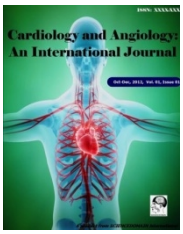

Cardiology and Angiology: An International Journal
2(1): 49-61, 2014, Article no.CA.2014.004

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Prolactin Hormone and Cardiovascular System

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Mini-review Article

Received 13th December 2013
Accepted 15th March 2014
Published 28th March 2014

ABSTRACT

The Prolactin (PRL) hormone, a very ancient hormone, first discovered by Oscar Riddle and his colleagues in the late 1920s, is a 199 amino acid multifunctional polypeptide hormone, that has been found in all vertebrates to influence more than 300 physiologic functions of the body. This review discusses the prolactin structure, mechanism of synthesis, control of secretions, receptors, its intracellular signal transduction and its possible implications on the cardiovascular system.

Keywords: Prolactin; cardiovascular system; signal transduction; pregnancy.

1. INTRODUCTION

Prolactin is a multifunctional hormone whose receptors are expressed in almost all organs of human body which in turn enables it to influence multiple physiological processes including endocrine, metabolic, immune system functions and cardiovascular properties. In comparison with the majority of the pituitary hormones, Prolactin is found to have the most physiological functions [1], estimated at approximately 300 different biological actions in vertebrates [2].

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2. HISTORICAL OVERVIEW

In the late 1920s, Dr. Oscar Riddle Fig. 1 and colleagues were involved in the discovery of prolactin [3]. Earlier reports from his laboratory had described lactational inducing effects of the anterior pituitary.

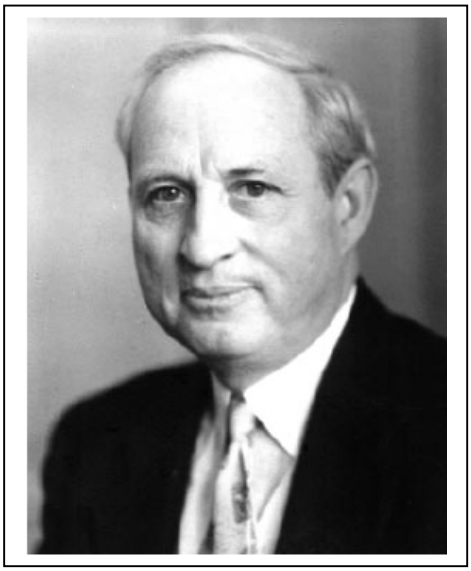

Fig.1. Oscar Riddle. Courtesy of the Cold Spring Harbor Laboratory Archives

However, at that time, only the growth- promoting and gonad- stimulating actions had been characterized [4]. Riddle and coworkers found that this substance, which they named prolactin (PRL), could be differentiated from the known growth- and gonad-stimulating substances [3,5,6]. In their experiments, they showed that PRL stimulated milk production in guinea pig mammary glands and a milk-like substance from the crop sacs of pigeons and doves, giving rise to the pigeon crop sac bioassay for PRL [3,5,6].

Over the ensuing years, PRL was characterized, sequenced and specific radioimmunoassay (RIAs) were developed for PRL from a number of species. Because of the high lactogenic activity of even very highly purified preparations of human growth hormone (GH), however, it was impossible to separate human PRL from GH using the relatively crude pigeon crop assay. However, several human disease states provided strong evidence that these two hormones were separate. For example, it was observed that most patients with pituitary tumors with galactorrhea and amenorrhea being the cardinal clinical features did not show acromegalic features, whereas patients who were known to have isolated, congenital GH deficiency were able to undergo postpartum lactation [7]. Finally, in 1970, Frantz and Kleinberg developed a sensitive in vitro bioassay which involved staining milk produced by cultured, lactating mouse mammary tissue in response to PRL that was capable of measuring PRL levels as low as 5ng/ml. In this assay they added excess antibody to the GH to neutralize any potential lactogenic effects it may have had and, for the first time, were able to demonstrate measurable PRL levels in women with puerperal and non puerperal galactorrhea, but not in most normal men and women [8]. Shortly thereafter, an RIA for human PRL was developed which could finally measure PRL levels in the sera of normal

individuals, permitting the eventual sequencing of human PRL [9] and determination of its cDNA sequence [10].

