Recent findings on hyperprolactinemia and its pathological implications: a literature review

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ABSTRACT

The prolactin hormone (PRL) is often secreted by lactotrophic cells of the anterior pituitary and has been shown to play a role in various biological processes, including breast feeding and reproduction. The predominant form of this hormone is the 23 kDa form and acts through its receptor (PRLR) on the cell membrane. This receptor is a member of the superfamily of hematopoietic/cytokine receptors. PRL also has a 16 kDa subunit with anti-angiogenic, proapoptotic, and anti-inflammatory effects which is produced by the proteolytic breakdown of this hormone under oxidative stress. Although the common side effects of hyperprolactinemia are exerted on the reproductive system, new studies have shown that hyperprolactinemia has a wide variety of effects, including playing a role in the development of autoimmune diseases and increasing the risk of cardiovascular disease, peripartum cardiomyopathy, and diabetes among others. The range of PRL functions is increasing with the discovery of multiple sites of PRL secretion as well as PRLR expression in various tissues. This review summarizes current knowledge of the biology of PRL and its receptor, as well as the role of PRL in human pathophysiology.

INTRODUCTION

Prolactin (PRL) is a polypeptide hormone that is mostly synthesized and secreted by lactotroph cells of the anterior pituitary gland and is mainly inhibited by dopamine released by the hypothalamus.[1 2] Although pituitary lactotrophs are the most important producers of PRL, extrapituitary tissues, such as the brain, breast, prostate, uterine decidualized endometrium, adipocytes, lymphocytes, skin, etc, also produce this hormone.[3 4]

Two promoter regions, which are independent of each other, are responsible for the *PRL* gene transcription. One of them is proximal or downstream which is responsible for the direction of pituitary-specific expression and the other is distal or upstream and directs the extrapituitary expression.[5]

In humans, the principal PRL-related symptoms, such as hypogonadism and infertility, result from the hypersecretion of this hormone, and its low level is not a common complication and has no specific side effects.[6] This may be due to the production of PRL outside the pituitary gland and probably pituitary hyperprolactinemia.[7] On the other hand, these side effects may be prevented by lowering the PRL levels.[8] Although many aspects of hyperprolactinemia have been revealed over the past decades, recently new functions have been discovered for PRL and its receptor, such as the role of hyperprolactinemia in the incidence and recurrence of autoimmune diseases,[9] cardiovascular diseases (CVDs),[10] impaired metabolism of glucose and lipids,[11] hypertension,[12] etc.

Therefore, the present review aimed to focus on the latest findings on hyperprolactinemia, especially complications other than the ones affecting the reproductive system.

PRL GENETICS

In humans, the *PRL* gene has five coding exons; four introns and one non-coding exon in the chromosome 6p22.2-p21.3. The prohormone contains 227 amino acids, is transcribed from a 914-nucleotide area, and its encoding messenger RNA (mRNA) contains a 681-nucleotide open reading frame.[13] In the rough endoplasmic reticulum (RER), 28 amino acids of pre-PRL, known as the signal peptide, are proteolytically cleaved and the mature 199-amino acid PRL polypeptide with a molecular weight of 23 kDa is released.[14]

For the transcription of the *hPRL* gene, there are two promoter regions that are not dependent on each other. One of them is proximal or downstream and is responsible for the direction of pituitary-specific expression and the other is distal or upstream and directs the extrapituitary expression.[15]

Pituitary lactotrophs are the most important producers of PRL, but extrapituitary tissues, such as the brain, breast, prostate, uterine decidualized endometrium, adipocytes, lymphocytes, skin, etc, produce it as well.[13] In these tissues, there is a promoter named the superdistal PRL promoter located ~5.8 kb upstream of the pituitary transcription outset point that transcribes PRL mRNA exon 1a, which is an additional exon.[16] POU homeodomain transcription factor is another protein that plays a key role in regulating the expression of growth hormone, PRL, and thyroid-stimulating hormone β in

somatotrophs, lactotrophs, and thyrotrophs, respectively, specifically in the anterior pituitary.[17 18]

