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REVIEW

Prolactin system in the hippocampus

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Abstract

Among the more than 300 biological actions described for prolactin, its role in the neurogenic capacity of the hippocampus, which increases synaptogenesis and neuronal plasticity, consolidates memory and acts as a neuronal protector against excitotoxicity—effects mediated through its receptors are more recently known. The detection of prolactin in the hippocampus and its receptors, specifically in the Ammon's horn and dentate gyrus, opened up a new field of study on the possible neuroprotective effect of hormones in a structure involved in learning and memory, as well as in emotional and behavioral processes. It is currently known, although controversial, that prolactin may be related to sex and age and that the hormone could be synthesized in the hippocampus itself. However, the regulatory mechanisms of changes in prolactin or in its hippocampal receptors still remain unknown. This review introduces the reader to general aspects concerning prolactin and its receptors and to what is currently known about the role prolactin plays in the brain and, in particular, in the hippocampus.

Keywords Prolactin · Hippocampus · Prolactin receptor · Neuroprotection · Learning and memory

Prolactin and its receptor

Prolactin (PRL) is a peptide hormone present in all vertebrates. It is phylogenetically well-conserved (Brooks 2012) and is known to have more than 300 different biological functions, including the stimulation of neurogenesis, modulation of stress responses, calcium transport, immune system regulation and reduction of anxiety, among others (Larsen and Grattan 2012; Ferraris et al. 2013; Patil et al. 2014).

The synthesis of prolactin occurs mainly in the anterior pituitary and it is released into the peripheral blood in a pulsatile manner.

Prolactin acts on its specific receptor, PRLR, which belongs to the transmembrane type I cytokine receptor superfamily. PRLR is encoded by a single gene located on chromosomes 5, 15 and 2 in humans, mice and rats, respectively, with multiple specific variants in numerous tissues and cell types (Patil et al. 2014; Sangeeta Devi and Halperin 2014).

This gene has a complex genomic structure, which includes the presence of a promoter region and multiple first exons whose alternative activation regulates the transcription of the gene (Swaminathan et al. 2008). Up to five first exons have been described in rat, designated E11, E12, E13, E14 and E15, where exon E14 seems to be responsible for the expression of the PRLR gene throughout development and especially in the choroidal plexuses during postnatal development and lactation (Tejadilla et al. 2010; Hirai et al. 2013).

Variants of the receptor can be generated by alternative splicing of the first transcript or by post-transcriptional division, obtaining different isoforms that share a large part of the structure and that constitute the two halves of the complete

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receptor (Patil et al. 2014). In humans, up to five membrane-bound and soluble isoforms of the receptor have been described: the long form (PRL-RL); the intermediate form (PRL-RI), present in humans but not in mice (Sangeeta Devi and Halperin 2014); and the three short isoforms (PRL-RS) ΔS1, S1a and S1b, which share a common extracellular domain but have a divergent intracellular domain. On the contrary, fewer isoforms have been described in rodents, although the main isoforms, PRL-RL and PRL-RS, have been found in rats and mice (Ben-Jonathan and Hugo 2015).

The PRL-RL isoform is the prototype receptor of this family and is involved in the complete signaling spectrum and actions attributed to prolactin, including its proliferative and neuroprotective effects (Swaminathan et al. 2008; Wagner et al. 2009; Sangeeta Devi and Halperin 2014). It has an extracellular domain that acts as a ligand-binding, transmembrane and intracellular domain.

The extracellular domain includes two regions, designated S1 and S2 (or D1 and D2) and together they form the ligand binding site. The transmembrane domain is the place of union between the extracellular and intracellular domains (Fig. 1). Lastly, the intracellular domain contains the receptor signaling unit and consists of two main regions, Box1 and Box2, separated by the variable V-Box domain. The X-Box region acts as an extension of the Box2 region.

Box1 is hydrophobic and has a tyrosine-protein kinase Janus 2 (Jak2) binding domain and the C-terminal end of this region contains some tyrosine residues, crucial for the binding and activation of the signal transducer and activator of transcription 5, STAT5 (Morales et al. 2014; Swaminathan et al. 2008).

The remaining isoforms exhibit different properties, due to a reduced C-terminal tail. In this way, the isoforms S1a and S1b lack the Box2 and X-Box regions and therefore STAT5. The intermediate isoform, on the other hand, does contain these regions and the isoform ΔS1 has an entire deletion of the S1 region, which is attributed to its low affinity for prolactin that is seven times lower than that of the long isoform (Swaminathan et al. 2008).

