Chapter 4

Prolactin in the Immune System

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1. Introduction

Prolactin (PRL) is a protein hormone, as well as a cytokine, which is synthesized and secreted from specialized cells of the anterior pituitary gland, named lactotrophs. More than 300 functions exerted by PRL in vertebrates have been recognized; and they reflect the ubiquitous distribution of its receptors, as well as the fact that PRL is synthesized in many extrapituitary tissues. Among these sites of PRL synthesis are cells of the immune system, such as macrophages, natural killer cells, and T- and B-lymphocytes. Regulation of PRL synthesis is organ specific, which confers additional complexity to the spectrum of PRL actions. In the physiology of the immune system, PRL acts by stimulating the secretion of other cytokines and the expression of cytokine receptors, and also as a growth and survival factor. In pathological conditions, increased levels of PRL could cause deterioration of the subject's condition. In this review, we integrate the information on regulation of PRL synthesis with that concerning its physiological and pathological actions in extrapituitary tissues, highlighting those in the immune system.

2. Regulation of prolactin expression and secretion in the pituitary and at extrapituitary sites

PRL was originally identified as a neuroendocrine hormone of pituitary origin; however, its synthesis is not limited to the hypophysis since numerous extrapituitary tissues also express this protein, including the placenta, ovary, testis, mammary gland, skin, adipose tissue, endothelial cells, and immune cells [1]. This wide-spread PRL expression might explain its involvement in very different processes such as reproduction, metabolism, immunology, and behavior.

PRL expression and secretion are regulated by different stimuli provided by the environment and the internal milieu. Although pituitary PRL secretion is under a tonic and

predominantly inhibitory control exerted by dopamine of hypothalamic origin, other factors within the brain, pituitary gland, and peripheral organs have been shown to inhibit or stimulate PRL secretion as well [2-5]. Therefore, pituitary PRL expression depends on the balance between inhibitory and stimulatory molecules such as hormones, cytokines, and other factors that orchestrate the cascade of intracellular events involving numerous signaling pathways. Prominent among these signaling cascades are the cAMP/protein kinase A (PKA), the phosphatidylinositol/Ca^{++}/protein kinase C (PKC), and the mitogen-activated protein kinase (MAPK) pathways. In addition, the PRL gene seems to follow a pulsatile transcription dynamic with refractive phases in the transcription cycles [4]. In the pituitary, a direct relation between transcribed mRNA and released protein cannot be easily established, since different, post-transcriptional processes may alter the final protein production; these include mRNA degradation, protein storage, and regulation of secretion. Pituitary PRL secretion depends on the action of secretagogues which act on the cell membrane of lactotrophs, rapidly releasing stored PRL by means of calcium-dependent exocytosis. In contrast, extrapituitary cells seem to have little storage capacity and consequently, PRL is released after synthesis [2, 5]. Therefore, extrapituitary PRL is basically

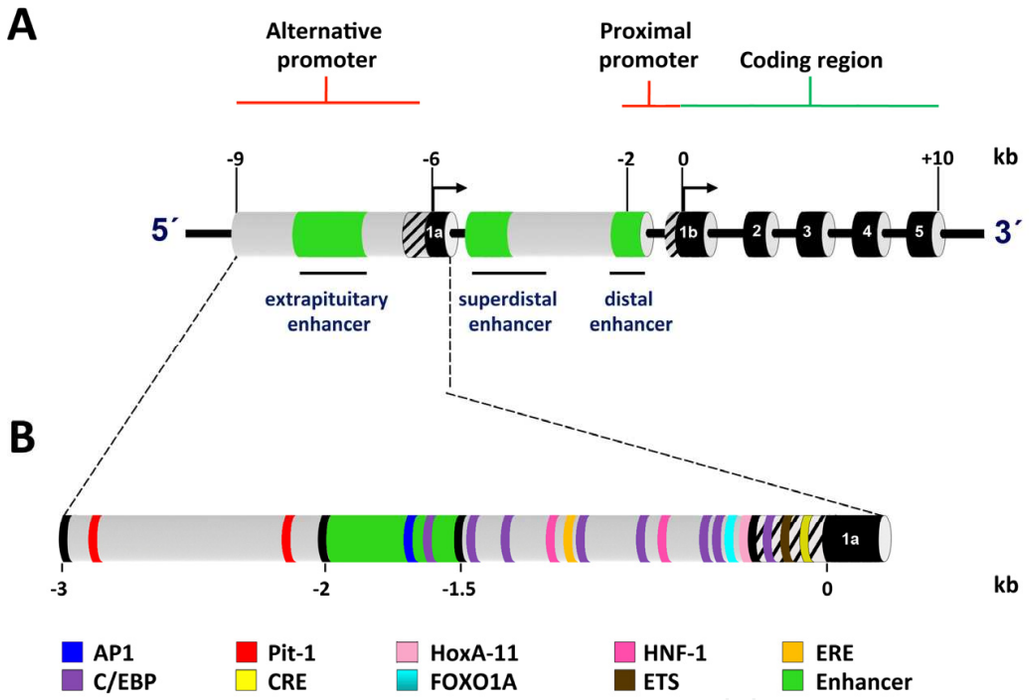

Figure 1. Schematic representation of the human PRL gene. A) The alternative and proximal promoters, as well as the coding region are depicted. Exons are represented by black boxes with corresponding exon numbers (1a, 1b, 2-5). Exon 1a, located 5.8 kb upstream of the proximal start site, drives extrapituitary PRL expression. B) Extended diagram of human PRL alternative promoter showing the location of predicted transcription factor binding sites. The superdistal promoter is about 3.0 kb in length. Consensus sequences for transcription factors are depicted and shown in different colors. The figure is not drawn to scale. AP1: activator protein 1; C/EBP: CCAAT/enhancer binding protein; Pit-1: pituitary-specific transcription factor 1; CRE: cyclic-AMP response element; HoxA-11: homeobox A11; FOXO1A: forkhead box protein O1A; HNF-1: hepatocyte nuclear factor 1; ETS: E-twenty six; ERE: estrogen response element. Enhancer regions are represented in green.

regulated at the level of transcription. The regulation of PRL gene expression is quite complex, due to the presence of several enhancer and silencer domains as well as the formation of chromatin loops with consequences for transcription dynamics. Two independent promoters with differential responses to regulatory mediators direct PRL transcription in a cell-type specific manner [4].

