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Review article

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PROLACTIN - NOT ONLY LACTOTROPHIN
A "NEW" VIEW OF THE "OLD" HORMONE

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Prolactin (PRL) is a hormone mainly secreted by the anterior pituitary. Recent studies have shown that it may also be produced by many extrapituitary cells. The PRL gene expression is controlled by two independent promoter regions, which may be differentially regulated in the pituitary and extrapituitary organs. Proteolytic modifications of PRL generate variants of the hormone. A 16 kDa PRL fragment, acting through a specific receptor, has both an antiangiogenic activity as well as an inhibitory effect on tumor growth. Stimulation of the PRL receptor involves many signal transduction pathways, for example JAK2/STAT, MAPK, c-src and Fyn kinase cascade, and these pathways may vary in different tissues. PRL synthesis and secretion is mainly regulated by the inhibitory influence of dopamine but other hormones are also involved in these mechanisms. The essential biological action of PRL is the stimulation of lactogenesis and galactopoesis. Apart from its classical functions, PRL affects other aspects of human body function including osmoregulation, metabolism and regulation of the immune and the central nervous system. Hyperprolactinemia is a common syndrome affecting both men and women. It is manifested by the presence of galactorrhoea and through the symptoms of hypogonadotrophic hypogonadism. Following on from the fact that PRL has so many pleiotropic tissue specific effects it is not surprising to learn that hyperprolactinaemia is a systemic condition which may predispose to numerous cardiovascular and immune-mediated reactions. The exact effects of PRL on both immune and cardiovascular systems are being currently unraveled and may lead to the introduction of novel therapeutic approaches in the future.

Key words: *prolactin, immune system, endothelium function, metabolic effects, hormonal influence, central nervous system reparation*

INTRODUCTION

Prolactin (PRL) is a 23 kDa hormone composed of 199 amino acids forming a single polypeptide chain with three intramolecular disulfide bonds. It is produced by the anterior pituitary gland and has been primarily identified as a major stimulating factor for lactation in the postpartum period (1). However, apart from its classical functions this hormone affects other aspects of human homeostasis, including osmoregulation, metabolism and regulation of both the immune and the nervous systems. In the present review we will focus on these important "pleiotropic" effects of prolactin and the mechanisms of its actions. The potential clinical importance of prolactin will be also discussed.

GENETIC AND MOLECULAR CHARACTERISTICS OF PROLACTIN

PRL is mainly secreted by the lactotrophs, cells that constitute 20-50% of the anterior pituitary cells. There are also many extrapituitary sources of PRL, including lymphocytes, skin fibroblasts, the brain, the breast, the decidua, and prostate and adipose tissue cells (2-6).

The prolactin gene in humans is located on chromosome 6 and is composed of 5 exons and 5 introns. The transcription of this gene is regulated by two independent promoter regions. In the pituitary gland transcription starts from the promoter of the 1b exon. The second promoter, that of the 1a non-coding exon (also named the "0" exon), is active in the extrapituitary organs (3, 7), and thus is very important for the pleiotropic actions of PRL. The extrapituitary transcript of the PRL gene is 150 nucleotides longer than that of the pituitary PRL mRNA, due to the presence of the non-coding exon 1a (8). Products of PRL mRNA translation (proPRL) are found to be of the same length in both the pituitary and in other tissues as the initiation site of translation is localized within the exon 1b transcript. The two promoters have different regulatory elements. The promoter of the 1b exon is mainly controlled by the Pit-1 transcription factor (1, 9). Acting together with Pit-1, some other transcription factors such as the complex of the estradiol-estrogen receptor or the nuclear factor-κB (NF-κB) may activate PRL gene transcription in the 1b exon promoter (10, 11). The upstream extrapituitary promoter of the 1a exon has not been extensively characterized and defined so far.

Some data indicate the role of cAMP and protein kinase A in the activation of this promoter. (12).