3. PROLACTIN STRUCTURE

Prolactin belongs to the family of hormones known as group I of the helix bundle protein hormones [11], which includes growth hormone (GH) and placental lactogen. Genes encoding this group evolved from a common ancestral gene by duplication approximately 400 million years ago [10], hence there is 40% homology between the genes encoding prolactin and GH. In the human genome, a single gene, found in chromosome 6, encodes prolactin [12]. Transcription is regulated by two independent promotor regions: one of which directs pituitary-specific expression; and the other more upstream region is responsible for extra pituitary expression [13]. Several factors influence PRL gene expression, including estrogen, dopamine, TRH, and thyroid hormones [14].

The prolactin molecule is arranged in a single chair of amino acids, 199-amino-acid polypeptide containing three intramolecular disulfide bonds. It is found to circulate in the blood in various sizes Fig. 2 including the 23kd monomeric PRL ("little prolactin"), 48- to 56-kd dimeric PRL ("big prolactin"), and polymeric forms larger than 100kd ("big, big prolactin") or macroprolactin [15-17]. The monomeric form is the most bioactive PRL. In response to TRH, the proportion of the more active monomeric form increases.

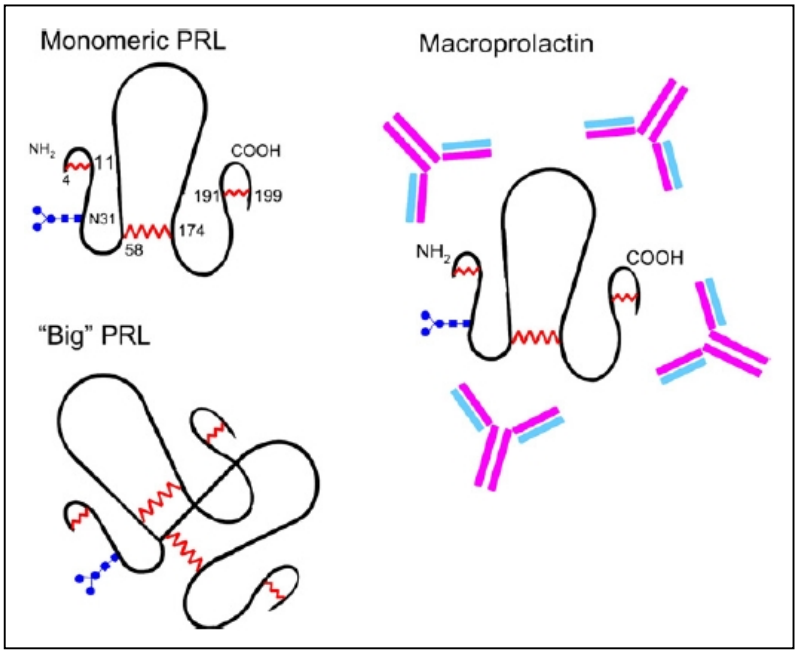

Fig. 2. Schematic illustration of prolactin(PRL) proteins as they exist in the serum as three forms: monomeric 23kDa PRL (>95%),"big prolactin", consisting of prolactin aggregates, and "big, big PRL", or macroprolactin, consisting of PRL bound to IgG [18]

A glycosylated form of PRL identified in pituitary extracts is less biologically active than "little prolactin" [19]. Monomeric PRL is cleaved into 8- and 16kd forms, [20] and the 16kd variant

is antiangiogenic [21,22]. Small amounts of 16K and 8K cleavage products are present in the normal pituitary and plasma of humans [23]. The 16KhPRL variant results from enzymatic activity of two enzymes: Kallikrein, an estrogeninduced serine protease that is found in the Golgi cisternae and secretory granules of lactotrophs [24] and bone morphogenetic protein 1, a metalloproteinase that activates latent complexes of the TGFb superfamily members [25].

3. SITES OF SYNTHESIS AND SECRETION OF PROLACTIN

Prolactin is synthesized and secreted by lactotroph cells of the anterior pituitary [26]. Lactotroph cells comprise about 15 to 25% of functioning anterior pituitary cells. Although their absolute number does not change with age, lactotroph hyperplasia does occur during pregnancy and lactation [27] and resolves within several months of delivery. Dependent on their location within the pituitary, lactotrophs display marked functional heterogeneity in their response to secretagogues: Those located in the outer zone of the gland are more responsive to thyrotrophin releasing hormone (TRH), a potent prolactin releasing factor (PRF) [28], while those in the inner zone are more responsive to dopamine [29]. It is also of note that the anterior pituitary lies outside of the blood–brain barrier, thus exposing the lactotroph to the direct influence of compounds with low lipid solubility [30].