The human PRL locus consists of a single gene containing 5 coding exons transcribed directly from a pituitary-specific promoter (proximal promoter) and a non-coding exon (1a) transcribed from an alternative promoter (also known as the decidual or superdistal promoter) with a transcriptional start site located 5.8 kb upstream of exon 1b (Figure 1). This alternative promoter drives expression in extrapituitary tissues [4, 5] and seems to have evolved from a long terminal repeat transposable element, previously described as primate specific [6]. The differential promoter usage produces different sized gene products, which may vary in a cell-specific manner depending on the functional elements used within the particular promoter. In general, extrapituitary PRL mRNA is ~150 bp longer than pituitary PRL mRNA; however, mRNA identical to that in the pituitary gland has been found in normal and tumoral breast tissues, breast cell lines, and prostate [7, 8]. Therefore, the dichotomy of promoter usage in pituitary versus extrapituitary sites is not absolute [9].

As a consequence of the distal transcription start site, the alternative promoter does not respond to the same regulators of gene expression that operate with the proximal promoter, such as the pituitary transcriptional factor-1 (Pit-1), which is paramount for the activation of pituitary PRL transcription. An exception to this generalization is the hormonal form of vitamin D, calcitriol, which stimulates PRL expression in pituitary cells as well as in decidua and resting lymphocytes. Other cell-specific cases will be further discussed below.

2.1. Regulation of PRL in the immune system

In the immune system, PRL is thought to act as a locally produced cytokine with relevance for immune regulation and modulation of T- and B-cell function. Nevertheless, the molecular mechanisms regulating PRL expression in the immune system and the factors implicated are still not fully understood. Within the immune system, PRL is produced by T- and B-lymphocytes, macrophages, thymocytes, mononuclear and natural killer cells. However, in peripheral blood-mononuclear cells (PBMC), PRL production is mainly associated with the T-lymphocyte fraction [2, 10]. Because it uses the alternative promoter, lymphocyte PRL expression is independent of Pit-1, progesterone, estrogen, thyrotropin-releasing hormone (TRH), dihydrotestosterone, and insulin, among other classical modulators of PRL in the hypophysis. In contrast, PRL expression in T-lymphocytes is stimulated by cAMP, retinoic acid, and calcitriol, while it is inhibited by dexamethasone and some interleukins [10-15].

2.1.1. cAMP and modulators of the cAMP/CREB pathway

Consistent evidence, including studies in different leukemic cell lines as well as PBMC from normal patients, has shown that PRL gene expression is significantly stimulated by cAMP,

its analogues and first messengers that signal through the cAMP/PKA pathway [12, 13, 16]. The second messenger cAMP induces PRL gene expression by activating PKA, which migrates to the nucleus and phosphorylates target proteins such as the cAMP response element binding protein (CREB). However, in the eosinophilic leukemia cell line EoL-1, it seems that cAMP induces PRL expression by two different signaling cascades: the classic PKA-dependent pathway leading to the phosphorylation of CREB, and a PKA-independent pathway leading to the phosphorylation of p38 [12]. Known first messengers that activate the cAMP/PKA pathway are prostaglandin-E_2 and terbutaline, a β_2-adrenergic agonist that enhances PRL expression in PBMC and some leukemic cell lines either alone or in combination with PMA or ionomycin [17]. These observations are most likely explained by the cAMP response element (CRE) located -25 bp upstream of the PRL alternative promoter (Figure 1). Furthermore, this CRE encourage additional studies of the regulation of PRL by other physiological modulators of the immune system that operate through cAMP as a second messenger. This would be especially relevant in pathological conditions associated with increased PRL levels such as autoimmune diseases and cancer, where alterations in extrapituitary PRL promoter regulation might play a role in the pathophysiology of these disorders.

2.1.2. Dopamine and cell-activating factors

Quite interestingly, the nervous and the immune systems use a common chemical language for intra- and inter-system communication. Indeed, both systems produce a common set of neurotransmitters and cytokines that act on a shared repertoire of receptors [18]. Regarding dopamine, which is the primary neuroendocrine inhibitor of PRL secretion in the anterior pituitary gland, some evidence supports the involvement of this neurotransmitter in the regulation of lymphocyte PRL production and release [3]. Indeed, differential expression of all dopamine receptor subtypes has been detected by flow cytometry in human immune cells [19]. Specifically in lymphocytes, pharmacological studies indicate expression of the dopamine receptors D_2, D_3, D_4, and D_5 [3, 20, 21]. In the secondary lymphoid tissues, D_3 is the predominant dopamine receptor and it is highly and selectively expressed in naive $CD8^+$T cells of both humans and mice [22]. The differential expression of dopamine receptor subtypes in the lymphocyte subsets as well as the alterations in dopamine-mediated effects under conditions of stress [23]; need to be taken into consideration when studying regulatory mechanisms involved in cell activation/suppression processes. Indeed, since D_1 and D_5 couple with $G_{\alpha s}$ proteins increasing cAMP, while D_2, D_3, and D_4 couple with $G_{\alpha i}$ proteins, inhibiting the production of cAMP, a different cell response is to be expected depending on the receptor subtype that is expressed, as seen in activated T cells [24].

In addition, some immune cells such as lymphocytes produce endogenous dopamine, which may induce autocrine/paracrine actions. The effects of dopamine in the immune system are highly dependent on the context and dopamine concentration [25]; moreover, its effects on immune cells also depend on their activation state, which, at the same time, is modulated by dopamine itself [25, 26]. Indeed, dopamine interacts directly with dopaminergic receptors on normal human T-cells, triggering characteristic features of activated lymphocytes [26].

These data are in agreement with unpublished observations from our group which indicated that dopamine regulates prolactin expression in PBMC, as well as expression of its own receptor [27]. Moreover, our results showed that activation of PBMC with phytohemagglutinin (PHA), concanavalin-A (Con-A), or phorbol myristate acetate (PMA) significantly reduced PRL mRNA in all cases. Notably, the inhibitory effect of Con-A upon PRL mRNA expression persisted in the presence of a cAMP analogue (Figure 2), suggesting that cell activation with this lectin disrupts the cAMP/PKA signaling pathway, which is involved in PRL upregulation in lymphocytes as previously mentioned. In accordance with our results, Gerlo *et al* showed that PMA and ionomycin inhibited PRL gene expression in normal PBMC, but elicited differential effects in several leukemic cell lines [17]. Altogether, these observations suggest that under an *in vivo* scenario, modification of the lymphocytes activation status by dopamine might alter their PRL expression, an idea which warrants further investigation. *In vitro*, even if PRL gene expression is decreased by cell activation, the final PRL concentration in the culture media might be elevated due to the larger number of PRL-producing cells. This agrees with several other studies showing that mitogen stimulation is not required for PRL mRNA expression and exerts no appreciable effect on the level of PRL transcripts [10].

