

Luis Henrique Almeida Castro  
(Organizador)

# CIÊNCIAS DA SAÚDE:

PLURALIDADE DOS  
ASPECTOS QUE  
INTERFEREM NA  
SAÚDE HUMANA

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## APRESENTAÇÃO

Este e-book intitulado “Ciências da saúde: pluralidade dos aspectos que interferem na saúde humana” leva ao leitor um retrato da diversidade conceitual e da multiplicidade clínica do binômio saúde-doença no contexto brasileiro indo ao encontro do versado por Moacyr Scliar em seu texto “História do Conceito de Saúde” (PHYSIS: Rev. Saúde Coletiva, Rio de Janeiro, 17(1):29-41, 2007): “O conceito de saúde reflete a conjuntura social, econômica, política e cultural. Ou seja: saúde não representa a mesma coisa para todas as pessoas. Dependerá da época, do lugar, da classe social. Dependerá de valores individuais, dependerá de concepções científicas, religiosas, filosóficas”.

Neste sentido, de modo a dinamizar a leitura, a presente obra que é composta por 107 artigos técnicos e científicos originais elaborados por pesquisadores de Instituições de Ensino públicas e privadas de todo o país, foi organizada em cinco volumes: em seus dois primeiros, este e-book compila os textos referentes à promoção da saúde abordando temáticas como o Sistema Único de Saúde, acesso à saúde básica e análises sociais acerca da saúde pública no Brasil; já os últimos três volumes são dedicados aos temas de vigilância em saúde e às implicações clínicas e sociais das patologias de maior destaque no cenário epidemiológico nacional.

Além de tornar público o agradecimento aos autores por suas contribuições a este e-book, é desejo da organização desta obra que o conteúdo aqui disponibilizado possa subsidiar novos estudos e contribuir para o desenvolvimento das políticas públicas em saúde em nosso país. Boa leitura!

Luis Henrique Almeida Castro

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# CAPÍTULO 12

## PROLACTIN: A HORMONE OF SEVERAL PROTECTIVE EFFECTS

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**ABSTRACT:** Prolactin (PRL), a protein hormone encoded by a gene on chromosome 6, is produced in and secreted by the adenohypophysis and several other organs. This hormone has more than 300 biological functions, acting, for example, in lactogenesis, mammatogenesis, galactopoiesis, homeostasis, angiogenesis, cell growth and proliferation and as a neurotransmitter. Upon activating its receptor, PRL can activate signal transduction pathways until the responsive genes that are related to the various functions exercised by this hormone are activated in turn. This function may also be linked to the protective effects of PRL. This review analyses studies that demonstrate or investigate the actions of this hormone in terms of its neuroprotective, anti-apoptotic and cytoprotective effects. Neuroprotective effects are observed during the stimulation of antioxidant defenses, cell proliferation and anti-apoptotic effects. Anti-apoptotic effects are also observed in other tissues / organs, and are characterized by the regulation of genes that suppress apoptotic mechanisms and favor cell proliferation. This evaluation of the protective effects of PRL considers both in vitro and in vivo studies. In both

types of study, the versatility of this hormone, related to the metabolic pathways induced by the activation of its receptor is evident.

**KEYWORDS:** Prolactin, anti-apoptotic effects, cytoprotection, neuroprotection.

### PROLACTINA: UM HORMÔNIO DE DIVERSOS EFEITOS PROTETORES

**RESUMO:** A prolactina (PRL), um hormônio proteico codificado por um gene no cromossomo 6, é produzido e secretado pela adenohipófise e por diversos outros órgãos. Este hormônio possui mais de 300 atividades biológicas, atuando, por exemplo, na lactogênese, mamogênese, galactopoiese, homeostase, angiogênese, crescimento e proliferação celular e como neurotransmissor. Ao ativar seu receptor, a PRL pode ativar vias de transdução de sinal até a ativação de genes responsivos que estão relacionados as diversas funções exercidas por este hormônio e também podem está ligadas aos efeitos protetores que a PRL desempenha. Esta revisão traz estudos que demonstram ou analisam ações deste hormônio com efeitos neuroprotetor, antiapoptótico e citoprotetor. Os efeitos neuroprotetores são observados a partir da estimulação de defesas antioxidantes, da proliferação celular e de efeitos antiapoptóticos. Os efeitos antiapoptóticos também são observados em outros tecidos/órgãos, e se caracterizam pela regulação de genes que suprimem os mecanismos apoptóticos e favorecem a proliferação celular. A avaliação dos efeitos protetores da PRL é realizada em tanto em estudos in vitro quanto em estudos in

vivo e, em ambos o que se evidencia é a versatilidade deste hormônio, relacionada as vias metabólicas induzidas pela ativação de seu receptor.