When Fuxe discovered prolactin within hypothalamic axon terminals, he became the first to observe its production within the brain [31]. Prolactin has since been found in numerous brain structures, including the cerebral cortex, hippocampus, amygdala, brain stem, cerebellum and spinal cord [32,33]. While a significant proportion of brain prolactin is of pituitary origin, entering the CNS via the choroid plexi, the hypothalamus is also capable of synthesizing an identical variant of the hormone [32]. In addition to the anterior pituitary gland, PRL gene expression has been confirmed in various regions of the brain, decidua, myometrium, lacrimal gland, thymus, spleen, circulating lymphocytes, and lymphoid cells of bone marrow, mammary epithelial cells and tumors, skin fibroblasts, and sweat glands [34]. PRL can thus be found in several fluid compartments in addition to serum, such as cerebrospinal fluid, amniotic fluid, tears, milk, follicular fluid, and sweat. Neutralization of circulating PRL with anti-PRL antibodies results in immune dysfunction and death [35], suggesting that extra pituitary PRL is important and, under some circumstances, can compensate for pituitary PRL.

Pituitary PRL acts via a classic endocrine pathway, i.e. it is secreted by a gland, transported by the circulatory system, and acts on target cells at some peripheral sites via specific receptors located on the plasma membrane. The PRL that is produced by many different cell types can act in a more direct fashion, i.e. as a growth factor, neurotransmitter, or immunomodulator, in an autocrine or paracrine manner. Thus, locally produced PRL can act on adjacent cells (paracrine) or on the PRL-secreting cell itself (autocrine). Using paracrine or autocrine mechanisms, it would thus be possible to activate many of the actions associated with PRL without ever affecting the circulating concentration of the hormone [2].

4. CONTROL OF PROLACTIN SECRETION

In non-pregnant mammals, the basal secretion of prolactin is low. However, prolactin secretion by anterior pituitary lactotroph cells occurs at a relatively high spontaneous rate [36,37], which is unique in that all other pituitary hormones require stimulating or releasing factors to promote their release. The main control of secretion, therefore, is by inhibition from the hypothalamus, through the actions of the hypothalamic hormone, dopamine [38].

Dopamine is synthesized by the tuberoinfundibular dopamine (TIDA) neurons in the arcuate nucleus, and released from nerve terminals in the median eminence. Dopamine is released into the extracellular space surrounding the portal vessels, and travels via the long portal vessels to the anterior pituitary, where it binds to dopamine D2 receptors on lactotrophs, decreasing the secretion of prolactin by suppressing spontaneous action potentials in the lactotroph [39,40]. Dopamine is also synthesized in the rostral arcuate tuberohypophysial dopamine neurons (THDA), and is transported to the terminals in the intermediate and posterior lobes of the pituitary. Moreover, dopamine is synthesized in the periventricular-hypophysial dopamine neurons (PHDA), and is transported to terminals in the intermediate lobe of the pituitary. Dopamine from both THDA and PHDA neurons accesses the anterior pituitary via the short portal vessels, and this contributes to the physiological suppression of prolactin secretion [41].

Several substances act as PRL releasing factors. Epidermal growth factor (EGF) induces PRL synthesis and secretion. Vasoactive intestinal polypeptide (VIP) stimulates PRL synthesis via c AMP [18]. Oxytocin and pituitary adenylate cyclase activating protein also release PRL [42]. TRH stimulates PRL[43] but does not likely play an important role in PRL secretion . Estrogen stimulates PRL gene transcription and secretion, which further explains why the female gender more so than the male gender are found to have higher PRL levels and more specifically those that still are menstruating versus those that are postmenopausal [44].

Serotonin may be found to be an additive with VIP in releasing PRL, and infusion of 5–hydroxytryptophan (5HT), a serotonin precursor that elicits PRL release. Nocturnal PRL secretion is attenuated by cyproheptadine. Thus, serotonin may mediate nocturnal PRL secretion. Opiates acutely induce PRL release, although naloxone does not consistently suppress PRL levels. GnRH also stimulates PRL in women, especially during the periovulatory menstrual phase [18]. Normal Prolactin levels are below 625mU/litre in women [45]. Prolactin levels are physiologically elevated in pregnancy, the postpartum period, and in states of stress.

5. PROLACTIN RECEPTOR AND ITS DISTRIBUTION

The PRL activities are mediated by the PRL-R, a member of the cytokine receptor superfamily that includes receptors for the growth hormone, many cytokines, and some growth factors [46,47]. It localizes to chromosome 5p13 and 10 exons [48]. The PRL-R is characterized by a single hydrophobic transmembrane domain which divides the receptor into an extracellular ligand binding domain and an intracellular domain homologous to the GH receptor [49] .