Pit-1 is the main transcription factor for hPRL and following a signaling pathway, it can recruit many regulatory and nuclear receptor factors such as Ets, Oct1, ER, c-Jun, GR, TR, Ptx-1, GATA2, basic region-leucine zipper (B-Zip) transcription factors, and P-Lim to Pit-1 regulated promoters, and by modifying histone acetylation it can induce or repress the transcription.[19 20] Pit-1 is composed of two motifs including the DNA-binding domain (DBD) in the carboxy-terminal and the transcriptional activator domain (TAD) in the amino-terminal. TAD has a region that is basal and a Ras-responsive region.[21] DBD has two motifs that are essential for the facilitation of DNA binding.[22] In rats, the determinative factor for being a dimer or a monomer is the balance between the corepressor and coactivator agents.[23 24] Moreover, the phosphorylation of Pit-1 by protein kinase A, protein kinase C (PKC), and cyclin-dependent kinases inhibits its binding to DNA and leads to the reduction of its transcriptional activity.[25]

One of the most important physiological factors in the activation of *PRL* gene expression is estrogen. It acts through estrogen receptors (ERs), three of which have been identified so far. These receptors include ERα, ERβ, and G protein-coupled estrogen receptor 1 (also known as G protein-coupled receptor 30); the first two are nuclear receptors and the third is a transmembrane receptor and binds to estradiol (E2).[26–28] Approximately within the distal rat PRL enhancer, there is an estrogen response element (ERE) near the monomeric Pit-1d site at about 1.5 kb upstream of the transcription initiation point. In humans, the affinity of hPRL ERE for ERα, when stimulated with E2, is relatively low, but when E2 is accompanied by tumor necrosis factor-α, the affinity is elevated and transcriptional activity becomes higher.[29 30] Moreover, other transcription factors also play a role in regulating the PRL promoter, such as SMAD4, Pitx factors, CCAAT/enhancer-binding protein (C/EBPα), Ikaros, and thyroid hormone receptor.[31 32]

PRL SIGNALING PATHWAYS

PRL gene expression is dependent on several major agents including neurotransmitters (serotonin and acetylcholine), hormones, and growth factors and also several pathways such as G-protein-coupled receptor (GPCR) and receptor tyrosine kinase pathways. These agents and pathways ultimately induce or suppress the transcription by impacting the PRL promoter.[33 34]

The PKC-dependent pathway is another signaling pathway regulated by epidermal growth factor and thyrotropin-releasing hormone (TRH), and insulin can phosphorylate the cAMP response element-binding protein (CREB) and then recruit Pit-1 and subsequently could regulate the *PRL* gene. Insulin by inducing phosphoinositide 3 kinase (PI3K)-Akt phosphorylates CREB and through an interaction with an E26 family member, it probably regulates PRL promoter activity. On the other hand, there is an extracellular signaling pathway to regulate the *PRL* gene through kinase-1/2 (Erk-1/2), which is stimulated by several factors including pituitary adenylyl cyclase-activating polypeptide (PACAP), fibroblast growth factor 2 (FGF2), vasoactive intestinal peptide (VIP), and insulin-like growth factor 1 (IGF-1) using monomeric G-proteins to initiate a signal. For the stimulation of the *PRL* gene expression, VIP and IGF-1 use the Raf/Erk/Ets route, PACAP signals through the Rap1/Braf/Erk cascade, and FGF2 acts through Rac-1/phospholipase C/PKC/Erk.[35 36]

Moreover, in vitro studies have shown that there are some crosstalk signaling pathways involved in controlling the *PRL* gene expression, such as estradiol and bone morphogenetic protein 4 dependent on Smad-1 and independent of EREs, as well as transforming growth factor-β that suppresses this action and inhibits PRL transcription.[37] Also, epidermal growth factor receptor and ERα are both involved in activating PRL expression. In addition, ERα elevates the hPRL expression through nuclear factor kappa B signaling.[38] Nevertheless, further investigations are needed to confirm these signaling behaviors in the *hPRL* gene expression.[39]

STRUCTURE OF PRL

A mature hPRL protein has 199 amino acids.[40] Among different species, primate PRL has the highest homology with hPRL, and it is shown that rat PRL can induce the human prolactin receptor (PRLR) unlike the mouse PRL.[41 42] The 199-aa PRL is a single-chain polypeptide with three intrachain disulfide bonds, has a secondary structure with four antiparallel α-helices, and is similar to the growth hormone.[43]