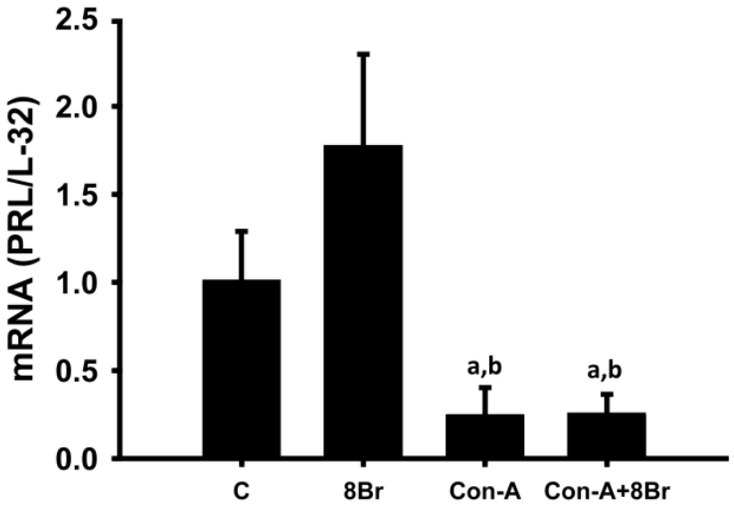

Figure 2. Effect of lymphocyte activators on PRL mRNA levels. PBMC from 3 pregnant women were incubated for 24 h in the presence of 8-Bromo-cAMP (8Br, 1 mM), concanavalin-A (Con-A, 1 mg/mL), or both. PRL mRNA expression was evaluated after normalization against L-32 mRNA by real time PCR. a = $P < 0.05$ vs control (C); b = $P < 0.05$ vs 8Br. An arbitrary value of 1 was given to control data.

2.1.3. Calcitriol

Previous findings in human lymphocytes suggested that calcitriol effects were exerted only after cell activation, which is necessary for the induction of the 50-kDa classic vitamin D receptor (VDR). Nevertheless, recent findings from our group clearly showed VDR-mediated effects in resting lymphocytes. We also described a constitutive, 75-kDa VDR species that might participate in calcitriol-dependent PRL upregulation in these cells.

Indeed, as in the case of decidua and the pituitary, calcitriol stimulated both, PRL mRNA expression and protein production in resting PBMC through a VDR-mediated mechanism [15]. Interestingly, this effect was only seen in quiescent lymphocytes and was not detected in Jurkat T-lymphoma cells. Genomic effects of calcitriol upon the alternative PRL promoter are likely to occur in lymphocytes, in view of previous results in decidua [28] together with the fact that the decidual form of the PRL transcript is expressed in human blood lymphocytes [10, 29]. Nevertheless, further studies are required to clarify the specific interaction of the VDR with the PRL promoter region in lymphocytes, since it is known that the pituitary promoter contains functional sequences that confer VDR responsiveness. Indeed, calcitriol stimulated PRL promoter activity in cultured pituitary GH3 cells [30, 31], an effect that was further corroborated *in vivo* [32]. The fact that calcitriol regulates PRL in immune cells might be relevant in specific physiological contexts, considering the immunomodulatory actions of this secosteroid. Certainly, calcitriol effects in the immune system appear to occur at the level of T-helper (Th) cells, where it acts as an immunosuppressive factor. Calcitriol inhibits mainly Th1 cytokines [33], as confirmed by its abilities to prevent or ameliorate autoimmune diseases and to inhibit allograft rejection responses [34, 35]. The upregulation of lymphocyte-derived PRL by calcitriol could help explain the condition of hyperprolactinemia reported in some granulomatous disorders such as sarcoidosis, a disease associated with increased calcitriol production by macrophages, and characterized by abnormal accumulation of inflammatory cells such as T-lymphocytes [36, 37]. Indeed, calcitriol is synthesized by macrophages, dendritic cells, and both T- and B-cells by means of expressing the enzyme CYP27B1, which catalyzes the synthesis of the secosteroid from its inactive precursor, calcidiol [38]. Thus, in immune cells, PRL secretion might be regulated by locally produced calcitriol providing, at this level, paracrine and or autocrine immunomodulatory effects.

2.1.4. Cytokines

Structural analyses of PRL and its receptors have revealed their relation to the cytokine/hematopoietin family. Standing as a leukocyte-derived cytokine in the immune system, PRL is regulated by other cytokines in an autocrine and paracrine manner. In T-lymphocytes, interleukin (IL)-2, IL-1β, and IL-4 reduced PRL mRNA, while IL-10 and interferon-γ had no effect [11]. On the other hand, in myeloid leukemic cells, the PRL alternative promoter was activated by the proinflammatory cytokine tumor necrosis factor alpha (TNF-α). A TNF-α-responsive region was located between -1842 and -1662 of the extrapituitary PRL promoter. Interestingly, the stimulatory effect of TNF-α upon PRL was blocked by a protein kinase C (PKC) inhibitor [14]. Since TNF-α is a master proinflammatory cytokine, its involvement in PRL stimulation might have clinical relevance in view of several studies indicating that leukocyte-derived PRL is involved in autoimmune and hematological disorders [39-41]. Indeed, hyperprolactinemia and increased secretion of lymphocyte PRL have been reported in systemic lupus erythematosus (SLE) [42], which is an autoimmune disease characterized by abnormal production of autoantibodies and proinflammatory cytokines [43]. Moreover, hyperprolactinemia has been associated with SLE disease activity [41, 42, 44, 45].

2.2. Regulation of PRL in the placenta and endometrium

PRL functions in reproduction vary within species. For example, while in rodents the presence of PRL is mandatory to achieve a normal estrous cycle, support the corpus luteum for progesterone production and maintenance of gestation, in humans the role of PRL is more likely relevant during lactation, since it does not support the corpus luteum nor significantly participates in the menstrual cycle [5]. The decidua develops from the uterine lining throughout the late luteal phase of the menstrual cycle, and during pregnancy the decidua constitutes the maternal component of the placenta. Considered a marker of decidualization, PRL is one of the most dramatically induced genes in decidualized endometrial cells. The placental decidua secretes very large amounts of PRL that accumulates in the amniotic fluid, peaking between 16 and 22 weeks of gestation (~5000 ng/mL) and falling to ~500 ng/mL at term [46]. Regarding PRL regulation, activation of the cAMP/PKA pathway is known to induce the activity of the alternative PRL promoter in human decidual cells through the transcription factors CREB and CCAAT/enhancer-binding protein (C/EBP) [47, 48]. In this regard, eight C/EBP binding sites have been described in the decidual PRL promoter (Figure 1). Decidualization is mainly triggered and supported by progesterone. Accordingly, upregulation of PRL gene expression steadily increases due to high progesterone levels during pregnancy. Indeed, progesterone potently stimulates decidual PRL production [49, 50], which is achieved in part by cross-talk with the cAMP/PKA signaling pathway [51], and is synergized by a number of factors such as prostaglandin E, corticotropin releasing factor, and the free α-subunit of gonadotropin [52-54]. Furthermore, in human endometrium explants and endometrial stromal (ES) cells, progesterone and relaxin induced stromal differentiation (decidualization) and PRL secretion [50, 55]. Interestingly, in primary ES cell cultures, cAMP activated the alternative PRL promoter in a biphasic manner, with an initial, weak induction during the first 12 hours, followed by a more intense induction afterwards. It was concluded that the early response depended upon the CRE located at approximately -12 bp upstream of the PRL alternative promoter, whereas the major activation depended upon a region between positions -332 and -270 bp, which kinetics differed from classic CRE-mediated responses [55].