The distribution of these isoforms in the tissue is asymmetric, where the PRL-RL isoform is more highly expressed in the hippocampus and in certain types of cancer (Swaminathan et al. 2008; Torner et al. 2009; Tejadilla et al. 2010; Kang et al. 2014; Harvey et al. 2015), which could be related to cell proliferation.

Additionally, a form of the receptor, the prolactin-binding protein (PLR-BP), has also been detected in humans and contains a freely circulating extracellular domain. This domain is capable of binding up to 36% of the prolactin circulating in blood, which is why it is considered to be a natural prolactin antagonist (Swaminathan et al. 2008; Ben-Jonathan and Hugo 2015).

The relative amount of the different isoforms of the receptor, expressed in various tissues, could help to explain the different biological actions of prolactin. It has been thought that prolactin modulates its activity in target cells by inducing internalization and degradation of its own receptor and by regulating the expression of receptor isoforms (Ferraris et al. 2012). In addition, taking into account that a large number of cells expressing the prolactin receptor also express the estrogen receptor, it is possible that estradiol may also regulate the expression of the prolactin receptor (Grattan 2015; Harvey et al. 2015). Therefore, many of the actions carried out by prolactin through its receptor may be dependent not only on prolactin itself but also on the presence of estradiol.

In order for a receptor to become activated, the isoforms must first dimerize. In this way, the union of the same or different isomers forms PRLR homodimers or heterodimers that are activated through the binding of PRL to the receptor (Fig. 1). This in turn constitutes a functional heterotrimer capable of initiating the actions attributed to prolactin.

In some cases, the correct dimerization of the isoforms and the binding of PRL are not sufficient for generating a fully functional receptor. The PRL-RS isoform shows a natural tendency to polymerize with PRL-RL and also the ability to inhibit its activation (Ferraris et al. 2012).

This is because the presence of a tyrosine 580 residue located in the cytoplasmic tail of the intracellular domain is required for phosphorylation of STAT5. Since only the long isoform of the receptor contains this residue and because it is necessary that each receptor monomer has its own tyrosine 580, the heterodimer consisting of PRL-RL and PRL-RS would not have an effective binding site for the phosphorylation of STAT5. Therefore, the heterodimer would not be functional and the activity induced by PRL-RL would be insufficient for the activation of the expression of PRL response genes (Kang et al. 2014).

This theory is further supported by observations in which the elimination of the S1 domain changes the affinity of the PRL-RS isoform, in such a way that its ability to bind to the PRL-RL isoform is decreased. This situation favors the dimerization of PRL-RS with itself, increasing the formation of PRL-RS homodimers (Brooks 2012; Kang et al. 2014). Although this hypothesis would substantiate the formation of receptor dimers independently of the ligand, most likely both types of dimerization, dependent or independent of PRL, are involved in the formation of a functional receptor.

The binding of PRL to PRLR produces its activation, initiating the processes responsible for the biological activities of the hormone.

The proximity of PRL to the S1 and S2 regions of the extracellular domain within the receptor allows PRL to bind to the binding pocket. This in turn causes the receptor to move in a piston-like manner, which leads to a structural change in the intracellular domain that promotes the activation of the signaling cascade (Brooks 2012).

This would facilitate the coupling of Jak2 to the Box1 region (Fig. 1), causing Jak2 to autophosphorylate and

