in learning and memory, decreasing high-affinity choline uptake, choline acetyltransferase (ChAT) activity, and ChAT mRNA levels[13]. It is also known that E2 is closely related with both the nerve growth factor and the brain-derived neurotrophic factor mRNA expression, since ovariectomy (OVX) reduces its levels[14]. Interestingly, the majority of these effects are reversible with appropriate hormone-replacement therapy[15-18]. For instance, early studies show that E2 replacement increases the expression of both nerve growth factor and brain-derived neurotrophic factor in cortex and hippocampus[19-21], while the acetylcholine synthesis is improved after the chronic treatment with E2 in OVX rats due to the increase in ChAT activity[13].

It is well known that E2 is also a potent regulator of cellular events at hippocampus, since in this brain region, E2 increases the expression of synaptic proteins such as synaptophysin, spinophilin, and syntaxin[22-24], activates the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK)

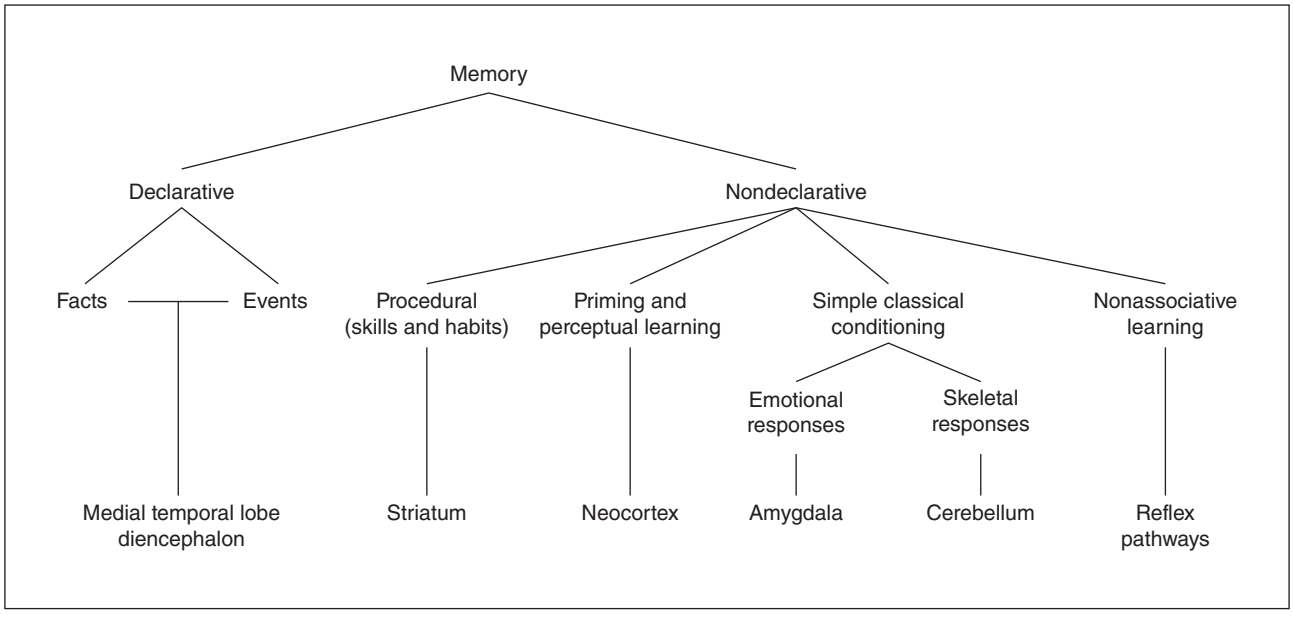

Figure 1. Classification of the long-term memory according to Squire2 with a simplistic relation of the main brain structures regulating each form of memory.