In addition to the decidualized endometrium of the late luteal phase and of pregnancy, the human myometrium, which is the muscle layer of the uterus, is considered to be a secondary source of PRL. Nevertheless, the regulation of myometrial PRL differs significantly from that of the decidua. Indeed, myometrial PRL expression seems to be under inhibitory control *in vivo*, as concluded from experimental findings showing that myometrial PRL release increased with time in culture. Moreover, in myometrial explant cultures, medroxyprogesterone acetate inhibited PRL production [2, 56]. This observation, together with the fact that PRL circulating levels are unchanged throughout the human menstrual cycle, suggests that further studies are needed to completely clarify the mechanistic details of PRL regulation by progesterone in the human myometrium.

Besides progesterone, other stimulators of decidual PRL synthesis and release are insulin, insulin-like growth factor-1, and calcitriol [28, 57, 58]. Since the human decidua is able to synthesize calcitriol and express the VDR, PRL regulation by this secosteroid is more likely

autocrine in nature. However, considering that inflammatory cytokines such as TNF-α, IL-1α, IL-1β, IL-2, IL-8, and transforming growth factor-β (TGF-β1) inhibit decidual PRL expression [59, 60], and that calcitriol is a potent inhibitor of placental inflammatory cytokine production [61, 62], calcitriol might also be acting as a paracrine upregulator of decidual PRL. In addition, IL-4 decreased both the level of PRL mRNA and its release from myometrial tissue, whereas IL-6 exerted no effect [63]. Recently, the transcriptional regulators HoxA-10, HoxA-11, and FOXO1A, which are essential for decidualization, have been shown to interact physically and functionally to upregulate the expression of a gene battery in differentiating endometrium. In particular, this core set of transcription factors cooperatively upregulate PRL in differentiating ES cells by binding to an enhancer region located between positions −395 and −148 of the decidual prolactin promoter (Figure 1) [64].

2.3. Regulation of PRL in the breast and adipose tissue

In addition to uptake of PRL from the blood, mammary epithelial cells synthesize PRL during pregnancy and lactation. It has been suggested that the production of mammary PRL requires a systemic trophic factor, because PRL mRNA declined with time in cultured rat mammary gland explants [65]; however, this proposal requires further investigation since PRL regulation is thought to differ between species. Interestingly, the number of PRL variants in human milk exceeds that found in serum, indicating that the breast may be a post-transcriptional processing site [66]. In support of this possibility, incubation of mammary slices in the presence of PRL resulted in the formation of fragments of PRL [67]. Although there are two Pit-1 consensus sequences located at -2186 and -2800 bp within the alternative promoter (Figure 1), the expression of extrapituitary PRL is thought to be independent of Pit-1. However, Pit-1 expression in normal and cancerous human breast tissue has been reported [68]. Moreover, the experimental over-expression of Pit-I in MCF-7 cells significantly increased expression of PRL mRNA, while PRL protein expression was significantly reduced after Pit-I knockdown, suggesting that in this cell line, PRL transcription is driven by the proximal pituitary promoter and is due to Pit-I binding to this region [69]. Alternatively, distal upstream Pit-1 consensus sequences could also be participating.

As in the case of the pituitary, studies performed in the human mammary cell line T47D showed that estrogen directly induces PRL gene expression [70]. A functional, non-canonical, estrogen responsive element (ERE) and an AP1 site have been located in the PRL distal promoter (Figure 1). Moreover, both estrogen receptors α and β bind directly to this ERE, which suggests that estrogens regulating autocrine PRL in the human breast may contribute to breast development and cancer progression.

It is noteworthy that most local PRL production in the breast occurs in adipose rather than in glandular tissue [71]. Whereas PRL release from glandular explants was suppressed by progesterone, neither estrogen nor progesterone altered PRL expression in adipose explants [71]. This dissimilar regulation of PRL in adjacent tissues is not unusual, and was also observed in decidua and myometrium. Therefore, the interactions between stromal, glandular, and adipose tissue should be taken into consideration for PRL regulation studies

in the mammary gland. Even if the main source of PRL in breast adipose tissue seems to be the mature adipocyte, both the subcutaneous and visceral adipose depots also produce PRL [72]. As in other locations, the regulation of PRL release from primary human breast preadipocytes is stimulated by activators of the cAMP/PKA pathway. Indeed, recent studies have shown that, similar to its action in the pituitary, dopamine suppresses PRL gene expression and release in adipocytes through inhibition of cAMP, followed by the suppression of PKA activity [73]. Moreover, in primary human breast preadipocytes, isoproterenol, a β-adrenergic receptor agonist, and the pituitary adenylate cyclase activating peptide, increased PRL mRNA expression and release. This effect was suppressed by several protein kinase inhibitors, suggesting involvement of multiple signaling cascades [74].

Another interesting issue to be addressed is whether regulators of metabolic and endocrine activities of adipocytes such as insulin and cytokines affect PRL secretion in these cells. This question is particularly relevant in conditions such as obesity and inflammation. Contrary to results obtained in cultured rat mammary gland explants [65], PRL release from human adipose explants and mature adipocytes increased with time, indicating removal from inhibition [72]. Interestingly, insulin suppressed PRL expression and release from differentiated adipocytes but moderately stimulated PRL release from non-differentiated cells. Nevertheless, considering that preadipocytes represent only a small fraction of the total cell population within adipose tissue, the overall effect of insulin on PRL is likely inhibitory [72].

3. Prolactin in the physiology of the immune system

PRL is a highly versatile hormone/cytokine that displays a wide spectrum of effects in a variety of tissues. In fact, more than 300 actions by PRL have been described in vertebrates. In pancreatic beta cells, pancreas, liver, and T-lymphocytes, PRL can regulate proliferation [75, 76] while in prostate, pancreatic beta cells, lymphocytes, ovarian carcinoma cells, breast cancer cells, and others, PRL acts as an antiapoptotic factor. [77-81]. These effects are mediated by its receptors, which are members of the class I hematopoietin/cytokine receptor family [76]. In the immune system, PRL receptors expression have been detected in several cells such as splenocytes, thymocytes, bone marrow cells, PBMC, lymphocytes, and monocytes [76]. Both PRL and the PRL receptor are constitutively expressed by resting T-cells [29], which indicates that PRL may influence the immune system even during steady-state conditions.