Three major PRL-R isoforms have been described based on their amino acid sequence; the short, intermediate, and long forms–each of which contains an identical extracellular domain, in addition to a transmembrane and intracellular domain [50].

Within the hypothalamus, both long and short forms of the receptor are expressed, with the long isoform being predominant in the arcuate and periventricular nuclei [51]. Both of these regions are integral to the inhibitory dopaminergic tone, which the hypothalamus provides to the lactotroph, and the expression of prolactin receptors in these nuclei therefore allows PRL to participate in a feedback mechanism, which ultimately influences its own secretion [30].

Activation of the PRL-R involves ligand-induced sequential receptor dimerization. First, the prolactin molecule binds to a receptor forming an inactive hormone-receptor complex. Consequently, through a second binding site on the hormone, it binds a second receptor that leads to receptor dimerization and activation of a cascade of intracellular events as seen in Fig. 3 [50].

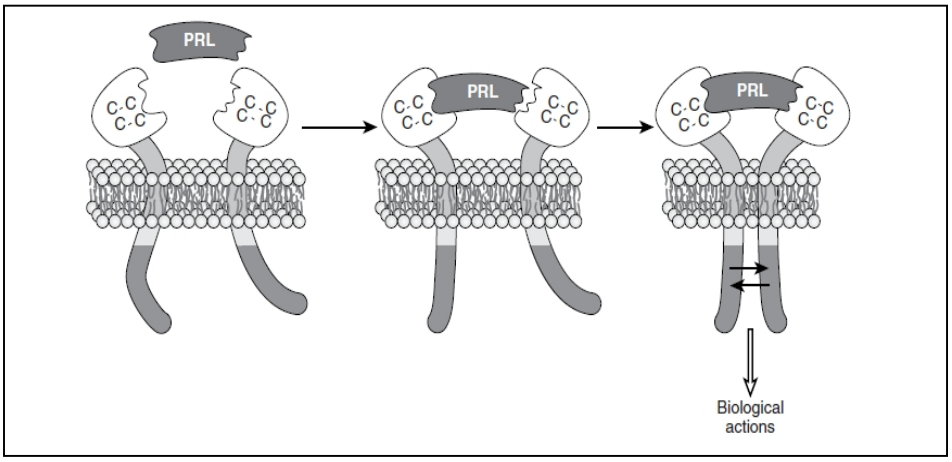

Fig. 3. Dimerization and conformational changes in the prolactin (PRL) receptor cause activation [52]

6. THE JAK-STAT PATHWAY

While PRL can involve several different second messenger cascades in signal transduction, the predominant pathway employed is known as the JAK2-STAT (Janus kinase signal transducer and activator of transcription) cascade. Ligand-mediated activation of PRL-R results in tyrosine phosphorylation of numerous cellular proteins, including the receptor itself [53].

JAK2 has been shown to be essential PRL-regulated protein kinase by both biochemical and genetic experiments [54,55]. JAK2 which is constitutively associated with a region of the intracellular receptor domain, becomes activated within seconds of PRL binding, and is subsequently responsible for the phosphorylation of a signal transducer and activator of transcription (STAT) protein when it docks to the activated receptor Fig. 4. The signal transducer and activator of transcription (STAT) protein family consists of eight members, four of which (STAT1, STAT3, STAT5a and STAT5b) have been identified as intracellular transducer molecules of the PRL-R[56] . The activated STAT molecule dissociates from the receptor complex and forms a dimer with another phosphorylated STAT molecule, which then translocates it to the nucleus to activate a STAT DNA-binding motif in the promoter of a target gene [2,57] (Bole-Feysot et al. 1998; Carter-Su and Smit, 1998). Of the three STAT proteins involved in signal transduction of the activated prolactin receptor, STAT5 is recognized as being the most important [58,58] .

PRL-binding sites or receptors have been identified in a number of cells and tissues of adult mammals. The expression of short and long forms of receptors have been shown to vary as a function of the stage of the estrous cycle, pregnancy, and lactation [59-62].