**PALAVRAS-CHAVE:** Prolactina, efeito antiapoptótico, citoproteção, neuroproteção.

## 1 | INTRODUCTION

Prolactin (PRL) is a protein hormone, from the same family that affects growth and placental lactogenics; it is produced and secreted mainly by adenohypophysis lactotrophs (Soares Jr & Gaderlha, 2004). In addition to being apparent in the pituitary gland, PRL synthesis and secretion have already been observed in the brain, placenta, uterus, mammary gland, immunocompetent cells, bone marrow lymphoid cells and sweat glands. PRL secreted by the pituitary gland acts in an endocrine manner on target cells that have prolactin receptors on their plasma membrane. The PRL produced in other organs can act in an autocrine or paracrine manner; thus, many functions of PRL can be activated without its concentrations in the blood being changed (Bole-Feysot *et al.*, 1998; Ignacak *et al.*, 2012; Marano & Ben-Jonathan, 2014).

In humans, PRL is encoded by a gene on chromosome 6, composed of five exons and five introns and 10kb in length. PRL has 199 amino acids. This hormone, in addition to stimulating milk production in the mammary glands (lactogenesis), also acts in mammatogenesis and galactopoiesis, and has more than 300 biological functions, even acting on homeostasis, by regulating the immune system, osmotic balance and angiogenesis. Additionally, it has an effect on cell growth and proliferation and acts as a neurotransmitter (Bole-Feysot *et al.*, 1998; Freeman *et al.*, 2000; Ignacak *et al.*, 2012).

PRL is involved in osmotic balance (of water and electrolytes) in all classes of vertebrates; in mammals, PRL receptors are present in kidney cells and other organs involved in this process. Many effects of PRL are associated with cell proliferation. In the skin, it stimulates the proliferation of melanocytes and keratinocytes; it can influence the growth of hepatocytes, inducing many different genes related to cell growth in liver cells. The increase in intestinal mucosa, vascular smooth muscle, proliferation of  $\beta$  cells in the pancreas, astrocytes and several cells of the immune system have already been associated with PRL (Bole-Feysot *et al.*, 1998; Marano & Ben-Jonathan, 2014).

The hormone PRL activates signal transduction pathways from the activation of its receptor. The PRL receptor is constitutively associated with Janus kinase 2 (JAK2) proteins. When activated, JAK2 phosphorylates tyrosine residues can be found in target proteins, including the receptor (with the exception of the short isoform) and the STAT1, STAT2 and mainly STAT5 proteins. These proteins dimerize and translocate until the signal reaches the nucleus, activating promoters of PRL-responsive genes. In addition to the JAK/STAT pathway, other pathways can be activated by PRL receptors. These include the Ras/ Raf/ MAP kinase pathway, which can be related to the proliferative effects of this hormone (Bole-

Feysot *et al.*, 1998; Soares Jr & Gaderlha, 2004; Silva-Pereira *et al.*, 2014).

All of these functions performed by PRL, and the activated signaling pathways, can be related to the protective effects that this hormone has on different tissues and in varying experimental situations. This review aims to offer a comprehensive overview of the actions of PRL that have been studied in the last 35 years, in terms of neuroprotective, anti-apoptotic and cytoprotective effects.