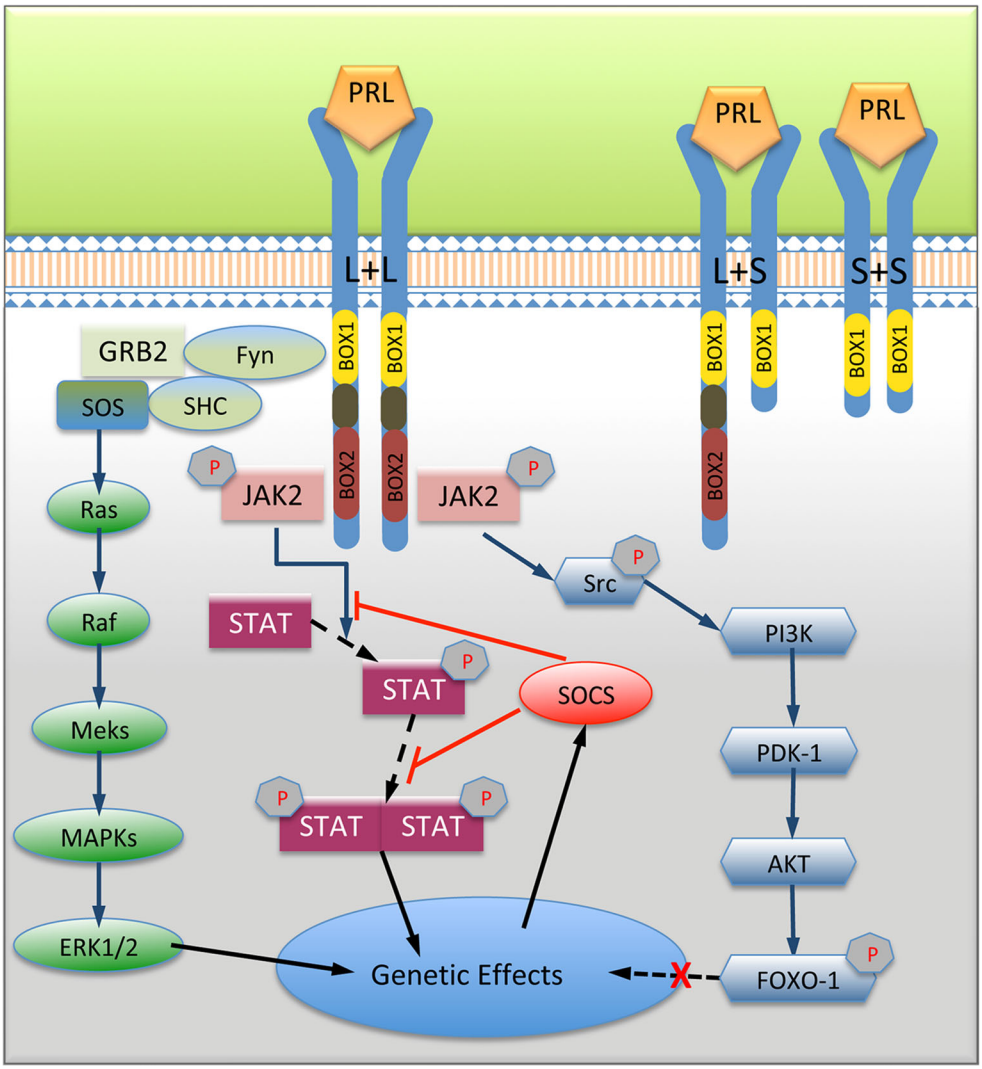

Fig. 1 Image showing the typical intracellular signaling pathways activated by the binding of prolactin to its receptor (partially modified and amplified from Furigo et al. 2016). There are three main routes, MAPK, STAT and PI3K, through which prolactin can induce long-lasting genomic responses. In addition, there are three forms of dimerization for the long (L) and short (S) isoforms of the receptor: L + L, L + S and S + S. The effects of prolactin can be affected depending on the type of association between the isoforms. AKT, ak strain transforming/protein kinase B; ERK1/2, extracellular signal-regulated kinases; FOXO-1, forkhead box protein O1; Fyn, proto-oncogene tyrosine-protein kinase Fyn; GRB2, growth factor receptor-bound protein 2; JAK2, janus kinase-2; MAPKs, mitogen-activated protein kinases; Meks, mitogen-activated protein kinase kinases; P, phosphate; PDK-1, phosphoinositide-dependent kinase-1; PI3K, phosphatidylinositol-4-5-biphosphate 3-kinase; PRL, prolactin; Raf, raf proto-oncogene serine/threonine-protein kinase; Ras, family of small GTPase; SHC, SHC-transforming protein; SOCS, suppressor of cytokine signaling; SOS, son of sevenless (set of genes encoding guanine nucleotide exchange factors); Src, proto-oncogene tyrosine-protein kinase Src; STAT, signal transducer and activator of transcription

phosphorylate numerous proteins, such as STAT5, which is the main mediator of the prolactin signal (Sangeeta Devi and Halperin 2014) and the way in which PRL increases the expression of its own receptor (Kavarthapu et al. 2014). Although this seems to be the main cascade induced by prolactin for initiating proliferation and neurogenesis (Patil et al. 2014), associated mainly with the PRL-RL isoform due to the presence of the STAT5 binding site in the cytoplasmic tail of the intracellular domain (Hirai et al. 2013), other pathways can also be activated, such as the MAP-kinases pathway, the phosphoinositide 3-kinase (PI3K) pathway, Src-kinase, NeK3-kinase or ERK1 (Swaminathan et al. 2008; Ferraris et al. 2012, 2013; Sangeeta Devi and Halperin 2014).