While transcriptional regulation of PRL expression is important, a large part of the differential effects of PRL variants result also from either posttranslational modifications or from the alternative splicing of mRNA. The presence of PRL variants may be responsible for some of the pleiotropic actions of this hormone. There are several mechanisms regulating the generation of these molecules. Cathepsin D-like protease processing of the PRL results in the formation of a 16 kDa fragment. This 16 kDa variant has a much lower affinity to the classical PRL receptor than the native form of PRL. However, this short form of PRL is responsible for numerous effects in endothelial cells, which have a specific receptor for this variant. These effects include inhibition of proliferation and migration of the endothelial cells (13-15) as well as an anti-angiogenic influence, or an inhibition of tumor growth (13, 16, 17). Other forms of post-translational processing include proteolytic cleavage by kallikrein, which results in a 22 kDa PRL fragment. However, no specific actions of this protein have been identified so far (9, 18).

The PRL polypeptides also undergo glycosylation, phosphorylation, or deamidation that reduce their biological activity. PRL can form dimers, polymers, and aggregates as well. These three forms, however, demonstrate lower biological activity and are likely to participate in the storage, modification, and release of PRL (9, 19).

THE PROLACTIN RECEPTOR: ITS STRUCTURE, DISTRIBUTION AND ACTIVATION MECHANISMS

The diversity of PRL actions is made possible not only through the posttranslational modification of the molecule but also due to the diversity of the PRL receptors. The classical prolactin receptor (PRLR) is a member of the class 1 cytokine receptor superfamily, and is expressed in various tissues including mammary gland, gonads, liver, kidney, adrenal gland, brain, heart, lung, pituitary gland, uterus, skeletal muscle, skin and the immune system cells. The human PRLR gene is located in chromosome 5 and contains 11 exons. These include the 5 alternative first exons $E1_1$ to $E1_5$. Each of them has its own tissue-specific promoter. Exons 4-11 are coding exons, whereas exon 2 is a non-coding one. Sequences from exon 11 onwards are present solely in the short PRLR forms. Translation starts within exon 3.

Several isoforms of PRLR have been described, that result from alternative splicing and from proteolytic cleavage. The most common isoforms of PRLR are: the full length activating receptor - long form (LF), intermediate (IF) and short (SF), including the soluble isoform of PRLR known as the PRLR binding protein, which results from the proteolytic cleavage of the membrane-bound PRLR. These PRLR isoforms have a different cytoplasmic domain and show certain functional differences (9, 20).

PRLR consists of a single transmembrane domain, a ligand-binding extracellular domain and a cytoplasmic domain required for signal transduction (*Fig. 1*). Within the cytoplasmic part of PRLR there is a proline rich BOX-1 domain - the JAK-2 kinase docking site.

Signal transduction consists of the binding of the ligand- the PRL to the receptor, forming a ligand-receptor complex and subsequent receptor dimerisation (*Fig. 2*). The JAK-2 tyrosine kinase, constitutively associated with the PRLR cytoplasmic domain, is autophosphorylated. This results in JAK-2 activation and in the phosphorylation of the tyrosine residues located in the intracellular domain of the long and the intermediate PRLR isoform. These isoforms, activated by the tyrosine residues phosphorylation, bind to the STAT protein. STAT proteins (STAT1, STAT3 and mainly STAT5) are a major transducer in cytokine receptor signaling. They undergo phosphorylation and can form homodimers (two phosphorylated proteins) or heterodimers (a phosphorylated protein binds to an unphosphorylated one). The STAT dimers translocate to the nucleus, where they regulate the expression of numerous different genes (*i.e.* β-casein, β-lactoglobulin , whey acidic protein, interferon-regulatory factor-1 and others) by binding to the gamma-interferon-activated sequences. PRLR can involve other signal transduction pathways as well. Phosphorylated tyrosines can serve as docking sites for adaptor proteins (Shc/Grb2/SOS) that bind the receptor to the mitogen activated protein kinase (MAPK) cascade. Activation of c-src and Fyn kinase cascade is also possible (9, 20, 21). The three PRLR isoforms are able to activate JAK-2 but the short isoform does not undergo phosphorylation (22).