To become active, PRL must undergo post-translational changes such as proteolytic degradation, phosphorylation, and glycosylation and these modifications are the determining factors for PRL biological activity.[32] It is shown that in the human pituitary, there are non-phosphorylated, monophosphorylated, and diphosphorylated forms of PRL in a relatively wide range of 62%, 19%, and 19%, respectively, and Ser-163 and 194 are responsible for this phosphorylations.[44 45] Based on previous studies, the role of phospho-PRL is probably reducing the power of the unphosphorylated form in proliferative action.[46 47] Hence, the phospho-PRL to non-phospho-PRL ratio changes in some physiological situations such as pregnancy or estrous cycle, representing the significant role of this ratio in various situations.[48 49] N-glycosylation of PRL on N31 could induce low affinity to receptor binding and decrease its biological role.[50] Hyperprolactinemia in unexplained forms may be due to the increase of glycosylated PRL.[51]

The proteolysis of 23 kDa PRL isoform can generate some variants with different actions. For example, the 16 kDa form in the adjacency of the capillary blood of the interstitial medium is probably responsible for some antiangiogenic activity via binding to endothelial cells; therefore, the 16 kDa PRL is a prominent vasoinhibin factor.[51] Additionally, it has been shown that the 22 kDa and 16 kDa isoforms produced by kallikrein and cathepsin D, respectively, may be essential in non-reproductive functions. Hence, there is a category of PRL isoforms in the bloodstream as shown in table 1.[51] There are also two more isoforms of PRL with unknown biological roles. The first is big PRL (molecular weight 48–56 kDa) and the second is macroprolactin, also known as big-big PRL with a molecular weight over 100 kDa.[52 53]

Table 1 The prolactin (PRL) isoforms, and their structures and roles

Isoform	Structure	Role
23 kDa (small prolactin)	Monomeric, non-glycosylated, high receptor affinity	The main form: biological and immunological
25 kDa glycosylated forms (G1 and G2)	Carbohydrate unit chains are different	Low immunoreactivity (G2 is 75% more immunoreactive than G1)
50 kDa (big PRL)	Combination of dimeric and trimeric glycosylated isoforms	Unknown
100 kDa (big-big PRL)	Probably a G-PRL	Covalently binds to immunoglobulins

PRLR STRUCTURE AND SIGNAL TRANSDUCTION

The PRLR is a transmembrane protein and a member of the cytokine-1 receptor superfamily and its gene is located on chromosome 5 (5p13.2) and has 15 exons, 8–9 coding and 2 non-coding.[54] Its extracellular domain has four Cys residues forming two disulfide bridges that are necessary for binding the ligand to the receptor as well as for tertiary folding. In the extracellular domain, there is a second signature domain with a motif that has a repetitive Trp-Ser tandem and an interrupter amino acid between them (WSXWSX…). Following the binding of the ligand to the extracellular domain, the intracellular domain, which has a box 1 elaborate motif with an 8-amino acid proline-rich region, is directly linked to the tyrosine kinase, and the signaling pathway starts.[55 56] It has been reported that in PRLR, there is a distal tyrosine that is very important and has a major role in the signaling of tyrosine kinase since it has been shown that in rats with a large deletion of amino acids between the distal tyrosine and proline rich-region(box 1 elaborate motif), the signaling is not interrupted.[57]

In summary, signal transduction needs the Janus kinase and signal transducer and activator of transcription (JAK-STAT) kinase pathway; after the binding of PRL to PRLR, JAK kinase phosphorylates STAT-5. Then STAT-5 is dimerized and interacts with Src homology 2 (SH2) domains, creating dimeric STAT complexes which are imported into the nucleus where the elements in the promoters of the PRL-regulated genes such as interferon (IFN) γ-activated site exist and initiate the transcription of target genes.[57] In the absence of PRL, JAK is dephosphorylated by phosphatase to keep the transcription of the target genes down and the signaling pathway blocked.[39]

PRL SECRETION

PRL can be secreted in specific periods such as pregnancy or by the placenta and has certain roles including changing the angiogenesis process, lymphocyte regulation, and hematopoietic functions.[58] PRL levels are enhanced in maternal blood due to pituitary secretion and it has previously been shown that the pituitary becomes enlarged due to this secretion.[59] Furthermore, the concentration of PRL in amniotic fluid is 10-fold to 100-fold higher than the fetal or maternal blood levels and this elevation may be due to the role of decidua PRL in controlling the epithelial cell differentiation of uterine, angiogenesis, and the regulation of the immune response and trophoblast growth.[60] Controlling the expression of decidua PRL is dependent on extrapituitary promoters and the factors affecting that include transcription factors, signaling peptides, and cytokines.[61]