Given that the PRL-RS isoform has lost the Box2 junction region of STAT5 but has the Box1 binding domain for Jak2, it has been hypothesized that the activation of PRL-RS can phosphorylate Jak2 activating the MAP-kinase pathways, ERK1 and PI3K (Fig. 1). This would be consistent with the results of an analysis carried out on cells containing homodimer and heterodimer receptors, where the levels of

phosphorylated Jak2 are constant, while there is a marked reduction in the levels of STAT5 in homodimers and heterodimers comprising PRL-RS isoforms (Kang et al. 2014).

Prolactin and its receptor in the brain

It is known that prolactin receptors are present in the choroid plexuses (Clemens and Sawyer 1974; Tejadilla et al. 2010; Larsen and Grattan 2012; Ferraris et al. 2013; Hirai et al. 2013; Patil et al. 2014) and also at varying levels in cerebrospinal fluid, being similar to those of peripheral PRL (Tejadilla et al. 2010; Grattan 2015). Consequently, it has been suggested that circulating prolactin in blood is capable of crossing the blood-brain barrier, reaching the cerebrospinal fluid through the choroid plexus by a mechanism of saturable transport mediated by its receptor (Fig. 2). Hence, prolactin could inhibit its production and release through a negative feedback mechanism facilitated by an increase in dopamine from the arcuate nucleus (Torner et al. 2009; Larsen and Grattan 2012; Ferraris et al. 2013; Patil et al. 2014; Sangeeta Devi and Halperin 2014; Grattan 2015).

However, the presence of prolactin in the brain of PRL receptor knockout mice has been observed (Brown et al. 2016), suggesting that PRL can pass from blood through the blood vessels, involving a not yet been described carrier, or that the hormone is synthesized in cells of the nervous system (Fig. 2).

In addition to prolactin being synthesized by the pituitary, it has also been described to be synthesized in other tissues. Furthermore, the possibility of prolactin production in the central nervous system, which would act locally, has also been reported (Ben-Jonathan et al. 1996). However, this has not been conclusively proven and discrepancies exist among authors (see Brown et al. 2016, for more detailed information).

Neural roles for prolactin

Neurogenesis

Neurogenesis is a complex process that includes the activation, proliferation, differentiation and migration of neural and glial stem cells, as well as the synaptic integration of new cells in existing neural networks (Walker et al. 2012).

There are two areas of the brain where neurogenesis has been described in adults: the subventricular zone (SVZ), which adjacently extends to the wall of the lateral ventricles and whose newly formed cells migrate through the so-called rostral migratory current to reach, for the most part, the granular and perigranular layers of the olfactory bulb and the subgranular zone (SGZ) located in the granular cell layer of the dentate gyrus of the hippocampus, which generates neurons that migrate short distances to make dentate granular cells that are directly related to learning, memory, object recognition and spatial orientation (Lévy et al. 2011). The hippocampus is, therefore, a region where neurogenesis persists in the adult.

The influence of hormones on neurogenesis is well-known, where the steroid hormones, androgens and estrogens, are efficient enhancers of neurogenesis in the hippocampus, as well as enhancers of synaptogenesis and memory consolidation, effects they achieve through their receptors (Fester and Rune 2015).

Prolactin (PRL) has also been linked to similar neurogenic processes in adults, especially to the SVZ (Larsen and Grattan 2012) and SGZ (Cabrera et al. 2009) where it has been shown to produce neuroprotection (Torner et al. 2009).

Neuroprotection

The oxidative damage produced in biomolecules is due to an alteration of the pro-oxidant-antioxidant equilibrium of the body that favors the pro-oxidant state, a situation called oxidative stress. Oxidative stress is due to an excess in the intracellular production of reactive oxygen species (ROS) and nitrogen (RNS), historically known as free radicals and to exposure to these highly reactive chemical species. Also, oxidative stress may be due to a partial inhibition of cellular antioxidant defenses, enzymatic and non-enzymatic, where glutathione (GSH) is the main non-enzymatic cellular antioxidant defense.