Cell proliferation is stimulated by the activation of the long PRLR isoform and, to a lesser degree, by the activation of the

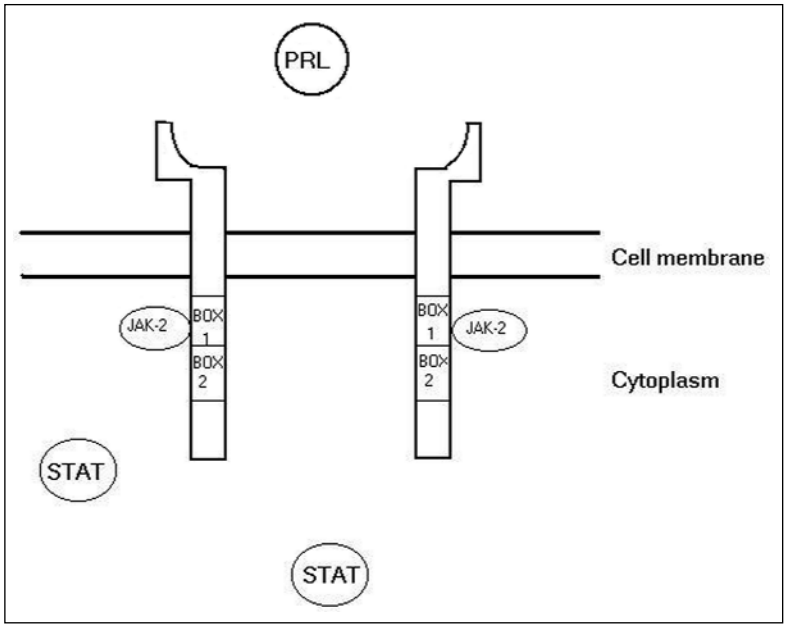

Fig. 1. Prolactin receptor.

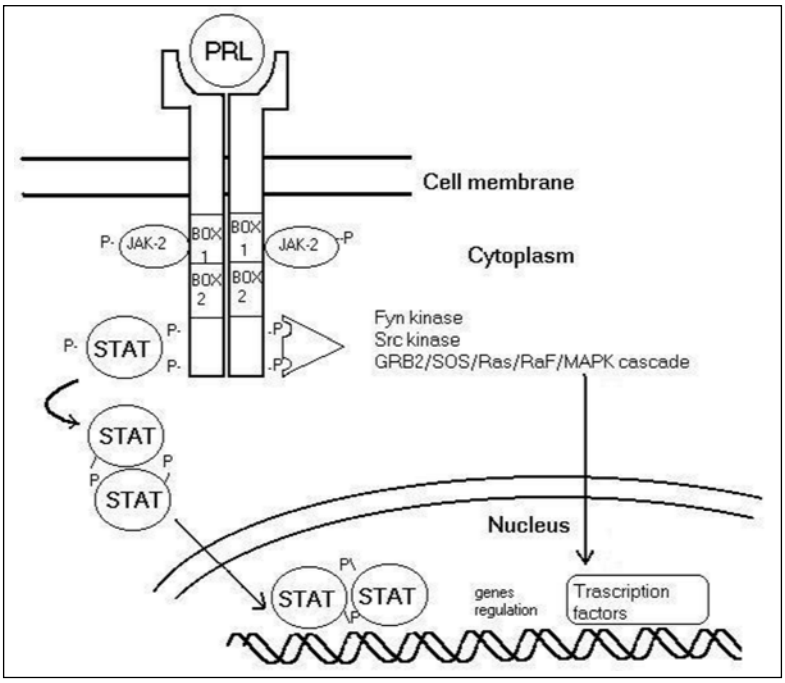

Fig. 2. Signal transduction pathways of the prolactin receptor activation.

intermediate isoform, whereas the activation of the short isoform suppresses the effects of long- and intermediate- isoform activation. It has been shown that SF-PRLR forms inactive complexes with other PRLR isoforms , producing heterodimers unable to stimulate JAK-2 autophosphorylation (23).The SF-PRLR functions as a dominant negative isoform, inhibiting the activation of milk protein gene transcription by the receptor complex through heterodimerisation (24, 25).