The major regulator of PRL is the hypothalamus and the main pituitary inhibiting factor is dopamine.[62 63] It is also shown that the GnRH-associated protein (GAP), a polypeptide with 56 amino acids located on the carboxy-terminal region of the GnRH precursor, has an inhibitory effect on PRL secretion in rats, but it is unclear whether it has an inhibitory effect in humans or not.[51] γ-Aminobutyrosineic acid (GABA) is another factor inhibiting PRL secretion both in vitro and in vivo in rats. In humans, it is also described that the prescription of GABA or activating its secretion by Na valproate leads to the reduction of PRL secretion for several days.[64 65]

Furthermore, TRH is another factor that via binding to TRH receptor type I in lactotrophs and thyrotrophs leads to an increased release of PRL in the pituitary.[66] Hence, it is shown that in human hypothyroidism, TRH and TRH receptors are increased, which leads to the increase of PRL. In contrast, in the hyperthyroidism state, the PRL levels are decelerated and after the treatment of hyperthyroidism, the PRL levels return to normal.[67] There are also other factors that impact PRL secretion, which are not necessarily real PRL-releasing factors. For example, a dopamine antagonist has an indirect role in increasing the PRL secretion, while suckling is a real physiological state that directly leads to the increase of PRL.[27 68] Other examples of these factors are VIP, galanin, PRL-releasing peptide, oxytocin, salsolinol, etc.[68] Estrogen is another factor that slightly inhibits the dopamine effect. This is probably due to the fact that the *PRL* gene promoter has an ERE and also it is shown that estrogen can reduce the number of dopamine receptors in rats.[69] As a result, it is now clear that most PRL-secretion stimulating factors are dopaminergic inhibitors. Previous studies have shown that PRL has a negative feedback on its own secretion, which is known as auto-feedback or short-loop feedback.[70 71] It is suggested that this feedback in mice and rats is mediated by tuberoinfundibular dopaminergic neurons in the hypothalamus.[71–73] In some studies focused on understanding the autocrine or paracrine action of PRL, it has been demonstrated that when PRLR in lactotroph cells was deleted in mice, the level of PRL remained normal and there was no adenoma in pituitary lactotrophs, but compared with the normal group, the dopamine inhibitory action was increased; this supports the hypothesis that PRL has an autocrine/paracrine feedback on lactotroph cells.[74 75]

HYPERSECRETION OF PRL

PRL secretion is under the tonic inhibition of the hypothalamus and the deficiency of this hormone is rare. It can, for example, be observed in Sheehan's syndrome. Usually, disorders of PRL secretion lead to hyperprolactinemia.[76]

Fasting PRL levels >25 ng/mL in women and >20 ng/mL in men are defined as hyperprolactinemia.[77] Fetal PRL levels increase until birth but decrease to pre-pubertal levels at 2 months after birth.[76] During breast feeding, the level of this hormone increases physiologically, but in various

diseases such as prolactinoma, hypothyroidism, and adrenal insufficiency, it also increases pathologically.[78] Hyperprolactinemia can be of physiological, pathological, pharmacological, or idiopathic origin. This disorder can have severe clinical symptoms or be completely asymptomatic.[79] The prevalence of hyperprolactinemia in the adult population (male and female) is 0.4%, but women are more prone to hyperprolactinemia; therefore, in adult women with infertility disorders, its prevalence is reported to be 17%–9%.[79 80]

CAUSES OF HYPERPROLACTINEMIA

Hyperprolactinemia can be due to physiological or pathological reasons. Some of the major causes of this disorder include:

1. Physiological hypersecretion which is observed in conditions such as pregnancy, lactation, chest wall stimulation, sleep, and stress.[18 50 71 81]
2. Idiopathic hyperprolactinemia.[82]
3. Hypothalamic-pituitary stalk damage caused by tumors (craniopharyngioma, meningioma, dysgerminoma, dermoid cyst, and pineal gland tumors), irradiation, trauma, pituitary stalk section, and suprasellar surgery.[79]
4. Pituitary hypersecretion caused by prolactinoma (microadenoma and macroadenoma), metastatic tumors, acromegaly, infections such as tuberculosis, sarcoidosis, Cushing disease, and Addison's disease.[79]
5. Systemic disorders including chronic renal failure, hypothyroidism, ectopic production (hypernephroma, bronchogenic sarcoma), cirrhosis, pseudocyesis, and epileptic seizures.[79]
6. Drug-induced hypersecretion caused by dopamine receptor blocking agents, dopamine depleting agents, histamine receptor antagonist, estrogens, anti-androgens, serotonin reuptake inhibitors, and calcium channel blockers.[79 83]