The brain is highly vulnerable to oxidative stress and therefore extremely susceptible to oxidative damage. This is due, above all, to the high rate of oxygen consumption that occurs in this organ, which increases the production of ROS; to the high content of polyunsaturated fatty acids, which are easily oxidizable; to the fact that antioxidant defenses are relatively weak and because the brain mainly comprises differentiated postmitotic cells (Mariani et al. 2005; Li et al. 2013).

The decline in brain function associated with aging is largely due to oxidative stress causing damage in different biomolecules (lipids, proteins, carbohydrates and nucleic acids), which can alter cellular function and affect the functioning of the central nervous system. In fact, oxidative stress is recognized as being a fundamental cause of various neurodegenerative diseases associated with aging, such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis and Huntington's diseases (Mariani et al. 2005).

In relation to prolactin, antioxidant effects have been described for the hormone in parts of the central nervous system, such as the retina (Thébault 2017), although these effects have not been studied in the hippocampus.

Prolactin and hippocampus

During pregnancy and lactation, serum prolactin levels are elevated, which seems to be related to the maternal behavior of pregnant females (Ferraris et al. 2013; Patil et al. 2014;

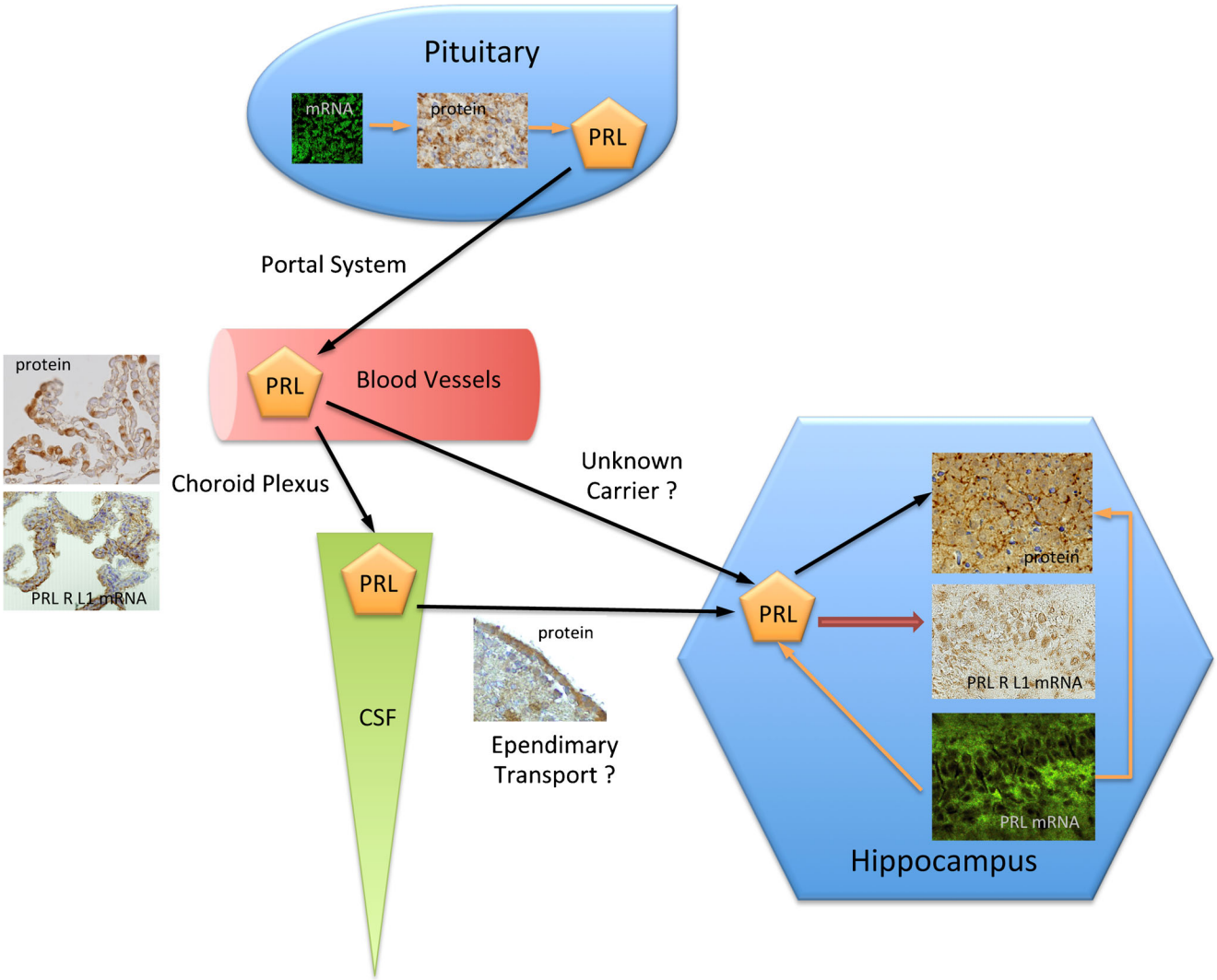

Fig. 2 Image showing the different non-mutually exclusive theories that try to explain the presence of prolactin in the hippocampus. The prolactin synthesized and released from the pituitary gland goes to the peripheral blood through the portal system. From the peripheral blood, prolactin could pass through the choroid plexuses to the cerebrospinal fluid (CSF), be captured by ependymocytes, and from there spread via the neuropil to act on the neurons of the hippocampus at a distance. Another possibility is that prolactin could cross the blood-brain barrier into the hippocampus itself from the peripheral blood unit using some still unknown carrier. Finally, another possibility could be that the hormone is synthesized by hippocampal neurons. Orange arrows: hormone synthesis route (in situ hybridization for mRNA and immunocytochemistry for the protein); black arrows: path followed by prolactin to reach the hippocampus; red arrow: prolactin binding to its receptor in the hippocampus

Sangeeta Devi and Halperin 2014). It is precisely in this phase of physiological hyperprolactinemia when the most significant effects of the hormone in relation to neuroprotection and neurogenesis have been observed. The neurogenic effects associated with the hormone take place through the activation of its receptor, which has been detected in both the subventricular zone and in the hippocampus (Torner et al. 2009; Larsen and Grattan 2012).