PHYSIOLOGY OF PROLACTIN SECRETION

Major control of PRL synthesis and secretion is based on the inhibitory effect of dopamine, produced in the arcuate and paraventricular nuclei of the hypothalamus. Dopamine is conveyed along the axons to the median eminence nerve endings, where it is released to the capillaries of the portal vessel system. This process enables the dopamine to reach the anterior pituitary lobe in order to inhibit PRL release by binding to the D2 receptor of the pituitary lactotroph cells (adenylyl cyclase-linked dopamine receptor). PRL secretion is pulsatile and is paced by a circadian rhythm. The lowest levels are observed in the morning about 2-3 hours after waking up and the highest - during sleep (26-28). PRL serum concentration is higher in women than in men. The level of the hormone increases during ovulation. (29, 30).

There are numerous substances regulating the secretion of PRL, both stimulating and inhibiting ones. Some mediators act upon the lactotrophs directly but others influence the PRL secretion *via* the dopamine neurons of the hypothalamus. Thyrotropin-releasing hormone (TRH), ghrelin, vasoactive intestinal polypeptide (VIP), angiotensin II, estradiol, endogenous opioids, but also serotonin, vasopressin, neurotensin, bombesin, substance P, oxytocin, neuropeptide Y, galanin and calcitonin can all stimulate PRL secretion (31-37). On the other hand, dopamine as well as noradrenaline, gamma-aminobutyric acid, serotonin, histamine, somatostatin, granin, cholecystokinine, orexin-A, cortistatin and nitrogen oxide exert inhibitory effects (38-43).

For there to be a increase of the PRL level during lactation, sleep, stress, and after estrogen administration requires the presence of a releasing factor for this hormone. The nature of this factor, however has not been conclusively identified. PRL concentration increases rapidly within one hour after the consumption of a meal in healthy individuals and in pregnant women but not in patients suffering from a PRL-releasing pituitary tumor (prolactinoma). The mechanism of this phenomenon is yet unknown.

During pregnancy, increasing estrogen secretion stimulates the growth and proliferation of the lactotrophs; as a result, PRL secretion increases. In pregnant women the pituitary gland doubles in size, and intensively secreted PRL prepares the mammary gland for the postpartum lactation. At the same time, the high estrogens concentration inhibits the lactotropic effect of PRL in the mammary gland. This results in the initiation of lactation after delivery when estrogens fall to nonpregnant levels. In the lactation period, each nipple stimulation by the suckling infant causes a substantial, short-term increase of PRL secretion which is based on a neuro-humoral axis. The control of suckling-induced prolactin secretion is not fully clear. In response to suckling stimulation opioid neurons of the hypothalamus are activated (44). The released opioids decrease the dopamine secretion in the hypothalamus and it relieves the lactotroph cells from dopaminergic inhibition (45). Prolactin releasing factors are also involved in the mechanism of the suckling-reflex: vasopressin, oxytocin and TRH are proposed (46-48).

BIOLOGICAL ACTIONS OF PROLACTIN

Lactotrophic effects

During pregnancy PRL together with estradiol, progesterone, placental lactogen, insulin and cortisol exerts a mammotropic effect manifested by mammary gland growth and development (49-51). In addition, PRL initiates postpartum milk synthesis (a lactogenic effect) and maintains its secretion - a galactopoietic effect (51).

Metabolic effects and influence to action of other hormones

While the lactotrophic role of PRL is unquestionably the most important, numerous other actions were observed.

PRL influences the gonads either directly or indirectly. Its direct action results in a decreased sensitivity of the luteinizing hormone (LH) and of the follicle-stimulating hormone (FSH) receptors in the gonads (20, 52). The indirect effect is exerted by a reduction of gonadoliberine (GnRH) secretion, more specifically by its pulsatile secretion inhibition caused by opiate system stimulation. Consequently, suppressed LH and FSH secretion inhibits ovulation (53-58). In the cases of hyperprolactinemia a hypogonadotrophic hypogonadism is observed.