signaling pathway[25], as well as promoting epigenetic processes necessary for declarative memory consolidation[25-27]. In line with this, two of the most important animal models used for exploring the cognitive actions of E2 on declarative memory have been the novel object recognition and several tests of spatial memory[28]. Accordingly, several clinical reports show beneficial effects of E2 administration on cognitive performance in women with Alzheimer's disease, specifically in the verbalization field[29-31] and several of these estrogenic actions have been related with an increase of the basal forebrain cholinergic function[18]. Thus, surgical menopausal women treated with E2 after oophorectomy and receiving placebo showed postoperative declines on tests of short-term and long-term verbal memory and logical reasoning, whereas performance was maintained in women who received hormone treatment[32]. More recently, Hampson and Morley[33] found in cycling women that high E2 levels were correlated with fewer errors on a spatial working memory task. Contrarily, other authors reported no changes in several types of working memory across the menstrual cycle[34]. Furthermore, some randomized clinical trials failed to find, in both surgically and naturally menopausal women, any beneficial effects of E2 on tests of attention, working memory, and visual memory[35-37]. Taken together, this evidence shows that the effects of estrogens in humans are less consistent than those observed in animals.

The role of progesterone on both cognition and neuroprotection is more controversial in comparison to E2. Progesterone seems to share neuroprotective properties with E2 since it counteracts the excitotoxicity induced by glutamatergic hyperactivity[38,39], inhibits the amyloid beta (25-35)-induced cell toxicity[40], blocks apoptosis[41], and enhances spatial learning in the water maze test[42,43]. However, other authors have found that instead of protecting neural tissues, P4 seems to attenuate the cognitive benefits derived from E2. For instance, OVX rats treated with a high dose of E2 for two weeks and tested in an autoshaping learning task (Skinner test) display more conditioned responses than those without hormonal treatment, but when the combination E2 plus progesterone is assayed, the pro-cognitive actions of E2 are diminished (J. Espinosa-Raya et al. 2011). Some of these progestagenic effects have been explained by a reduction in brain-derived neurotrophic factor protein levels, together with the inactivation of its receptor tropomyosin kinase B[44-46] and are in agreement with the finding that the continuous administration of E2 plus P4 has a negative effect on

high-affinity choline uptake and ChAT and acetylcholinesterase mRNA expression in the basal forebrain[13,17] (J. Espinosa-Raya et al. 2011). In the same line, allopregnanolone, the reduced metabolite of progesterone, produces a well-characterized impairment in hippocampal-dependent memory, specifically when rodents are evaluated in the Morris water maze test[47] and in the novel object recognition[48].

THE CRITICAL PERIOD HYPOTHESIS

Some of the contradictory results regarding procognitive actions of E2 have led to the formulation of the critical period hypothesis, which holds that E2 replacement therapy confers optimal benefits on cognition only when initiated closely in time to the menopausal transition (for a review, see Sherwin[49]). In line with this, several authors have found that impairment of cognitive abilities produced by OVX can be overcome by chronic estrogenic treatment initiated immediately after surgery[50], a phenomenon that has been observed by using working memory and spatial memory tests[51,52]. Contrarily, an E2 treatment initiated several months after OVX does not enhance acquisition of aged rats tested on a T-maze spatial memory task[17,53]. This phenomenon can even be observed in OVX younger rats, with hormonal deprivation for four months after surgery, and then treated for one week with E2. Under this schedule, rats show fewer conditioned responses in the Skinner test than the corresponding controls only injected with vehicle[54]. Clinical data also support the idea that there is a critical period in which estrogen replacement therapy should be initiated to remain beneficial for cognition. For instance, surgically induced menopause decreases the cognitive performance after surgery, but it is maintained at pre-surgery assessment level if women start E2 therapy immediately after oophorectomy[55]. The most important beneficial actions of E2 treatment were associated with better verbal memory, working memory, and visuospatial function, but these results were found particularly among women who had initiated treatment during, or soon after, the menopause (see Frick[56] for review).

Another study evaluated women who had undergone bilateral oophorectomy prior to the onset of natural menopause and had either used or never used E2 replacement. This study found that the group without E2 had an increased risk of cognitive impairment 30 years later in comparison to women who initiated treatment immediately after surgery[57].

To summarize, current data about the actions of ovarian hormones on neural tissue highlight the necessity for developing novel strategies for hormonal replacement treatments based on identifying the molecular mechanisms underlying steroidal modulation of memory, which could lead to better treatments for reducing age-related memory decline.

ACKNOWLEDGMENTS

This study was partially supported by COFAA and SIP-IPN.

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