Different studies have shown that prolactin is capable of reducing cell death by excitotoxicity, including hippocampal neurons (Cabrera et al. 2009; Tejadilla et al. 2010; Morales et al. 2014; Vergara-Castañeda et al. 2016). It has also been proven that prolactin is able to induce cell proliferation and reduce neuronal damage associated with stress in the hippocampus (Cabrera et al. 2009; Torner et al. 2009) and the toxic action of high levels of glucocorticoids present during gestation as a mechanism to ensure the supply of energy to the fetus.

Inconsistencies have been found in the literature regarding the effects of prolactin throughout the life of an organism. Although it has been described that exogenous prolactin administered to rats during the neonatal period decreases neurogenesis in the hippocampus (Lajud et al. 2013), it has also been reported that endogenous prolactin could be necessary in the hippocampus of adult rats for learning and memory (Walker et al. 2012). Prolactin, particularly in the hippocampus, could improve cognitive performance and spatial memory, neurodevelopment (Pardo et al. 2016), neurogenesis, cell

proliferation and neuroprotection (Morales et al. 2014; Reyes-Mendoza and Morales 2016; Rivero-Segura et al. 2017) and neuroplasticity and dendritic remodeling during gestation and postpartum (Kinsley et al. 2006; Brusco et al. 2008).

Overall, the results described relate circulating prolactin to possible neuroprotective and neurogenic effects in adults that seem to be associated mainly with pregnancy and maternal postpartum behavior.

Without discarding a neuronal role for circulating pituitary prolactin, it could be considered that the expression and probably the synthesis of the hormone in the hippocampus do occur, since the presence of the protein, detected by RIA and immunocytochemistry and mRNA, detected by RT-PCR and RT-qPCR, have been described (De Vito 1988; Emanuele et al. 1992; Fields et al. 1993; Roselli et al. 2008; Cabrera-Reyes et al. 2015).

The existence of a specialized type of neuron expressing prolactin still remains to be ascertained, as well as its possible relationship to the presence of any receptor isoform and if the hormone only acts locally or functionally intervenes in any of the afferent or efferent connections of the hippocampus.

In addition, it is currently unknown whether the regulation of the presence and synthesis of the hormone in the hippocampus develops independently of the level of prolactin in the blood. And, it is unclear if there are possible local or remote neuronal regulators that could influence prolactin in the hippocampus.

In summary, although there is evidence supporting the presence of a prolactin system in the hippocampus and some of its actions, there is still much to be explored regarding its organization and regulation, as well as its possible involvement in neurodegenerative pathologies and the influence that the presence of pituitary prolactinomas could have on this system.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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