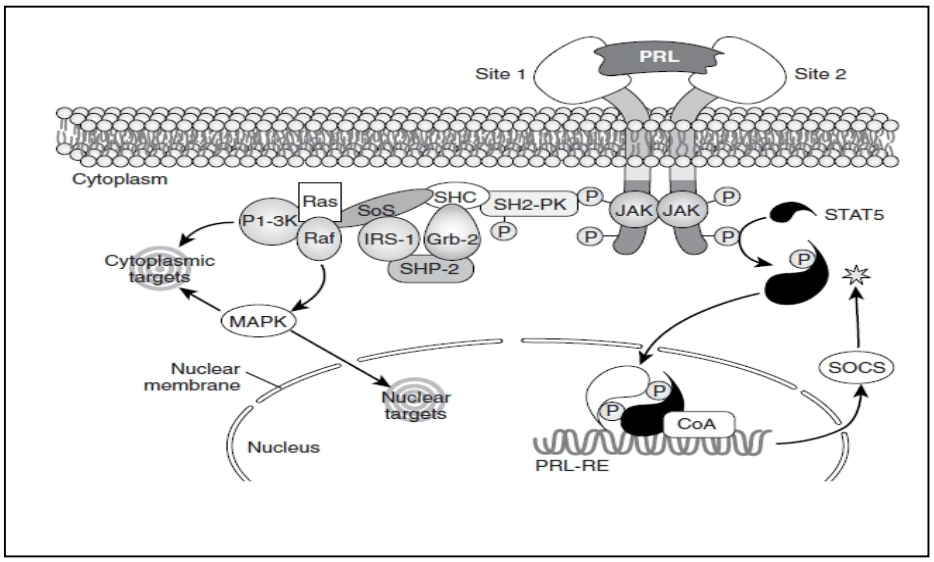

Fig. 4. Intracellular signal transduction by prolactin(PRL) [52].

7. PROLACTIN AND CARDIOVASCULAR SYSTEM

Studies involving a small number of subjects suggest that in the acute phase of acute coronary syndromes, ischemic strokes, and transient ischemic attacks, plasma prolactin levels are elevated [63,64]. Although this increase of systemic prolactin may be representative of the general neuroendocrine stress response, a role of prolactin as a causal factor in these thrombotic diseases is possible. Two studies involving a lesser number of patients suggest that hyperprolactinemia is associated with decreased insulin sensitivity, higher C-reactive protein (CRP), and impaired endothelial function [65,66]. Prolactin may play a role in accelerated arteriosclerosis in early menopause by increasing central as well as peripheral blood pressure and arterial stiffness [67]. In addition, in vitro studies show that prolactin stimulates integrin-mediated adhesion of circulating mononuclear cells to endothelium and induces vascular smooth muscle cell proliferation [68,69]. There is a possible association between long-term treatment with dopamine agonists and cardiac valve abnormalities [26]. Dopamine agonists, including cabergoline, brmocriptime, are the primary line of treatment for prolactinomas. Cabergoline is most commonly used, due to its clinical efficacy, tolerability, and favorable pharmacokinetic profile [70]. High doses and long duration of therapy with dopamine agonists have been associated in Parkinson's disease with an increased risk of regurgitant valve disease [71,72]. Although doses used for prolactinoma therapy are much lower than those used for Parkinson's disease, patients with prolactinoma may be treated for decades. This treatment duration, raises concern for increased risks of valvulopathy, including tricuspid, mitral and aortic regurgitation [73,74]. Although most reports do not show an association between the use of dopamine agonists and cardiac valve disease, clinicians are advised to use the lowest possible doses of dopamine agonists.

Echocardiographic monitoring should be considered, especially in patients requiring long-term and/or higher-dose therapy, and those with underlying heart or valvular disease [75].

Peripartum cardiomyopathy (PPCM) is a rare and life-threatening disease that affects young women in the last month of pregnancy or within 5 months of delivery. It is a form of dilated cardiomyopathy with left ventricular systolic dysfunction which may lead to symptoms and signs of heart failure [76]. Peripartum cardiomyopathy was first described in 1849 by Richie and Virchow but was not recognized as a distinct clinical entity until 1937 [77]. The pathogenic mechanisms of PPCM have been difficult to study as their incidence and prevalence are too low in Western countries to allow for meaningful evaluations. PPCM probably develops due to a complex interaction of inflammation, hemodynamic stress during pregnancy [76].