## 2 | PROTECTIVE EFFECTS OF PRL

### 2.1 Neuroprotection

One neuroprotective effect of PRL functions against the excitotoxicity caused by the maintenance of glutamatergic receptor stimulation. Primary cultures of neural cells from the hippocampus of Wistar rat embryos exposed to glutamate in the presence of PRL maintained intracellular  $\text{Ca}^{2+}$  homeostasis and mitochondrial activity. Additionally, a reduction in caspase-3 activation and apoptosis has been observed. The hormone also induces nuclear translocation of NF- $\kappa$ B, which can characterize its anti-apoptotic effects, mediated by the activity of this transcription factor and by the positive regulation of Bcl-2 protein expression (Rivero-Segura *et al.*, 2017).

As mentioned in the previous paragraph, PRL prevents mitochondrial dysfunction caused by glutamate excitotoxicity. Rivero-Segura *et al.* (2019), have evaluated this protective effect of PRL in more detail, verifying that it occurs due to the stimulation of the antioxidant defense of superoxide dismutase (SOD). In primary cultures of hippocampal neurons, an increase in SOD isoforms and activity of this enzyme have been observed, including during exposure to glutamate. A decrease in lipid peroxidation products produced during excitotoxicity induced by this neurotransmitter has also been observed.

The primary culture of neurons in the hippocampus was the focus of an *in vitro* study to analyze the expression of the PRL receptor in these cells, in addition to the neuroprotective role of PRL against the excitotoxic effects of glutamate. An increase in the expression of the PRL receptor was observed in the cells that received the treatment with the hormone and this increase was maintained even in the cells that received glutamate with the PRL; it was also observed that when the expression of these receptors was inactivated, the protective effect of PRL disappeared, demonstrating a direct relationship between the hormone's neuroprotective effect and the presence of its receptor (Vergara-Castañeda *et al.*, 2016).

PRL also acts against the excitotoxic effects of kainic acid (KA). Tejadilla *et al.* (2010) have evaluated this action in adult female Wistar rats with the ovaries removed; the progression of behavioral manifestations in motor convulsion and after euthanasia of the animals was evaluated, in addition to the morphology and immunohistochemistry of areas of the hippocampus. It was observed that PRL attenuated the severity of convulsions and cell

damage induced by KA. Morales *et al.* (2014), using the same animal model to evaluate the action of human PRL and a molecular mimic of phosphorylated human PRL on the effects of KA, observed the same results as Tejadilla *et al.* (2010) for both types of PRL, and suggest that this protective action may occur indirectly, through the modulation of input signals to the hippocampus, thus regulating the action of this glutamate agonist.

Turner *et al.* (2009) have studied the effects of PRL on cell proliferation, survival and neurogenesis in the dentate gyrus of the hippocampus of adult male rats subjected to chronic restriction stress conditions. They observed that the treatment with PRL reduced the decrease in cell survival caused by stress, without altering cell proliferation and that this hormone forwards newly generated cells to a neural destination; the presence of PRL receptors in the cells of the hippocampus of all animals was also identified, regardless of the treatment group.

Considering the presence of PRL receptors in brain regions, mainly in the hypothalamus, forming a “cerebral PRL system” and the fact that this system is highly activated in the peripartum period, in response to neuroendocrine stress, Donner *et al.* (2007) investigated the effects of PRL treatment on neuroendocrine behavior and neuronal stress parameters in ovariectomized female Wistar rats. Anxiety-related behavior was significantly reduced by PRL. In the rats which underwent treatment, there was an increase in the concentration of corticosterone in the blood plasma, revealing a positive regulation of adrenal secretion and a reduction in the neuroendocrine response to stress by restriction.

Some epileptic women find that their seizures decrease in frequency during pregnancy and higher levels of PRL are found in epileptic patients after seizures. To investigate the relationship between this hormone and the severity of the crisis, Doretto *et al.* (2003) used audiogenic Wistar rats, in which seizure was induced by high intensity sound stimuli. The evaluations of the PRL level in the blood and the intensity of the seizure crisis were carried out on female rats, pregnant or not and lactating or not. A direct relationship between seizures and PRL levels Was demonstrated.

Pregnancy was also considered in the work by Gregg *et al.* (2007), who observed an increase in the production of new oligodendrocytes and myelinated axons in the maternal central nervous system during this period, relating PRL to the proliferation of oligodendrocyte precursor cells during pregnancy, repairing damage to myelin present in virgin mice. These observations suggest that PRL is a factor which contributes to the remission of multiple sclerosis observed during the final stages of pregnancy.