COMMON SIDE EFFECTS OF HYPERPROLACTINEMIA

Common side effects of hyperprolactinemia in children

In children, before puberty, hyperprolactinemia can lead to primary amenorrhea or delayed puberty that occurs by microprolactinomas and macroprolactinomas in one-fifth and three-fourth of children, respectively.[84 85] Galactorrhea was reported in 27%–67% of children with microprolactinomas and 51%–91% of children with macroprolactinomas.[86–88] Gynecomastia is one of the other manifestations in boys, but distinguishing it from normal prepubertal gynecomastia is difficult. Notably, headache in 40%–90% and visual disturbances in 15%–50% of macroprolactinoma cases are the major symptoms reported.[86]

Common side effects of hyperprolactinemia in women

Hyperprolactinaemia is a common cause of gonadal dysfunction, especially in women. Hyperprolactinemia suppresses the release of GnRH and then decreases luteinizing hormone pulse amplitude and frequency.[89] Moreover, hyperprolactinemia could result in the decrease of estrogen positive feedback on gonadotropin secretion.[90] 3-Beta-hydroxysteroid dehydrogenase type II and IGF-II production are influenced by PRL in ovarian granulosa cells.[91] Its incidence in women with secondary amenorrhea is between 13% and 30%. Most people with hypogonadism due to pituitary tumors do not suffer from gonadotropin deficiency but from hyperprolactinemia. About 30% of people with hyperprolactinemia have galactorrhea.[76]

Hyperprolactinemia in women causes a range of symptoms from secondary amenorrhea or any menstrual irregularities to a normal menstrual cycle.[76]

In women with amenorrhea, osteoporosis, which is caused by a lack of estrogen, is a common condition that requires medical examination. Bone mineral density decreases by 25% in these individuals and may not be restored after normal PRL levels. Women with hyperprolactinemia sometimes show signs of chronic hyperandrogenism, such as hirsutism and acne. This is probably due to increased adrenal dehydroepiandrosterone sulfate secretion as well as decreased sex hormone-binding globulins resulting in increased free testosterone levels.[76]

Common side effects of hyperprolactinemia in men

The prevalence of hyperprolactinemia in men is lower than in women; however, it can cause hypogonadism in men. Galactorrhea is seen in 30% of cases. Sperm count and morphology are often normal.[76] Other complications of hyperprolactinemia in men include erectile dysfunction, decreased libido, infertility, gynecomastia, and decreased bone mass, but rarely galactorrhea. Over time, the patient may exhibit diminished energy, reduced muscle mass, and increased risk of osteopenia.[76]

In addition to the effects of hyperprolactinemia on children, women, and men, as summarized above, which are more about its effects on the reproductive system, recent studies have shown that hyperprolactinemia has several adverse effects on the human immune, endothelial, and cardiovascular systems, as well as diabetes, which are explained in the figure 1.

Hyperprolactinemia and autoimmunity

The prevalence of various autoimmune diseases varies between men and women, and there is a possibility that sex hormones may play a role in this difference.[76 92] The prevalence of autoimmune diseases is higher among women of childbearing age and the recurrence of these diseases is seen during pregnancy and after childbirth. In fact, women have enhanced immune reactivity, larger antigen-presenting capability, mitogenic responses, increased antibody production, higher immunoglobulin levels, and the ability to reject allografts more rapidly.[9 93] The immune system and the neuroendocrine system have many connections. PRL has a stimulating effect on the immune system, such as inhibiting

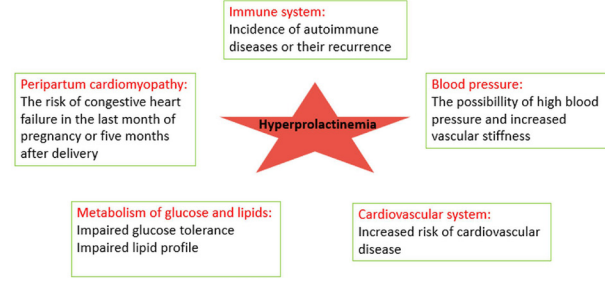

Figure 1 The common side effects of hyperprolactinemia on various systems.

the negative selection of autoreactive B lymphocytes, which is effective in the development of autoimmunity. As a result, increased PRL levels are effective in the development of autoimmune diseases and their pathogenesis.[94 95]