Apart from the effects on other hormones of pituitary-gonadal axis, numerous other various biological functions of PRL have been identified in many aspects of physiological and metabolic processes.

In mammals, it stimulates phospholipid synthesis in the alveolar cells of the fetal lung (59) and also stimulates lipoprotein lipase activity in hepatocytes (60). It increases bile secretion as well (61). The direct action of PRL on the pancreas results in augmented insulin secretion (62). PRL is also reported to have a direct effect on adrenal steroidogenesis. It increases androgens, dihydroepiandorsterone (DHEA), and also cortisol and aldosterone secretion by the adrenal cortex cells (1, 20).

Osmoregulatory effects

In mammals PRL is involved in osmoregulation. It reduces renal Na^+ and K^+ excretion and stimulates Na^+-K^+ adenosine triphosphatase activity in the outer medulla of the rat kidney (63, 64). Newer investigations show that PRL has an inhibitory effect on Na^+-K^+-ATPase of rat proximal tubular cells *via* interaction with renal dopaminergic system (65, 66). Furthermore, PRL increases sodium and chloride ion excretion with sweat and increases water and salt absorption in all segments of the intestine. Ultimately, it causes a reduction of water transport in the human amniotic membrane (1, 20).

Influence of prolactin on the immunological system

As discussed above, apart from being produced in the anterior pituitary, PRL is produced by lymphocytes and some other immune cells (67, 68). Prolactin receptors (PRL-R) are situated on the immune cells: T-lymphocytes, B-cells and macrophages (68). Moreover structurally PRL-R is related to the cytokine/hematopoetin family which includes the growth hormone (GH), the granulocyte-macrophage colony stimulating factor (GM-CSF), the erythropoietin, and the interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-13 and IL-15 receptors (68).

The autocrine and the paracrine actions of PRL locally synthesized by lymphocytes seem to have functional significance (68). *In vitro* investigations of human mononuclear cell cultures have shown that PRL alone is unable to induce proliferation of lymphocytes. However PRL acts as a co-stimulating factor for T lymphocytes, activated by an unspecific mitogen (concanavalin A) or by antigen presentations (68). The addition of neutralizing antibodies against PRL to the peripheral mononuclear cell cultures significantly decreases the activation and proliferation of T-lymphocytes (68). It indicates that PRL is secreted locally by activated and proliferating T-cells and that it affects the proliferation on the basis of a positive reciprocal circuit (68).

Targets for PRL actions in lymphocytes have been recently identified. Stimulation of PRL receptors in T-lymphocytes induces expression of the transcription factor T-bet through the phosphorylation of JAK-2 and STAT5 (but no STAT1). That effect was induced by a low concentration of PRL in the T-cells culture. T-bet is a key transcription factor for the production of Th1 type cytokines such as interferon. Therefore through its effect on TH1-lymphocytes PRL may promote T helper actions and stimulate participation of T-cells in inflammatory reactions (69). Interestingly while low concentrations of PRL caused stimulation of T-bet, use of high concentrations of prolactin and exposure of T cells caused inhibition of the phosphorylation of STAT5 and decrease of the T-bet transcription by induction of suppressors of cytokine signaling (SOCS) 1 and 3. This may indicate that high concentrations of PRL inhibit proinflammatory activation of T helper lymphocytes (69).

In many cases of autoimmune diseases (for example multiple sclerosis and rheumatoid arthritis) the severity of the disease is alleviated or even remitted during pregnancy (70, 71). This fact could be in part attributed to the fact that there is a very elevated serum level of PRL in pregnancy but we must remember about changes of multiple other hormones (in particular estrogens). In the first three months after delivery when the serum level of PRL is elevated but significantly lower than in pregnancy the disease commonly relapses (72). In line with this it is often characteristic for the initiation of autoimmune diseases to occur in the early periods after pregnancy has ended (70, 71).