Anagnostou *et al.* (2018) carried out a review of studies which demonstrated the participation of glial cells as mediators of the neuroprotective processes of PRL. PRL increases proliferation and acts in the cell differentiation process of astrocytes; it increases the proliferation of oligodendrocyte precursor cells, with PRL receptors expressed in these cells, in addition to having trophic actions in microglia.

The action of PRL influences, for example, the response of glial cells in hypoxia

ischemia lesions in the brains of young rats. After induced injury and treatment with PRL there is a significant increase in cortical cell loss, an increase in PRL receptors in astrocytes and an increase in microglia with PRL present in the injured area. This demonstrates a PRL action in providing trophic support for glial cells, participation in brain immunoregulation and the formation of glial scarring (Mödersheim *et al.*, 2007).

The protective effect of PRL on hypoxia ischemia has also been suggested by Tani *et al.* (2018), who evaluated changes in the PRL level in autopsy samples and cultures of blood and brain spinal fluid and observed higher levels of this hormone when the cause of death was hypoxia / ischemia by asphyxia. The hormone was mainly observed in the spinal brain fluid, suggesting a transport of blood PRL into this fluid in the early stages of hypoxia. These authors also observed high levels of PRL in cultures of rat pituitary cells (line SDR-P-1D5) and pig pituitary cells (line MSH-P3) submitted to hypoxia conditions for 10 min; the levels decreased when submitted to this condition for 20 min.

## 2.2 Anti-apoptotic effects

The Nb2 cell line comes from rat lymphoma and is dependent on PRL and other lactogen for its proliferation. PRL is related to the expression of several genes that can promote cell growth by suppressing apoptotic mechanisms and stimulating cell cycle progression in these cells (LaVoie *et al.*, 1995; Leff *et al.*, 1996). This cell line was used by LaVoie *et al.* (1995) to assess the action of intracellular mediators on the anti-apoptotic effect of PRL. Apoptosis was induced using dexamethasone and PRL was used to inhibit this process; in addition to the hormone, agonists and antagonists of the signaling pathways already assigned to PRL were analyzed and it was observed that a tyrosine phosphatase inhibitor significantly reduced DNA fragmentation, suggesting that tyrosine phosphorylation may be related to the anti-apoptotic effect of PRL.

Nb2-FSJCD1 cells were developed from the Nb2 lineage and are independent of PRL. Leff *et al.* (1996) used these two strains to evaluate the regulation of expression of the *BCL-2* and *BAX* genes by PRL, observing an increase in the expression of the *BCL-2* gene and a reduction in the expression of *BAX* influenced by the action of the hormone in Nb2 cells. Autonomous cells, although not dependent on PRL for proliferation, are sensitive to the hormone in the expression of *BCL-2*. The relationship between these genes is important in the process of apoptosis. Thus, the action of PRL in both strains demonstrated a possible protective effect against programmed cell death. The Nb2-11 strain was also used to evaluate the expression of apoptosis regulatory genes. Krumenacker *et al.* (1998) used dexamethasone to induce the cell death process and PRL to inhibit that process. Even at the lowest concentrations, PRL reduced apoptosis and increased transcription of *BCL-2* and *PIM-1* was observed. It has thus been suggested that these genes may play an important role in the anti-apoptotic actions of PRL.

The regulation of the *BCL-2* and *BAX* genes was also evaluated to characterize the

effect of PRL against programmed cell death (Ploszaj *et al.*, 1998). In this study, the HC11 cell line (mouse mammary epithelial cells) were used and an increase in *BCL-2* expression and the amount of Bcl-2 protein was observed, in addition to a reduction in PRL-related *BAX* transcripts; the authors suggest that this stimulation of *BCL-2* expression and *BAX* suppression may be an important mechanism for the action of PRL against apoptosis.