PRL has a wide range of effects on the regulation of the immune system. Administration of PRL to hypophysectomised rats provokes weight gain of two lymphoid tissues, spleen and thymus [82]. In lymphocytes, PRL reverses anemia, leukopenia, and thrombocytopenia induced by hypophysectomy [83], and it increases antibody production [84]. PRL has also been reported to increase receptor levels for interleukin (IL)-2 and PRL [76]. Using PRL receptor knockdown, autocrine PRL actions could be elucidated. In T- lymphocytes in which the PRL receptor was silenced, proliferation induced by phytohemagglutinin (PHA) was

significantly reduced. Moreover, the expression of certain co-stimulatory molecules (CD137, CD154) and the secretion of cytokines (IL-2 and IL-4) induced by PHA activation were suppressed in these cells [85]. Although PRL has been observed to act in a cooperative fashion with IL-2 to influence proliferation in the immune system, there is evidence indicating that PRL can act as a T-cell growth factor, independently of IL-2 [86-88]. In addition to stimulating proliferation, PRL has been shown to inhibit apoptosis of lymphocytes [79, 89, 90]. In BALB/c mice expressing a transgene for the heavy chain of a pathogenic anti-DNA antibody, inducing moderate hyperprolactinemia (a 2-fold increase in the serum PRL concentration) increases the number of autoreactive B-cells with the follicular phenotype and leads to their activation, with subsequent anti-DNA antibody production as well as IgG deposition in the kidneys [91]. The induction of hyperprolactinemia promotes autoreactivity inasmuch as it breaks B-cell tolerance, acting on the mechanisms of B-cell tolerance induction at three levels: B cells receptor-mediated deletion, receptor editing, and anergy [91].

Despite evidence of an immunomodulatory role of PRL, it has been shown that the development of the immune system was unaffected in both PRL and PRL-receptor knockout mice [92]. The effects due to the lack of PRL action were probably compensated by redundancy of the cytokine network. Data support the immunomodulatory role of PRL in normal murine and human cells and in *in vivo* models after procedures such as hypophysectomy and ovariectomy. More studies are needed to determine the involvement of PRL in physiological and/or pathological conditions, and to explore its therapeutic potential in diseases of the immune system.

4. Prolactin in the pathology of the immune system.

4.1. Prolactin and autoimmunity

The interrelationship between PRL and the immune system has been elucidated over the last 2 decades, opening important new horizons in the field of immunoendocrinology [93]. The autoimmune diseases are more common in females, and sex hormones could have an important role in this gender bias. Estrogens and PRL modify the immune phenotype and functions; furthermore, they are able to modulate both the innate and adaptive immunological response. PRL exerts an immunostimulatory effect and might promote the development of autoimmune diseases by different mechanisms, such as impairing the negative selection of auto reactive B-lymphocytes occurring during B-cell maturation into fully functional B-cells [94]. Moreover, PRL induces an anti-apoptotic effect, enhances the proliferative response to antigens and mitogens, and increases the production of immunoglobulin, cytokines, and autoantibodies. In murine models of some autoimmune diseases there is a clear association between hyperprolactinemia and disease progression. Indeed, moderate hyperprolactinemia has been found in a cohort of patients with autoimmune diseases like SLE, rheumatoid arthritis (RA), Sjogren´s syndrome (SS), Hashimoto´s thyroiditis (HT), and multiple sclerosis (MS) [95-98]. These data are controversial, since some studies have not found a consistent correlation between PRL levels

and disease activity in humans [99]. These discrepancies could be explained by genetic, environmental, and hormonal factors related to susceptibility; these factors might influence the progression of autoimmune disorders, might alter PRL circadian rhythm thereby contributing to disease by modifying the immune response [100], and could even change PRL isoforms and anti-PRL antibodies that reduce the biological activity of PRL [101]. The PRL molecule undergoes posttranslational modifications generating several molecular species. In contrast to high molecular weight PRL species (>100 kDa), monomeric PRL (23 kDa) is associated with SLE clinical activity [102]. An association of PRL levels with anti-dsDNA antibodies and with anti-Ro and anti-La antibodies has been reported [94].

The physiology of the immune system involves a balance between the two arms of the cellular immune response. T-helper cells type 1 (Th1) and type 2 (Th2) elicit cell- and humoral-mediated responses, respectively. PRL is involved in regulating both Th1 and Th2 responses, particularly the former. Altered PRL levels associated with either Th1 or Th2 dominance often characterize autoimmune diseases [103]. Evidence observed in animal models and human disorders suggest that Th1 cytokines (IFN-γ, IL-2 and TNF-α) are involved in the genesis of organ-specific autoimmune diseases, such as RA, MS, insulin-dependent diabetes mellitus (IDDM), and thyroid autoimmunity. In contrast, Th2 responses tend to dominate in circumstances such as SLE, and in systemic and allergic conditions, such as HT (Figure 3) [103].

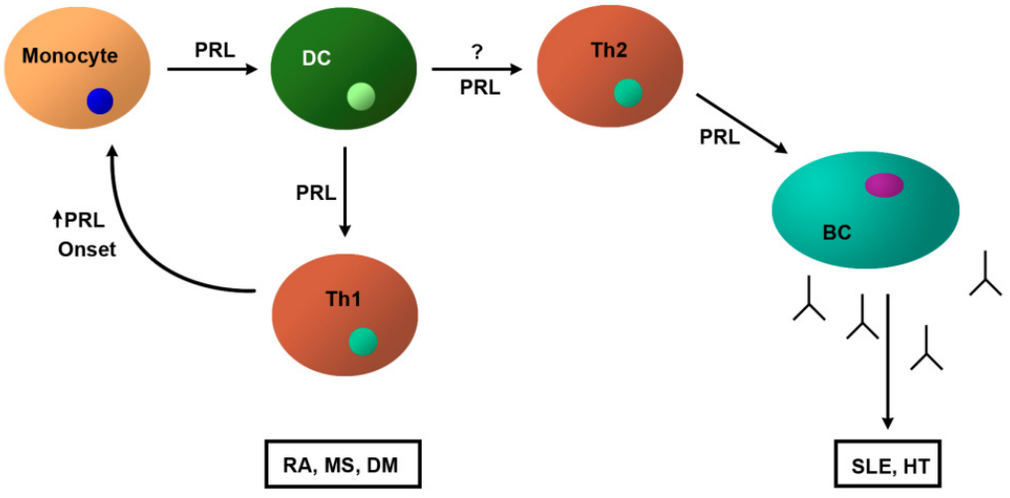

Figure 3. The role of PRL in autoimmune diseases. PRL induces monocytes maturation to dendritic cells (DC) through increasing major histocompatibility complex and co-stimulatory molecules. Furthermore, PRL induces T-cell activation and production of pro-inflammatory cytokines. Imbalances between Th1 and Th2 result in different autoimmune diseases. BC, B-cells; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MS, multiple sclerosis; DM, diabetes mellitus; HT, Hashimoto's thyroiditis.