According to studies over the past two decades, PRL can also be produced in extrapituitary tissues, including the ovaries, prostate, mammary glands, adipose tissue, brain, and immune cells. PRL has different biological activities when produced in extrapituitary tissues. On the other hand, PRL secretion is affected by some cytokines, including PRL-stimulating cytokines, such as interleukin (IL)-1, IL-2, and IL-6, but endothelin-3 and IFN-γ play an inhibitory role in its secretion.[96 97]

The PRLR is a member of the type 1 cytokine receptor superfamily, which is expressed in various cells of the immune system, such as monocytes, macrophages, lymphocytes, natural killer cells, granulocytes, and thymus epithelial cells. As a result, the binding of PRL to its receptor on the surface of these cells can have various effects including affecting their proliferation, differentiation, secretion, and survival.[78 98 99] PRL controls the maturation of $CD4^-$ $CD8^-$ thymocytes into $CD4^+$ $CD8^+$ T cells through IL-2 receptor expression. A significant correlation was reported between PRL levels and B and $CD4^+$ T lymphocyte counts. Hyperprolactinemia can cause B cell clonal degradation, destroy receptor editing, reduce B cell activation threshold, and cause an autoimmune reaction.[95] Moreover, PRL is able to alter the production of T-helper (Th1 and Th2 cytokines, increase the production of IL-6 and INF-γ, and control IL-2 levels. It also increases the production of immunoglobulins, stimulates antigen cells, which express the complexity of the main class II tissue adaptation, and supports CD86, CD80, and CD40 molecules.[78]

Due to the importance of PRL in regulating the immune system and based on previous studies, there is a significant relationship between hyperprolactinemia and various autoimmune diseases such as systemic lupus erythematosus (SLE)[100] and Behçet's disease.[101]

Endocrine/Paracrine PRL stimulates immune cells by binding to its receptor. Elevated PRL levels, which are often seen in autoimmune diseases, may be related to the bidirectional communication between PRL and the immune system. Elevated PRL levels have been reported in the active phase of some autoimmune diseases, including SLE and rheumatoid arthritis, celiac disease, type 1 diabetes, Addison's disease, and autoimmune thyroid disease.[78 82] Previous reports have demonstrated that bromocriptine, a dopamine agonist, has an effective role in reducing the production of autoantibodies, affecting the function of lymphocytes, and modulating the expression of surface molecules by reducing PRL levels.[102] In other words, bromocriptine plays an important role in treating various autoimmune diseases by reducing PRL levels.[102 103]

Hyperprolactinemia, endothelial dysfunction, and the risk of cardiovascular events

PRL is a pituitary hormone with a variety of metabolic functions that are not unique to the mammary glands. With receptors expressed in almost all organs, PRL is involved in many physiological and pathophysiological processes, including the reproductive, metabolic, regulatory, and immune regulatory systems.[104] It should be noted that PRLR is found in atherosclerotic plaques. However, the correlation between serum PRL levels and the extent and severity of coronary atherosclerosis has not yet been fully elucidated.[105]

In patients with prolactinoma, elevated serum PRL is pathologically associated with cardiovascular problems and typically linked with insulin resistance, prone to inflammation, and endothelial dysfunction.[104 106 107] High serum PRL levels in women are significantly associated with systemic hypertension, aortic stiffness, and hypertension.[12] A population-based study revealed positive associations between serum PRL concentrations and inflammatory biomarkers and anthropometric measurements.[104] Moreover, other studies have shown that hyperprolactinemic states are associated with low-grade inflammation, impaired endothelial function, increased platelet aggregation, increased thrombosis risk, and dyslipidemia. Also, fibrinogen levels were a little increased in patients compared with the controls. Additionally, patients with stroke, myocardial infarction, and acute coronary syndromes had significantly higher serum PRL concentrations in comparison with healthy controls.[104 108]

The association of hyperprolactinemia with subsequent mortality may be due to the wide range of biological effects of PRL, from the production of atherogenic phenotypes, proliferation of vascular smooth muscle cells, and increased vasoconstriction to increased oxidative stress. Oxidative stress causes PRL to fragment into a 16 kDa angiostatic and proapoptotic fragment.[109] This 16 kDa fragment adversely affects the endothelium as well as the coronary arteries and cardiovascular function and has also been hypothesized to be a potential factor in the pathogenesis of peripartum cardiomyopathy. In general, PRL is a hormone that affects various stages of vascular formation or heart regeneration (stimulation or inhibition), and can therefore cause coronary heart disease, heart failure, and subsequent mortality.[104 110]