Fernández *et al.* (2003) used the Nb2 strain (dependent PRL), previously mentioned, to evaluate the protective effects of PRL and placental lactogen against nitric oxide-induced apoptosis. They used different types of nitric oxide donors and, in combination, treatment with different concentrations of PRL. The protection exerted by this hormone was evaluated using a cell viability test, analysis of DNA fragmentation, analysis of cell death by differential staining and determination of caspase 3 activity; all tests demonstrated that nitric oxide donors induced apoptosis and when present, PRL reduced these effects. A reduction in the activity of caspase 3, which had increased with the presence of nitric oxide donors, was also observed. The authors suggest that the anti-apoptotic action observed is related to the action of PRL in the regulation of members of the Bcl-2 family.

The action of PRL on intervertebral disc degeneration was evaluated by Wu *et al.* (2018), who observed the expression of PRL and its receptor in pulpy nucleus tissue (in the central part of the intervertebral disc) obtained from human patients diagnosed with this degeneration; in this tissue, the expression of the hormone and its receptor was lower than in non-degenerated pulpy nucleus tissues. It was also observed that applications of PRL decreased the intervertebral disc degeneration induced in Sprague-Dawley rats; these effects were associated with inhibition of the inflammatory response, with a reduction in the expression of TNF- $\alpha$  and IL-1 $\beta$ , in addition to a decrease in apoptosis, inhibiting the NF-kB pathway. The authors suggest that in this way, PRL and its receptor can be considered as a therapeutic strategy. This study highlights yet another anti-apoptotic action of PRL.

An anti-apoptotic effect of PRL was also observed in the investigation of the action of the heat shock protein HSPB1 in the cytoprotection of  $\beta$  cells. This study was conducted in primary cell cultures of pancreatic islets isolated from the pancreas of human donors with brain death and in cultures of pancreatic islets isolated from the pancreas of Balb / c mice. PRL inhibits cell death in pancreatic islets and stimulates the production of HSPB1 in these cells. The production of this protein was shown to be directly related to the increase in the Bcl2 / Bax ratio, inhibiting the apoptosis cascades of both the extrinsic and intrinsic pathways. These results may offer an alternative strategy for preserving viable pancreatic islets for transplantation (Wailemann *et al.*, 2018).

The action of the HSPB1 protein as a mediator of the protective effect of PRL in  $\beta$  cells was evaluated in relation to the response of these cells to oxidative stress. Terra *et al.* (2019) used the MIN6 strain (derived from mouse insulinoma), treated with oxidative stress inducers and PRL, and observed an interaction between HSPB1 and proteins associated with the inhibition of cell death and protein degradation, also related to peroxide radical

dismutation enzymes, when the hormone was present. The authors infer the reduction of cell death from an endogenous pathway as a resource for successful pancreatic islet transplantation.

Nardelli *et al.* (2018) also evaluated the protective action of PRL on  $\beta$  cells, verifying that the anti-apoptotic action on rat  $\beta$  cells, exposed to pro-inflammatory cytokines occurs mainly through the STAT3 transducer. PRL altered the expression of pro- and anti-apoptotic proteins in the c-Jun N-terminal (JNK) kinase cascade, from the phosphorylation of AKT protein kinase, preventing the activation of JNK. Partial inhibition of NF $\kappa$ B was also observed. These effects, which promote greater survival of the cells exposed to inflammatory stress, characterize specific metabolic pathways that can be considered as tools for the protection of  $\beta$  cells in autoimmune attacks or in islet transplants.

Other studies demonstrate the anti-apoptotic effect of PRL, evidencing the action of the PRL/PRL receptor system in terms of inhibiting apoptosis and, thus, favoring cell proliferation in ovarian carcinomas (Asai-Sato *et al.*, 2005) and in cancer cells of the cervix uterus (Arellano *et al.*, 2015). The authors suggest that this system (hormone and its receptor) may be an important target in the treatment of these neoplasms. Although this action is not positive for the organism (since it favors carcinogenesis, its maintenance and progression), it characterizes how PRL and its receptor protect cells against cell death by apoptosis.

Likewise, Flore-Frenández *et al.* (2016) identified a relationship between the anti-apoptotic effect of PRL and the development of autoimmune diseases such as systemic lupus erythematosus, observing, in the cell line WEHI-231, a line of immature B cells, the increase in cell viability, the expression of Bcl $\chi$ L (anti-apoptotic factor) and the reduction of Bad expression (pro-apoptotic factor). Such factors can favor the maturation of these self-reactive clones and the development of disease.