Autoimmune diseases are associated with moderate hyperprolactinemia. It occurs in 45% of subjects with rheumatoid arthritis; 20-30% of those with systemic lupus erythematosus; 59% of patients with scleroderma and 46% of those with Sjögren syndrome (74). However when there was an attempt made to lower the PRL levels in these patients with bromocriptine, this couse of action did not seem to affect the course of those diseases (74). This might question the key importance of PRL in the immune mediated diseases. At the same time, however, it may indicate that PRL plays a role in the initiation of the autoimmune reactions, rather than at later stages of fully developed clinical syndromes.

In parallel to the above observations, autoantibodies (nati-ssDNA; anti-dsDNA, antihistons, anti-Sm, anti-RNP and others) are more often present in hyperprolactinemic patients than in healthy controls (75). In Buskila *et al.* study as many as 75.7 % examined women with hyperprolacinemia presented various autoantibodies in serum (75).

Therefore the effect of PRL action on the immunological system requires further studies and analysis. The final result of PRL influence depends on the local production by immunocompetent cells and the local concentration of PRL and other hormonal factors and cytokines. To summarize generally the effects of PRL depend on concentration and are immunostimulatory at modest levels and may be inhibitory at high levels achieved during pregnancy.

Effects of prolactin on central nervous system regeneration

The influence of PRL on central nervous system (CNS) repair has been recently discussed, especially in the context of multiple sclerosis. Studies in mice with chemically-damaged myelin have shown that injections of PRL caused enhanced remyelination (76). PRL and the growth hormone (GH) promote neuronal stem cells (NSCs) migration *via* the process of PRL receptors activation, (whereby the GH is able to activate both its own receptor and PRLR). Both hormones also stimulate proliferation of NSCs (77). When applied to differentiating NSCs , PRL and GH induce neuronal progenitor proliferation, but only prolactin has proliferative effects on glial progenitors (77). Prolactin also influences other steps of neurogenesis. It promotes proliferation of oligodendrocyte precursor cells, which bestows an enhanced capacity to generate oligodendrocytes and induce myelination in CNS (76, 78). These observations are another hope for patients with demyelinative diseases.

Prolactin and cardiovascular system

PRL with other humoral factors may play a role in the pathogenesis of primary and pregnancy-induced hypertension

(79-85). This may be related to the vasoconstrictive actions of PRL. In animals (guinea pigs), intravenous infusion of PRL caused coronary, mesenteric, renal and iliac artery constriction (86). Another study showed that PRL directly stimulated vasoconstriction in an isolated rat aorta although this was not related to the modifications of the basal levels of nitric oxide (NO) (87). Clinical studies support these observations. PRL blood levels are higher in patients with essential hypertension (79, 80). The antihypertensive effect of bromocriptine suggests that the dopaminergic system and PRL are both involved in the mechanisms of blood pressure elevation and hypertension (79, 80). One of the studies found that high-serum PRL levels are associated with pregnancy-induced hypertension and preeclampsia (88), but other studies have failed to demonstrate such an association (89, 90). On the other hand, urinary PRL exertion is markedly elevated in preeclampsia and that parameter is a reliable biomarker for preeclampsia and its severity (91).

PRL and its cleaved 16 kDa derivate play a role in the pathogenesis of peripartum cardiomyopathy (92). 16 kDa PRL is an antiangiogenetic and proapoptopic factor (13, 14, 93). Hilfiker-Kleiner *et al.* used female mice which were developing peripartum cardiomyopathy, showed elevated cardiac cathepsin D expression and activity, both of which are associated with an enhanced generation of 16kDa PRL. This variant of cleaved prolactin may be responsible for cardiac capillary network impairment and for the development of cardiomyopathy (92). Treatment with an inhibitor of PRL secretion (bromocriptine, cabergoline) causes recovery in patients with peripartum cardiomyopathy (94, 95).

