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Review

The role of progesterone in memory: An overview of three decades

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ABSTRACT

Memory comprises acquisition, consolidation and retrieval of information. Many substances can influence these different phases. It is well demonstrated that sex hormones, mainly estrogen, impact cognitive function. More recently, progesterone has also been documented as playing an important role in cognition, since it influences brain regions involved in memory. Currently, many women are under hormone treatment, which contain progesterone to decrease the risk of development of endometrial cancer. This affords the opportunity to study the real effects of this hormonal replacement on cognition. There are many contradictory results regarding the role of progesterone in memory. Therefore, the aim of this review was to synthesize these studies using the new perspective of the influence of hormone replacement on cognition in women.

Contents

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1. Introduction

Substances can have different influences on the separate phases of memory formation (acquisition, consolidation, and retrieval). Sexual hormones such as estrogen and progesterone also impact this cognitive process, either impairing or improving it. The relationship between estrogen and memory is well established, but the role of progesterone in cognition is more controversial. Since many women are under hormone therapy containing progesterone, it is important to understand the impact of this hormone on the formation and maintenance of memories. Thus, in this review we will analyze and discuss the main studies about this topic in order to clarify the influence of hormonal replacement on women's cognition.

1.1. Progesterone

1.1.1. Synthesis, degradation and function

Progesterone is a steroid hormone constituted by 21 carbons and is produced in the adrenals, ovaries and Leydig's cells. It is synthesized from cholesterol, which is converted to the progesterone precursor, pregnenolone, by the cytochrome P450scc. Pregnenolone is then converted to progesterone in a reaction catalyzed by 3β-hydroxysteroid dehydrogenase. Progesterone can be metabolized to 5α-dihydroprogesterone by the action of the enzyme 5α-reductase. Although typically known as a female hormone, progesterone is also found in males. Once synthesized, progesterone can play both anti-androgenic and anti-mineralocorticoid functions.

This hormone is essential for normal female reproductive function. During the menstrual cycle, a peak in progesterone levels occurs in the luteal phase (for review see Obr and Edwards, 2012). Progesterone is also kept at high levels during pregnancy, since it is essential for its maintenance (Anderson and Clarke, 2004). Moreover, progesterone has a myriad of functions in other activities of the female organism. In the uterus and ovaries, progesterone is responsible for the release of mature oocytes and for the facilitation of embryo implantation, since it promotes uterine growth and suppresses myometrium contractions. In mammary glands, it prepares milk secretion and inhibits its production before parturition. Lastly, progesterone also acts in the brain, leading to the release of neurochemical signals essential to sexual behavior (Graham and Clarke, 1997).

In men, progesterone may hold promise as a treatment for prostate hyperplasia, which leads to cancer (Kaore et al., 2012). Moreover, our group has demonstrated that progesterone can affect erectile function and sleep patterns (for review see Andersen and Tufik, 2006; Andersen et al., 2006). We observed that this hormone increased the frequency and number of penile erections in castrated and paradoxical sleep-deprived male rats (Andersen et al., 2004). Also, the administration of a progesterone receptor antagonist, mifepristone, decreased the duration of and increased latency to paradoxical sleep episodes in male rats (Andersen and Tufik, 2005).

Progesterone release by the *corpus luteum* is cyclical and mediated by many hormones, such as luteinizing hormone (LH) and follicle stimulating hormone (FSH). After the release, progesterone binds to progesterone receptors (PRs), which were initially discovered in the hypothalamus, suggesting for the first time that progesterone acts directly on neural cells. With the advance of research, PRs were also found in several other brain areas, including the cortex and many subcortical regions (for review see Schumacher, 2013). In these regions, PRs may be localized in the nucleus Q2 of cells or in extra-nuclear sites, acting as a transcription factor or possibly influencing other aspects of the neurotransmission system.

1.1.2. Progesterone receptors

The PR presents two different isoforms: A and B (Schrader et al., 1972), arising from the cleavage of a single gene, which both belong to the superfamily of steroid nuclear receptors (Graham and Clarke, 2002). The gene for the synthesis of these receptors is located on chromosome 11 in humans and 9 in mice. PRA and PRB have distinct functions, although the action of the A isoform is dominant over the B when both are expressed (Tung et al., 1993). The amount of A and B also varies: in human cells there are equal amounts of PRA and PRB (Tung et al., 1993), whereas in rodents PRA predominates over PRB in a ratio of 3:1 (Ilenchuk and Walters, 1987).

The binding sites of progesterone are very diverse: uterus, ovaries, brain, and bones (Graham and Clarke, 1997). Within these tissues, PR activation is related to estrogen action through induction of estrogen receptors (ER), showing that these two hormones act together (Lydon et al., 1995). Progesterone effects can be both excitatory and inhibitory and the latency for the observation of these effects ranges from a few seconds to hours, depending on the tissue and hormone concentration (Mahesh et al., 1996).

Progesterone is considered a neurosteroid with protective effects on the central and peripheral nervous system, decreasing the loss of neuronal cells and accelerating repairs (Djebaili et al., 2004). In addition to the functions described above, progesterone appears to have an important role in cognitive functions, since it influences brain regions involved in memory, such as the hippocampus and the forebrain (McEwen and Alves, 1999).

1.2. Memory

Memory is the capacity to encode, consolidate and retrieve information available in the central nervous system (CNS) (for review see McGaugh, 2000). During encoding, a memory trace is formed and in this phase memory is very susceptible to decay or forgetting, since it is not yet incorporated into the systems of the brain. In the consolidation phase, the labile memory starts to be stabilized by many cellular and synaptic mechanisms. Finally, during retrieval, the consolidated memory is accessed and can be reconsolidated or extinguished.

1.2.1. Short and long term memories

An experience triggered by a sensory stimulus can be stored as memory. If this storage lasts from seconds to a few minutes, it is termed a short term memory (STM), whereas if it lasts from hours to days, it is considered a long term memory (LTM). These two types of memory rely on different neural mechanisms. The information is stored by dramatic synaptic plasticity in glutamatergic, dopaminergic and GABAergic synapses (Bonci et al., 2003). An

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