### 2.3 Other protective effects

The induction of cell proliferation and/or anti-apoptotic effects are also related to the protective action of PRL in other tissues or organs. Adult male hyperprolactinemic Sprague-Dawley rats and a primary culture of neonatal rat cardiomyocytes were used to demonstrate a protective action of PRL for the cardiovascular system. Both animals and cultured cells were subjected to normoxic and hypoxic environments to assess the effects of intermittent hypoxia and the action of PRL against these effects. The results suggest large amounts of PRL in plasma protect cardiomyocytes from stimulating cell proliferation and survival. They also suggest an increase in proteins involved in these mechanisms, such as IGF-I, PI3 $\alpha$ , phosphorylated AKT, Bcl-2, c-Myc., cyclins D1, E and A. These increased molecular factors may be related to the pathway activated by PRL, since an increase in phosphorylated JAK2 and STAT5 proteins has also been observed (Hsieh *et al.*, 2015). Other evidence of cardioprotective effects can be seen in the study undertaken by Hilfiker-Kleiner *et al.*



(2007). They demonstrated that the STAT3 signal transducer is important for preserving angiogenesis and cardiomyocyte function; changes in its pathway may be directly related to the onset of postpartum cardiomyopathy. The authors also observed a relationship between the increase in oxidative stress in cardiomyocytes and the cleavage of PRL in a harmful way. According to these findings, it can be inferred that the PRL intact, or its non-cleavage, could reduce inflammatory and apoptotic events related to this disease.

Wahlberg *et al.* (2013) investigated a possible protective effect of PRL in thromboembolic diseases; they analyzed the action of PRL on platelets, in vitro and in patients with hyperprolactinemia. In vitro evaluations did not identify any influence of PRL on platelet activation; however, the analysis of platelet activation by flow cytometry in the blood of hyperprolactinemic patients indicated an indirect inhibitory effect of PRL on platelets, from a significant reduction in P expression. -selectin. The influence of PRL on platelet activation has also been observed in other studies (Wallaschofski *et al.*, 2001; Anaforoglu *et al.*, 2010; Ishioka *et al.*, 2015), however, not with a protective effect, but rather in the context of the relationship between hyperprolactinemia and the increase in coagulation markers and platelet activation.

Antioxidant and anti-apoptotic actions of PRL were evaluated in the retinal pigment epithelium of rats (of different ages), with and without PRL receptors. For this study, the rats' eyes were enucleated after euthanasia in order for the tissue to be used for in situ and immuno hybridization-histochemistry, in addition to histology assessment, production of reactive oxygen species, apoptosis and RNA extraction. The human cell line ARPE-19 (retinal pigment epithelium cells) was also used. As a result, the PRL receptor was identified in the retinal pigment epithelium and PRL was characterized as a trophic factor for the cells of that tissue; the presence of this hormone reduced the damage caused by hydrogen peroxide and the levels of reactive oxygen species in cells of the ARPE-19 lineage. This effect was related to the action of PRL inhibiting the increase in  $Ca^{2+}$  induced by deacetylase SIRT2, mediated by the TRPM2 receptor. These two factors are considered targets of the antioxidant action of PRL. In rats null for the PRL receptor, degeneration of the retinal pigment epithelium was observed to increase with advancing age (García *et al.*, 2016).

Arnold *et al.* (2020) also studied the effect of PRL on retinal functionality with aging. Young and elderly adult mice were used, null or not for PRL receptors, and it was observed that, in elderly mice null for the PRL receptor, disturbances in functionality induced by aging were more intense and apoptosis was more frequent, with a differential expression of pro-apoptotic mediators; in addition, microglia cells were activated, demonstrating the need for PRL for the proper functioning of photoreceptor cells and the possible therapeutic value of this hormone against age-related retinal disorders.