Moreover, Horrobin *et al.* demonstrated the influence of PRL on heart rhythm. Studies using isolated rat hearts with coronary circulations perfused by PRL solution revealed that perfusion with a moderate concentration of PRL (50 ng/ml) caused cardiac rhythm acceleration, but the perfusion of a high concentration of PRL (200 ng/ml) caused heart rate to slow down. Both doses of PRL caused disturbances in the cardiac rhythm (96). There were however no clinical observations to confirm of the presence of any arrhythmic tendencies in hyperprolactinemic patients.

Some data also showed that PRL may play a role in accelerated arteriosclerosis in early menopause, by affecting blood pressure and arterial stiffness. In early menopausal women the PRL level correlated with the arterial blood pressure, and also with the central aortic systolic and diastolic blood pressures and with the pulse wave velocity, a maker of aortic stiffness (97).

The results from Reuwer *et al.'s* research on the subject demonstrates an association between hsCRP level and the serum concentration of PRL in patients with acute myocardial infarction. It suggests that prolactin is involved in the systemic inflammatory response in these patients (98).

The presence of an elevated PRL serum level is a common hormonal change in patients with chronic heart failure (99).

The PRL serum level is suggested to be one of the prognostic factors in cases of chronic heart failure. Parissis *et al.* showed that PRL levels were significantly correlated with the New York Heart Association (NYHA) class and also with a reduction of left ventricular ejection fraction and with plasma B-type natriuretic peptide level (100). Higher prolatcin levels also predicted the occurrence of cardiovascular events. Patients with baseline PRL levels over 4.5 ng/ml had a significantly lower event-free survival rate (100). In another study of patients with chronic kidney disease, increased risk of cardiovascular events was reported. This included risk increase of 27% in the group of nondialyzed patients and by 15% in the group of hemodialyzed patients for each 10 ng/ml incrementation of the PRL level (101).

Other studies, however, do not confirm the relationship between the left ventricular impaired ejection fraction and the PRL plasma level (99, 102, 103). Moreover in Landberg *et al.* study of 462 elderly patients with chronic heart failure show no correlation between the degree of PRL plasma concentration and cardiovascular mortality or any clinical and biochemical markers of the heart failure (102).

Hyperprolactinemia

Physiological hyperprolactinaemia is essential for the survival of human species, being the main causal factor of milk production during pregnancy and lactation. Physiological functions that influence hyperprolactinemia include nipple and uterine cervix stimulation, the duration of both fetal and neonatal period, and also the sleep, stress, exercise and food consumption (1).

There are two types of hyperprolactinaemias, with relation to the etiopathogenesis: the organic or functional hyperprolactinemia.

Organic hyperprolactinaemia is mainly due to pituitary gland tumors such as prolactinoma, growth hormone/PRL-secreting adenoma and adrenocorticotropic hormone/PRL-secreting adenoma. Another cause for organic hyperprolactinemia is the damage to the dopaminergic neurons of the hypothalamus and the pituitary stalk caused by diseases of the hypothalamus and the pituitary such as granulomatous diseases (particularly sarcoidosis), craniopharyngioma and other tumours, empty sella syndrome, vascular malformations including aneurysms, lymphocytic adenohypophysitis, pituitary metastases and nonfunctioning pituitary adenomas compressing the pituitary stalk (104-106).

Pathological functional hyperprolactinemia occurs in such endocrinopathies as primary hypothyroidism and primary adrenocortical insufficiency. Functional hyperprolactinemia also occurs in hepatic cirrhosis, renal failure, lung cancer and renal cell carcinoma. (104-108).

Pharmacological hyperprolactinemia can be induced by drugs such as phenothiazines, butyrophenones, thioxantines, metoclopramide, sulpiride, risperidone, methyldopa, reserpine, estrogens, antiandrogens, opiates, antihistaminic (cimetidine), monoamine oxidase inhibitors and verapamil (54, 109, 110). It should be noted, that hyperprolactinemia can also occurs idiopathically, without any discernible reason. In such cases it is referred to as an idiopathic functional hyperprolactinemia (111, 112).