4.1.1. Systemic lupus erythematosus

SLE is an autoimmune disease nine times more common in young women of reproductive age than in men. The expected rate of hyperprolactinemia is 0.4% in healthy adults [104, 105], whereas mild to moderate hyperprolactinemia occurs in 15-33% of SLE patients of both genders [102, 106]. Furthermore, elevated lymphocyte PRL gene expression has been identified in a cohort of female SLE subjects [42, 44]. In the majority of SLE - hyperprolactinemia patients the cause of the enhanced PRL levels is unknown, which suggests impaired regulation of PRL synthesis in SLE. In this regard, observations from our group showed an increased central dopaminergic tone in SLE and normoprolactinemic female patients, but with enhanced levels of PRL from lymphocytes; this finding suggests that lymphocyte-derived PRL might contribute to altering the functional activity of the hypothalamic dopaminergic system in order to maintain serum PRL within a physiological range in SLE [42]. In this study, after metoclopramide administration, mRNA expression and secretion of lymphocyte-derived PRL increased only in PBMC from control women and not in those from SLE patients. These observations indicate that dopamine could have a direct effect on PRL synthesis in normal lymphocytes that is absent in SLE lymphocytes.

Murine SLE encompasses several strains of inbred mice and hybrids (NZB, NZB x NZW F1, MRL lpr/lpr, BXSB) that variably manifest autoimmune disturbances such as accelerated hypergammaglobulinemia, immune complex glomerulonephritis and mortality, increased anti-DNA antibody levels and immune complex formation, as well as suppression of lymphoproliferation, symptoms that closely resemble those of human SLE [107]. In this model, induced hyperprolactinemia exacerbates disease activity, which leads to premature death regardless of the gender. Interestingly, in non-lupus prone BALB/c mice, treatment with high or physiological doses of PRL favours the development of an SLE-like phenotype, because this hormone breaks down the B-cell tolerance [91]. In addition, administration of bromocriptine, a dopamine receptor agonist that blocks prolactin secretion by the anterior pituitary ameliorates disease progression in murine SLE models [108, 109], indicating a potential role of PRL in the pathogenesis of SLE. Furthermore, clinical trials treating SLE with bromocriptine, have suggested a beneficial effect in patients with mild and moderate disease activity. Bromocriptine suppresses the levels of immunoglobulins, autoantibodies, and immune complexes in lupus glomerulonephritis, both in animal models and SLE patients [103, 107]. This drug is also associated with lower cytokine secretion and proliferation of T- cells. Furthermore, a clinical trial using bromocriptine in pregnant SLE patients suggests that it may help prevent maternal-fetal complications secondary to this disease [110, 111].

4.1.2. Rheumatoid arthritis

Clinical observations in humans and experimental data in animal models have also implicated PRL in other autoimmune diseases such as RA. This common autoimmune condition is an inflammatory disease that presents a diurnal rhythm of disease activity. An imbalance in favor of proinflamatory hormones like PRL, as opposed to levels of anti-inflammatory hormones, could be responsible for this diurnal rhythm of disease [112]. In

both genders, however, associations between RA and PRL have been inconsistent [98, 100, 113-118]. A recent study shows an increase of PRL in serum and synovial fluid from subjects affected with RA perhaps indicating that this cytokine acts as a proinflammatory factor to increase disease severity and joint damage in RA [119]. However, further studies are still needed in this area.

4.1.3. Multiple Sclerosis

Patients with MS, a Th1-dominated autoimmune disease, have slightly, but significantly higher PRL levels than normal subjects, and an association between this biomarker and the course of the disease course should be considered [120]. One-third of MS subjects exhibit hyperprolactinemia, which is claimed to be a sensitive indicator for hypothalamic lesions [97]. In experimental animal models of MS, treatment with bromocriptine decreases both PRL secretion and disease severity [121]. These data support the idea that PRL is involved in the pathogenesis of MS.

4.1.4. Hashimoto thyroiditis

In HT, an endocrine autoimmune disease, hyperprolactinemia and low serum cortisol levels have been found [122]. In addition, the high prevalence of anti-thyroid antibodies in the presence of hyperprolactinemia in HT suggests a role for PRL in this autoimmune disease, particularly since hyperprolactinemia correlates with HT only in subjects with hypothyroidism, suggesting a role of PRL in this autoimmune disease. Furthermore, another association between PRL and endocrine autoimmune diseases has been noted in subjects with a combined deficiency of pituitary hormones (GH; PRL; TSH) due to antibodies against Pit-1 [123].

4.1.5. Prolactin and diabetes

Diabetes mellitus (DM) is a complex disease characterized by hyperglycemia, dyslipidemia and disorders of protein metabolism. High levels of glucose in serum are a consequence of defects in insulin secretion, insulin action, or both. Indeed, DM is classified as type 1 (DM1) with an autoimmune etiology that causes a total absence of insulin secretion, or as type 2 (DM2) caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretion response [124, 125].

Studies in human and murine experimental models have demonstrated a stimulatory effect of PRL and other structurally related hormones (placental lactogen and growth hormone) on both insulin secretion and proliferation of β-cells [126, 127]. Furthermore, studies in PRL receptor-deficient mice highlight the importance of these hormones in pancreatic islet development. PRLR-deficient mice had a 26-42% lower islet-cell density ($P < 0.01$), and beta-cell mass and insulin mRNA levels in pancreatic cells were 20-30% lower compared with wild-type mice [75]. Furthermore, insulin secretion in response to glucose was blunted in PRLR-deficient males in vivo. The precise mechanism by which PRL induces insulin gene

transcription is still unclear since PRL binding induces low promoter activation of STAT5b, indicating that other pathways might be involved. The effects of many of the insulin signaling inhibitors occur downstream of PRL signaling pathways; however, the mechanism by which PRL impairs insulin signaling remains to be elucidated [128].