In vitro studies have demonstrated that PRL is able to modulate the inflammatory response to stimulate the adhesion of mononuclear cells to endothelium, and to enhance vascular smooth muscle cell proliferation.[111] Research has also shown that PRL is an independent factor in the variance of flow-mediated dilation and pulse wave velocity (PWV) surface levels.[112]

Our main knowledge stems from the atherogenic effects of PRL in the context of senile/postpartum cardiomyopathy, a disease with symptoms such as contraction, autoimmunity, apoptosis, and endothelial dysfunction. Unbalanced prepartum/postpartum oxidative stress associated with proteolytic degradation of PRL has been linked to a potent 16 kDa anti-angiogenic and proapoptotic amino protein subtype that initiates atherosclerotic complications. These data, together with previous experimental results, show that PRL-mediated mechanisms alter vascular integrity.[113]

Coronary artery disease, which is the consequence of atherosclerosis, is still the leading cause of death worldwide, and with an is estimated mortality rate of seven million per year, it is responsible for 30% of all global deaths.[105] Atherosclerotic plaques begin to form when monocytes attach to the endothelial cells of the arterial wall. These cells express cell adhesion molecules and inflammatory cytokines after

being activated by oxidized low-density lipoprotein cholesterol (LDL-c).[114]

An in vitro research demonstrated that PRL has the ability to stimulate the adhesion of monocytes to the endothelium. On the other hand, PRL induces the proliferation of smooth muscle cells, which indicates that it stimulates the thickening of the intimate media, an important process in the formation of atherosclerotic plaques.[115] Disruption of atherosclerotic plaques leads to thrombus formation and arterial occlusion. Blood platelets are also an important component in thrombus formation. In general, research suggests that PRL may contribute to CVD by directly modulating local cellular processes in atherosclerotic plaques or thrombi or by affecting common cardiovascular metabolic factors.[116]

Hyperprolactinemia and peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a congestive heart failure occurring in the last month of pregnancy or 5 months after delivery, in the absence of pre-existing heart disease.[117] The disease can range from a mild form with unexplained symptoms, such as exercise intolerance, general discomfort, and peripheral edema, to a severe form with cardiogenic shock, including irritation, orthopnea, and pneumonia. The increase of knowledge and advancement of diagnostic and therapeutic insights have been effective in treating patients with PPCM in recent years.[118] The cause of this disease remains unclear, although plausible causes such as malnutrition, viral infections, stress-activated cytokines, pathological response to hemodynamic stress, inflammation, and autoimmune reactions have been reported.[116] Evidence supports the probable role of PRL in the pathophysiology of this disease. Increased oxidative stress leads to the production of the 16 kDa form of PRL, which disrupts the heart's vessels and metabolism and peaks in systolic heart failure.[119]

In summary, antimyosin sarcomere antibodies and troponin I have been found in women with peripartum cardiomyopathy, confirming the presence of an underlying autoimmune disorder. On the other hand, these antibodies were associated with the severity of left ventricular dysfunction and a lower rate of complete heart recovery at follow-up.[120]

Studies have shown a combination of increased oxidative stress in late pregnancy or early postpartum and high levels of PRL as a probable pathophysiological cause of PPCM.[121] Under various conditions that cause oxidative stress, 23 kDa PRL is cleaved by proteases such as cathepsin D or matrix metalloproteases to produce a 16 kDa fragment of PRL.[109 122] This 16 kDa PRL fragment has strong angiostatic, proapoptotic, and inflammatory effects, destroying blood vessels, and thereby reducing oxygen and nutrition to the heart, which can lead to heart failure.[123] The 16 kDa PRL fragment has destructive but often reversible effects on heart function. In addition to standard heart failure therapy and supportive care, bromocriptine has a potential role in improving PPMC.[123]

Hyperprolactinemia and blood pressure

Evidence has shown that PRL has positive vasoconstrictive effects.[124] In recent years, separate reports have shown the role of PRL in the human cardiovascular system to some extent. As recently shown, high levels of PRL have a pathogenetic role in pre-eclampsia. PRL is involved in renal retention of fluids and electrolytes and may therefore increase arterial pressure.[125] A rise in PRL levels can increase blood pressure, according to a study on male mice.[126]