The protective action of PRL against the effects of methylmercury (MeHg), in glial cultivation of the cortex of rats, was analyzed by Santos (2008). In the combined treatment, it was observed that PRL attenuated the effects induced by the metal, increasing cell

viability and reducing morphological changes characteristic of MeHg cytotoxicity in addition to inducing cell proliferation and the release of Interleukin-1 $\beta$ .

Jesus (2012) used the lymphocyte lineage of primates B95-A to investigate the action of PRL on the effects of MeHg, evaluating the viability and immune response of these cells, in relation to the concentration of tumor necrosis factor alpha (TNF  $\alpha$ ) in the culture supernatant. PRL was able to prevent the decrease in cell viability caused by MeHg and to reverse the release of the proinflammatory cytokine TNF  $\alpha$ , protecting cells against the toxic effects of mercury.

The cytoprotective action of PRL in vitro in human cell lines subjected to MeHg cytotoxic and mutagenic effects has also been identified. Silva-Pereira *et al.* (2014) evaluated the cytoprotective effect of PRL in lymphocyte culture and in the HL-60 strain; the influence of MeHg on cell cycle kinetics and the action of PRL on this effect was observed. PRL reduced the induction of polyploidy caused by MeHg, demonstrating the action of this hormone against the mutagenic effect of mercury; from the analysis of the mitotic index, a reduction in cytotoxicity caused by the metal was observed, evidencing the action of this hormone as a co-mitogenic factor and inhibitor of apoptosis.

Supplementation of the culture medium with PRL was used in the cultivation of pancreatic islets to verify if this hormone had any selective protective effect on  $\beta$  cells. In a similar way to the study by Wailemann *et al.* (2018), discussed in the previous section, the islets for cultivation were isolated from the pancreas of donors with brain death; an increase in the quantity of viable  $\beta$  cells was observed in culture with PRL. These islets were also transplanted to diabetic mice and it was observed that the induced hyperglycemic condition was reversed. These results demonstrate that PRL improves the viability and specific survival of  $\beta$  cells in vitro and in vivo, demonstrating a protective effect of PRL in pre-transplant islets (Yamamoto *et al.*, 2008).

To better understand the protective effect of PRL on  $\beta$  cells, Marmantini (2019) used the mouse insulinoma cell line INS-1E. These cells were pre-treated with PRL, and then treated with hydrogen peroxide, to induce oxidative stress; there was an increase in the survival of these cells and the production of the enzymes superoxide dismutase 2 and catalase, induced by the hormone. Bioinformatics analyses carried out in this study suggest that PRL activates receptors activated by peroxisome proliferators, which are involved in the transcription of antioxidant enzymes. This may explain the action of this hormone.

The protective action of PRL was evaluated in inflammatory arthritis, which was induced in male Sprague-Dawley rats and female C57BL6 mice, some of which were hyperprolactinemic to characterize the action of the hormone. PRL was shown to be protective against trabecular bone loss and osteoclastogenesis. Molecular analyses demonstrated that PRL and its receptor were related to a systemic reduction in C-reactive protein and TNF $\alpha$  levels and the expression of transcription factors and cytokines in the joints of rats and mice with inflammatory arthritis, in addition to inhibiting ligand activation of

the nuclear factor Kappa B activator receptor via the STAT3 activation pathway (Ledesma-Colunga *et al.*, 2017).

The effects of PRL on inflammatory arthritis have also been investigated by Adán *et al.* (2013). They evaluated, *in vitro* and *in vivo*, the effect of this hormone on chondrocytes, noting that PRL inhibited the apoptosis of these cells and its receptor deficiency favored it. Their survival was favored by PRL through the JAK2 pathway/STAT3, blocking the expression of pro-inflammatory cytokines and the consequent pro-apoptotic effects. The authors suggest that PRL may delay the onset and decrease the severity of the symptoms of inflammatory attrition.

A protective effect of PRL on gastric lesions was observed in Wistar rats subjected to cold chamber stress and food deprivation. In a study by Drago *et al.* (1985) some rats received a graft from pituitary glands in the renal capsule before being subjected to stress, while others received only PRL treatment. After lesion induction, it was observed that PRL reduced or prevented the formation of gastric lesions (Drago *et al.*, 1985). This same effect was investigated by Fujikawa *et al.* (2000), who used Sprague-Dawley rats submitted to water containment stress and observed an increase in serum PRL levels in the first hours after stress. In addition, as noted in the previous study, animals that received pretreatment with PRL did not develop lesions in the gastric mucosa, unlike animals that did not receive this treatment, demonstrating the protective action of PRL.