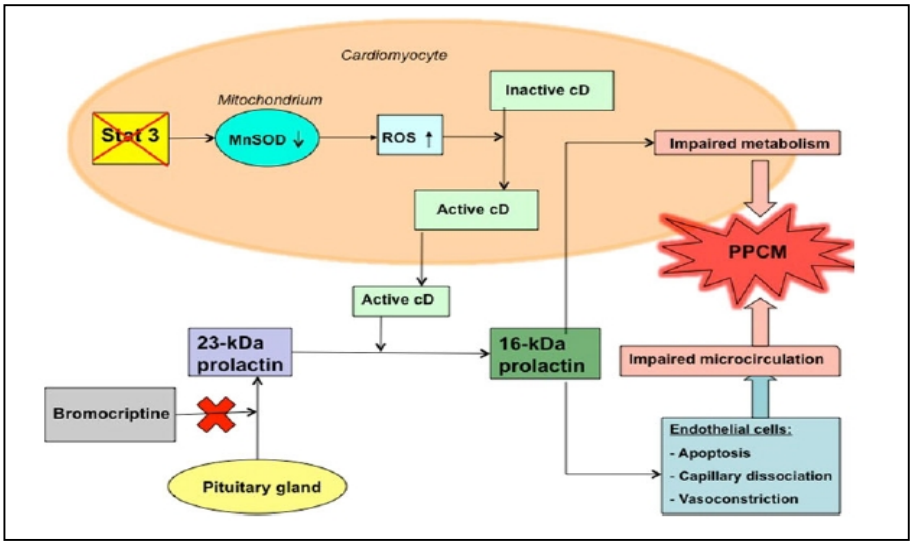

Fig. 5. Development of PPCM. In the absence of cardiomyocyte STAT3 activity, the amount of MnSOD will decrease. This leads to an increase of oxidative stress and the release of cathepsin D, which processes 23kDa prolactin into the 16kDa form

The 16kDa prolactin induces endothelial cell apoptosis, capillary dissociation, vasoconstriction and impairs cardiomyocyte metabolism, thereby promoting PPCM. Accordingly, bromocriptine, a pharmacological inhibitor of prolactin release, prevents PPCM by inhibiting 23-kDa prolactin. cD cathepsin D, ROS reactive oxygen species, MnSOD manganese superoxide dismutase

Pregnancy is a physiological state associated with enhanced oxidative stress related to high metabolic turnover and elevated tissue oxygen requirements. During pregnancy, the heart develops a reversible physiological enlargement in response to mechanical stress and increased cardiac output. In order to protect the heart, activation of the STAT3 pathway is necessary. STAT3 promotes myocardial angiogenesis and can mediate cardiomyocyte hypertrophy. In addition, STAT3 is involved in protection of the heart from pregnancy-induced oxidative stress by inhibition of the reactive oxygen species by upregulation of mangenase superoxide dismutase (MnSOD). Hilfiker-Kleiner and his colleagues, 2007 [78] published an article in which STAT3 knockout (KO) mice showed normal pregnancy-induced vessel growth and hypertrophy but displayed increased apoptosis, loss of myocardial capillaries, fibrosis and dilatation in postpartum period [78].

The STAT3 pathway is activated by prolactin. Prolactin exists in a full-length 23kDa form, which can be cleaved by the protease cathepsin D into an antioangiogenic and proapoptotic 16kDa fragment Fig. 5 [78].

A recent investigation demonstrated the unfavorable influence of 16kDa prolactin. Systemic infusion of 23kDa prolactin in wild-type mice and STAT3 KO mice had no adverse effects on the heart. However, expression of the 16-kDa prolactin in the heart destroyed the cardiac microvasculature, reduced the cardiac function (in vivo) and decreased the cardiomyocyte metabolism, even in absence of pregnancy. They showed that bromocriptine inhibits 23kDa prolactin. Thereby, it eliminates the substrate for the generation of 16-kDa prolactin and prevents PPCM in STAT3-KO mice [76,78].

8. CONCLUSION

Prolactin (PRL) is a polypeptide hormone, discovered more than 80 years ago. Although it was first described as an anterior pituitary hormone that stimulates lactation and mammary gland development, the wide range distribution of its receptors, suggested its large number of physiological functions. Indeed, there is a strong discrepancy between its physiological role and its pathological role especially in the cardiovascular system, seeing as the physiological full length prolactin 23kDs promotes angiogenesis and protects endothelial cells whereas the cleaved 16kDs derivate induces endothelial cell apoptosis and disrupted capillary structure [79]. Extensive elucidation of prolactin physiology and signaling will help in further clarifying the physiological and pathological role of prolactin in the cardiovascular system.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

ACKNOWLEDGEMENTS

Authors would like to thank Dr Ashraf Abd Rabou for his kind revision of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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