Based on studies performed in postmenopausal women, there was a positive and significant relationship between serum PRL levels and arterial blood pressure. On the other hand, this hormone is associated with systolic and diastolic blood pressure in the central aorta and PWV, which indicates aortic stiffness.[124] Significantly, according to the European Heart Association, PRL is related to the composite index that predicts the 10-year cardiovascular mortality. PRL levels >8.0 ng/mL were 100% sensitive in predicting high peripheral blood pressure.[124] Thus, hyperprolactinemia may be accelerated by affecting central/peripheral blood pressure and arterial stiffness, which plays a key role in atherosclerosis.[124 127]

Hyperprolactinemia, diabetes, and impaired glucose regulation

According to some studies, high levels of PRL can increase insulin resistance in the body and liver and impair insulin secretion in diabetic rats and patients with hyperprolactinemia. Patients with pituitary prolactinoma are often at higher risk for hyperglycemia associated with obesity and insulin resistance.[11]

Hyperprolactinemia has been reported to reduce glucose tolerance and increase insulin resistance in patients with and without obesity.[11 128] Importantly, in a study by Daimon *et al*, it was shown that higher serum PRL levels were physiologically related to insulin resistance.[128] To note, pancreatic β-cells and adipocytes widely express dopamine receptors type 2, and dopamine has been hypothesized to play a key role as a modulator of insulin and adipose functions.[11] Dopamine agonists, such as bromocriptine and cabergoline, significantly improve glucose tolerance and reduce the prevalence of metabolic syndrome in a significant proportion of patients. Therefore, control of hyperprolactinemia by dopamine agonists is an important strategy to improve glucose and insulin abnormalities.[129]

Hyperprolactinemia and lipid profile

PRL is known as a metabolic hormone and hyperprolactinemia can cause metabolic and inflammatory changes that are associated with accelerated atherosclerosis.[107] Studies have linked hyperprolactinemia to impaired fat profile. In particular, a decrease in high-density lipoprotein cholesterol and an increase in total cholesterol or LDL-c and triglycerides in patients with prolactinoma compared with healthy controls have been shown to be effective.[129] PRL directly affects adipose tissue because PRLR increases during fat cell differentiation and may be involved in lipid metabolism in adult adipocytes.[130] On the other hand, D2-like receptors, such as dopamine D2 receptor, are expressed on human adipocytes, indicating the regulatory role of environmental dopamine in the function of these cells,[131] and dopamine agonists prevent PRL expression and secretion by adipocytes in vitro. These findings support the hypothesis of the beneficial effect of dopaminergic activation on lipid dysfunction in patients with hyperprolactinemia.[132]

Potential applications of dopamine agonists on PRL production

Dopamine is an effective inhibitor of PRL secretion due to either a direct influence on the hypophysis or the stimulation of postsynaptic dopamine receptors in the hypothalamus, provoking the release of the PRL inhibitory factor.[9] As a result, it is worthy to mention that the most important known factor in regulating PRL secretion is dopamine, which has an inhibitory role in the secretion of this hormone. Dopamine has an inhibitory impact through a direct effect on the pituitary gland or stimulation of postsynaptic dopamine receptors in the hypothalamus.

Bromocriptine is an ergot alkaloid that binds to the dopamine receptor and inhibits central PRL synthesis. Bromocriptine has been shown to reduce the production of antibodies, affect the function of lymphocytes, and regulate the expression of surface molecules. However, it has no clear effect on the production of PRL outside the pituitary gland.[9] Cabergoline, an ergot derivative, is a potent dopamine receptor agonist in DD receptors. Studies have shown that cabergoline has a direct inhibitory effect on pituitary lactotrophic cells.[133] The beneficial therapeutic effects of these two dopamine agonists and their low toxicity are strong reasons for their potential in future treatment proposals.

CONCLUSIONS

PRL is a multifunctional pituitary hormone, which has metabolic actions that are not confined to the lactating mammary gland. PRLR is widely expressed in the human body and mediates PRL actions by activating JAK2/STAT5, PI3K, and MAPK pathways. Even though PRL is able to interact with PRLRs in different locations, the mechanisms regulating the expression of PRLR (and its different isoforms) in each extrapituitary tissue are essentially unknown. Therefore, considering the role of hyperprolactinemia in the incidence and recurrence of autoimmune diseases, CVDs, hypertension, impaired glucose tolerance, and impaired lipid profile, more comprehensive studies are highly recommended to reveal the exact mechanisms involved in the subsequent repercussion of hyperprolactinemia.

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