The action of PRL on the cells of the immune system was observed by Guzmán *et al.* (2008) when they evaluated the protective effect of this hormone against the effects of exposure to UV light. C3H/ Hej mice received PRL and, after 10 days of treatment, were irradiated with UV light in a dose sufficient to induce an inflammatory response; 11 days after irradiation, skin samples were obtained for immunohistochemical analysis. It was observed that exposure to UV light induced a decrease in the number of gamma-delta T lymphocytes and, in animals that had received PRL treatment, this effect was reduced. PRL also reduced the number of morphologically altered Langerhans cells.

Di Carlo *et al.* (1993) and Meli *et al.* (1996) evaluated the protective effect of PRL against *Salmonella typhimurium* infection. In both studies, Swiss rats were treated with PRL before and after being infected with *S. typhimurium*. In both cases, less lethality was observed when the animals had first been treated with the hormone. It is suggested that PRL appears to act on macrophage activities, since a significant increase in phagocytosis and intracellular death was observed in the peritoneal macrophages of infected rats previously treated with PRL. Meli *et al.* (1996) also observed that the protective activity of PRL may be related to the production of nitric oxide.

The immunomodulatory effect of PRL may also be related to an antiparasitic role played by this hormone, which has been observed in some studies. Filipin *et al.* (2011) evaluated the effect of PRL during the acute phase of Chagas disease. Male Wistar rats were infected with the parasite and treated with PRL; immune cells were characterized by

an increase in macrophages, thymocytes and CD3+ and CD4+ T lymphocytes in animals that received PRL, after 14 days of infection; an increase in splenocytes was also observed in these animals, after 21 days of infection. These results suggest that PRL affects the regulation of components of the immune response.

The immunomodulatory effect of PRL during experimental Chagas disease was also analyzed in the chronic phase of the disease. In addition to the characterization of cells, the profiles of cytokines TH1 and TH2 were evaluated. During the acute phase, PRL induced an increase in NK cells, an increased production of antibodies by B cells and an intense immune response by TH1; the reverse was observed in the later stage of the disease, characterizing an inverse modulation, which is important in protecting the affected organs against an exaggerated immune response during the chronic phase of this disease. The authors suggest that PRL may play an important role in conjunction with drug treatment for Chagas disease (Filipin *et al.*, 2019).

Dzitko *et al.* (2010) observed that, *in vitro*, PRL reduced the penetration of *Toxoplasma gondii* in host cells without a specific receptor for this hormone. Tachyzoites of this protozoan had previously been treated with different concentrations of PRL, and a reduction in parasite viability in the presence of the hormone had not been observed, but a reduction in protozoan proliferation was observed. The authors believe that PRL, by binding to the surface of parasitic cells, prevents the recognition of host cell receptors.

Inhibition of proliferation of *T. gondii* has also been observed in mononucleated cells isolated from the blood of patients with hyperprolactinemia, although a greater effect of the hormone of exogenous origin on parasite control is observed when compared to the effect of the hormone of endogenous origin. (Dzitko *et al.*, 2012). Mohammadpour *et al.* (2019) evaluated the relationship of serum PRL level and the frequency of *T. Gondii* infection. Blood samples were obtained and the PRL level and presence of anti-toxoplasma IgG antibody in plasma were measured; a lower prevalence of the parasite was observed in groups with a high PRL index, especially in hyperprolactinemic women, confirming the immunoregulatory role of the hormone.

### 3 | CONCLUSION

Many studies have already been undertaken with the aim of highlighting and understanding the protective effects of PRL, a hormone that acts on many tissues and performs numerous functions. These protective functions and effects are related to the metabolic pathways induced by this hormone when activating its receptor. These pathways mostly lead to the expression of factors that favor proliferation or inhibit apoptosis; such actions have been observed in the studies addressed in this review.

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