The effects of PRL have been studied in subjects with DM. For example, hyperprolactinemia has been identified in patients with DM1; however, the precise role of PRL in the progression of this disease is unclear. In contrast, PRL is one factor that can modify the clinical course of diabetic retinopathy (DR), one of the main complications of DM2 and a leading cause of blindness in working-age adults. The DR is associated with an excessive retinal vasopermeability and this could be inhibited by intraocular vasoinhibins, a family of peptides derived from proteolysis of PRL. Indeed, in a case-controlled study of diabetic patients, decreased serum PRL levels contributed to the development and progression of DR [129]. Furthermore, in a pharmacologically induced murine model of DM, hyperprolactinemia led to vasoinhibins accumulation within the retina, which reduced retinal vasopermeability induced by the vascular endothelial growth factor (VEGF) or streptozotocin, and this phenomenon is reversed by bromocriptine [130]. Therefore, circulating PRL influences the progression of DR after its intraocular conversion to vasoinhibins [130]. This important observation may provide a novel approach to protect DM subjects against the development of DR [131] , which was recently demonstrated in a murine model using gene therapy [132]. In summary, *in vitro* experiments and *in vivo* studies revealed that vasoinhibins are potent inhibitors of angiogenesis in the retina by several mechanisms, inhibiting proangiogenic effects of VEGF.

5. Effects of prolactin, circadian rhythms, and sleep on immune function

5.1. Background

Circadian rhythms are defined as ~24-h fluctuations in a variety of behavioral, physiological, and metabolic parameters driven by biological pacemakers and oscillators. The rhythmic changes are endogenous, meaning they are independent of environmental clues. At the same time, circadian rhythms are entrained by external inputs that are classified as photic (light–darkness alternation) and non-photic (food availability, pheromones, social interactions). Although they have been described across the entire phylogenetic scale (from prokaryotes to vertebrates), the various mechanisms that underlie circadian rhythms are better understood in mammals. In this group the principal pacemaker is the suprachiasmatic nucleus (SCN), which is a hypothalamic structure situated above the optic chiasm and close to the third ventricle. The SCN is synchronized by means of the conduction of photic stimuli from the melanopsin-enriched ganglionar retinal cells directly to the dorsal section of the SCN. Experiments done *in vitro* with isolated SCN preparations have demonstrated that this oscillator can show 24-h rhythmicity in electrical and metabolic activity for several weeks. The capacity for self-sustained oscillatory activity is based on the cyclic expression of a set of specialized genes and proteins that form the core of the molecular clock. The set of "clock" gene proteins interact in a network of positive and negative feedback loops, ultimately

giving the SCN the ability to measure ~24-h time periods. The circadian rhythmicity elicited by the SCN is eventually communicated to other tissues and organs through several output pathways that enable the circadian variations in endocrine patterns, physiological responses, metabolic activities, and behavior [133].

The circadian system is hierarchical; it is formed by the SCN as principal pacemaker, but also includes a set of peripheral oscillators which are dependent on SCN activity to accomplish a coordinated and harmonized overall day-to-day response. These peripheral oscillators are present, not only in thoracic and abdominal organs (heart, lungs, liver, pancreas, and others), but also in cerebral regions different from the SCN (amigdala, hippocampus, other hypothalamic nuclei, etc). Many of these peripheral oscillators are endocrine glands and biological targets for the secreted hormones. The coordination between SCN and peripheral oscillators is lost in some circumstances, such as restricted feeding schedules [134]. It has been proposed that a state of good fitness involves the appropriate coordination between the SCN (as a master pacemaker) and the other oscillators (slave clocks). Hence, a lack of communication among oscillators could promote adverse symptoms such as jet-lag and maladies associated with shift work [135].

Many biological functions are under the command of the circadian system. In the end, the evolutive explanation considers the 24-h rhythmic fluctuations as adaptations that allow biological tasks to be performed at a most appropriate time for the organisms, according to their diurnal or nocturnal profile. Some examples illustrating this concept are: 1) cortisol in humans is secreted a short time before awakening as a response to the fasting condition and in preparation for wakefulness; 2) growth hormone is released during the non-REM stage of sleep; 3) for predators, the search for food occurs when prey are most likely available and is coordinated with the time for rest and sleep.

Sleep is a complex process that is modulated by both circadian and homeostatic regulation. This dual control is evident in situations of sleep deprivation. In this circumstance, the animal will compensate for the lack of sleep regardless of the time of day, and the subject will fall sleep as a function of the amount of previous time awake. Not very much is known about the brain structures and neurotransmitters involved in the coordination and interplay between the circadian and homeostatic control of the sleep activity. The functions that have been attributed to sleep are diverse, but some of the principal ones are: energy restoration, memory processing, and neural plasticity [136].

In mammals and some birds, sleep is divided into 2 principal phases: sleep without rapid eye movement (NREM) and sleep with rapid eye movement (REM). These 2 stages are characterized mainly by polysomnographic criteria: for example, NREM sleep shows brain waves of high amplitude and low frequency and a clear muscular tone. In contrast, during REM sleep the brain waves become desynchronized, have low voltage, and the muscular tone is lost. Interestingly, the muscles that allow the ocular movements are the only ones that can become active. In humans, 75-80% of sleep time is dedicated to NREM and the rest to REM sleep, with the episodes of REM sleep becoming more frequent at the end of the night [137]. Because some characteristics of REM sleep and the wakeful state are similar, REM has been called paradoxical sleep.

Multiple factors have been invoked as having some role in the control of circadian rhythmicity, including the physiological adaptations in the sleeping activity. This section will be focused on the role of PRL in modulating both processes, acting as an endocrine signal and as an immunological mediator.

5.2. Circadian profile of prolactin in physiological and pathological conditions

PRL displays ultradian and circadian variations in humans [138]. On average, PRL is significantly higher at night, with a clear acrophase or peak close to midnight. However, between 6 and 8 peaks of PRL are also observed during the 24-h period, indicating a concurrent ultradian pattern [139]. The amplitude of the PRL diurnal rhythm is reduced during aging [140]. Hypothalamic PRL secretion is highly dependent on the suppression of the inhibitory input of dopamine. In rats, it has been shown that dopamine control of PRL release is modulated by circadian action from the SCN. In experimental animals, circulating PRL was reported to show complex rhythmicity under the regulation of several hypothalamic factors, including that is exerted by the vasoactive intestinal peptide (VIP) secreted by the SCN [141]. Levels of PRL produced by the lactotrophs of the anterior pituitary gland increase in the afternoon, but this PRL peak is abolished when VIP is not released from the SCN, indicating a circadian contribution to the temporal PRL profile. PRL secretion is also regulated by sexual activity, mainly in female rats. Mating promotes the release of oxytocin, which favors PRL synthesis and release. Hence, circadian modulation of blood PRL is coordinated with ultradian events and also with sporadic physiological responses. Most of the genes that show circadian rhythmicity contain a specific response element known as the E-box. However, PRL is an exception, since the circadian fluctuations involve daily chromatin remodeling carried out by the factors NONO (Non-POU domain-containing octamer-binding protein) and SFPQ (splicing factor proline-glutamine rich) [142]. PRL has also been implicated in circannual rhythmicity in rams. In this context, the role of PRL in reproductive physiology, which fluctuates according to the photoperiodic regulation during the year, is dependent mainly on the pineal gland, and it persists after the hypothalamo-pituitary connection is severed [143].

In patients with Parkinson´s disease, the rhythmic pattern of PRL secretion is not altered [139], but schizophrenic patients under treatment with atypical antipsychotic drugs such as perospirone show larger daily fluctuations of PRL [144]. However, loss of PRL rhythmicity during hyperprolactinemia episodes has been associated with obesity. One of the apparent causes of increased adipose tissue reservoirs is inhibition of the lipolytic enzyme lipoprotein lipase by PRL [145]. Hyperprolactinemia also affects daily changes of GABA and taurine concentrations in various hypothalamic areas, with potential consequences for eating and drinking behaviors [146]. Hypersecretion of PRL has been associated with the Carney complex (a syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas), which is a multiple neoplasia condition with various endocrine abnormalities [147]. Elevation of PRL at night has also been associated with the worsening of a pathological condition known as SUNCT (recurrent short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) [148]. High PRL

concentrations are involved in the pathogenesis of SLE in human beings and experimental animals by an unknown mechanism [149]. A hypothesis related to the onset of winter depression in women has postulated a defect of neural pathways afferent to the paraventricular nucleus that promote a reduction of serum PRL concentration. In this perspective, winter depression would also under the influence of estrogen responses [150]. Reduced PRL at night has also been associated with women suffering from fibromyalgia, a medical disorder characterized by chronic, widespread pain, and allodynia (pain due to a stimulus which does not normally provoke painful response) [151].

5.3. Prolactin and sleep

PRL concentrations are elevated during sleep, even if sleep is delayed [152], and short periods of sleep deprivation in humans are associated with lower nocturnal PRL levels in comparison to normal sleep [153]. PRL has been shown to be a hypnogenic factor, acting as a promoter of REM sleep: systemic or intracerebroventricular injection of PRL in rats and rabbits increased REM episodes, but in rats, only during the light period [154]. Supporting this observation, it was reported that antiserum against PRL and genetically PRL-deficient rodents showed reduced frequency of REM sleep [155]. It has been suggested that PRL may enhance a REM-promoting mechanism rather than initiate REM episodes. A putative mechanism by which PRL enhances REM sleep is the activation of the mitochondrial enzyme pyruvate dehydrogenase, which catalyzes the synthesis of acetyl-coenzyme A. This metabolic intermediate may favor the generation of acetylcholine in cholinergic terminals of brain areas that are involved in promoting REM sleep [156].

Besides its action in REM episodes, PRL has been postulated to be a modulator of NREM sleep in lactating women [157]. The predominant underlying hormonal alteration occurring in lactation is a marked increase in circulating PRL. Because the PRL concentration is elevated for several months in women that breastfeed, the increase in NREM sleep in this situation has been explained as a result of chronic hyperprolactinemia [158].

5.4. The circadian system and the sleep–wake cycle as modulators of the immune function. Role of prolactin

The immunological network is influenced by the physiological timing organization, but at the same time, the circadian rhythmicity is regulated by factors elicited by the immune system. This reciprocal modulation has been documented in physiological and pathological conditions in humans, and some related molecular and cellular mechanisms have been explored in experimental animals. It has been reported that the number and properties of cellular components of the immune system show circadian variations, for example: 1) IgE-dependent activation by mast cells [159], 2) cell-adhesion molecule expression by human leukocytes [160], 3) activation of natural killer cells [161], 4) deterioration of clinical symptoms associated with rheumatoid arthritis in the morning following the diurnal rhythm of the pro-inflammatory cytokine IL-6 [162].

The timing regulation of the immunological function is also influenced by the numerous changes that occur during the sleep period. Sleep promotes a striking increase in the number of myeloid dendritic cell precursors producing IL-12, which implies an induction of the Th1 responses. In addition, sleep reduces plasmacytoid dendritic cells and T-cell counts without affecting the production of IFNα. Sleep also substantially decreases the number of certain subpopulations of monocytes (CD14 and CD16+), probably reflecting margination of these cells upon a sleep-related drop in catecholamine release [163]. The number of undifferentiated naïve T cells and the production of pro-inflammatory cytokines exhibit peaks during the first hours of sleep, whereas the number of circulating immune cells with immediate effector functions and the anti-inflammatory cytokine activity peak during wakefulness. Sleep also facilitates the extravasation of T-cells and their redistribution to lymph nodes. In general, sleep enhances cytokines (such as IL-12) that promote the interaction between antigen-presenting cells and T-helper cells [164].

It has been postulated that NREM sleep facilitates the transfer of antigenic information from antigen-presenting cells to antigen-specific Th cells; as a consequence, sleep after vaccination has been observed to boost immunological memory [165]. The daily profile of circulating PRL, with elevated levels during the rest periods in mammals, raises the possibility that PRL could be one of the factors involved in the enhanced immunological response associated with sleep. This role could be related in particular to the stage of NREM sleep and its accompanying pro-inflammatory endocrine milieu with the high levels of growth hormone and PRL and low concentrations of glucocorticoids and catecholamine that occur during sleep [165]. This same idea provides a rationale for the chronobiological treatment of RA. In this protocol, a low-dose, chronotherapeutic application of prednisone at night (~03:00 h) has been suggested to improve the benefits and reduce the adverse side-effects of glucocorticoid treatment in patients with RA. The low dose of prednisone during the night is as effective as a higher dose applied during the day. Again, this pharmacological scheme could be favorable because of the conjunction between PRL and other immunological supportive peptides and the proven clinical drugs [166].

6. Conclusion

The multiple actions of PRL and its diverse sites of synthesis evidence the versatility of this hormone/cytokine in the homeostasis of the organism. Besides the well-known actions of PRL on reproduction, it exerts multiple actions unrelated to the reproductive area. In the immune system PRL functions as a survival factor inasmuch as it promotes proliferation and inhibits apoptosis. This important role could help to maintain the appropriate number of immune cells in physiological conditions, and to maintain immune tolerance. Abnormal synthesis and secretion of PRL could lead to the breakdown of balance in the immune system, and consequently, could promote autorreactivity and bursting or aggravation of the clinical condition in autoimmune diseases. A deregulation in the mechanisms that control PRL synthesis could lead to enhanced PRL secretion. Nowadays, available information is limited on the biological significance of posttranslational modifications of the PRL in vivo, such as glycosylation or cleavage, which may exert different biological functions related to

the immune function. In agreement with current knowledge, PRL at normal levels could be a permissive molecule, while at abnormal levels it could affect the organism homeostasis. Additional studies of PRL and its regulation, especially in the extrapituitary tissues, are needed in order to understand better the role of PRL in the physiology and pathophysiology of autoimmune diseases.

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