The clinical manifestations of hyperprolactinemia are variable and differ between women and men. In women clinical signs of hyperprolactinemia are primarily related to reproduction and include: anovulatory cycles (caused by inhibition of LH and FSH pulsatile secretion), oligo- and amenorrhoea, infertility (due to hypogonadotrophic hypogonadism), galactorrhoea, dyspareunia, premenstrual syndrome, hirsutism (dependent on increased adrenocortical androgens releasing), tendency to anxiety and depression. Osteoporosis or osteopenia occurs due to an indirect decrease in estrogens secretion and, as a consequence of hypogonadisim, progressive atherosclerosis also appears (104-106).

On the other hand, in men the symptoms of hyperprolactinemia are subtle and therefore are often only diagnosed at advanced stage. They include loss of libido, impotence, infertility (due to hypogonadotrophic hypogonadism-dependent on a reduction of LH and FSH pulsatile secretion), gynaecomastia (due to hypogonadism and the mammotropic effect of PRL), galactorrhoea (related to the lactotropic effect of PRL), atherosclerosis, osteoporosis/osteopenia and a tendency to anxiety and depression which are commonly-noted consequences of hypogonadism (104, 105, 107).

In cases of hyperprolactinemia accompanying macroadenoma additional symptoms may aid in differential diagnosis: hypopituitarism, headaches induced by elevated

intracranial pressure, optic chiasm compression with visual field defects and compression of intracavernous segments of the oculomotor (III), trochlear (IV), ophthalmic (V1), maxillary (V2), abducens (VI) nerves with consequent diplopia and sella enlargement (107).

Diagnosis of hyperprolactinemia

The diagnosis of hyperprolactinemia is based on repeated findings (at least twice) of an elevation of PRL serum concentration (above 20 ng/ml in women and 15 ng/ml in men). Blood samples should be collected in the morning from the patient in a fasting state, who should be in a comfortable setting after a good night's sleep at least 2-3 hours after waking up (samples drawn earlier may show sleep-induced peak levels). The metoclopramide test is helpful in distinguishing between organic and functional hyperprolactinemia. Metoclopramide blocks D2 receptors in lactorphic cells of the anterior part of the pituitary gland. Its action abolishes the inhibitory effect of dopamine on the lactothrophs.

In order to perform the test, 10 mg of metoclopramide should be administered orally and PRL level should be measured after 0, 60, and 120 minutes. A 60- or 120-minute concentration of the PRL level up to 6 times higher than the baseline is considered normal. A PRL level that exceeds 6 times the baseline value suggests functional hyperprolactinemia. If there is no elevation or only a slight elevation of the primarily high PRL concentration, to be observed, a diagnosis of prolactinoma should be made and confirmed by tan MRI imaging of the pituitary gland. In cases of damaged dopaminergic neurons of the hypothalamus and the pituitary stalk, there is no response in the metoclopramide test; however, after the administration of exogenous TRH intravenously, the PRL level rises substantially. Pregnancy and endocrinopathies leading to functional hyperprolactinemia have to be excluded. If the patient's medical history includes drug use, an unhealthy lifestyle and the occurrence of kidney and liver diseases, these should be taken into consideration (105-113).

In patients with clinical symptoms of hyperprolactinemia and "normal" serum prolactin levels, the high-dose hook effect needs to be considered. In that case large quantities of antigen (PRL) in the immunoassay system impair antigen-antibody binding, resulting in a low antigen (PRL) determination. The correct estimate of serum prolactin is obtained after a dilution of the serum sample (114, 115).

In other cases prolactin may bind to IgG and may form immune complexes called macroprolactin (there are also described forms containing IgA and IgM molecules or heavily glycosated forms of macroprolactin). It is detected by the same laboratory assays as prolactin, leading to a falsely elevated prolactin concentration result. Macroprolactin is biologically inactive. Presence of macroprolactin may lead to misdiagnosis of hyperprolactinemia in some patients with symptoms of menstrual problems or infertility. Polyethylene glycol precipitation is the method of removing macroprolactin from a suspicious sample (116-118).

Hypoprolactinemia

A syndrome of hypoprolacinemia has not been exactly characterized yet. Recent data have shown that hypoprolactinemia may be associated with sexual dysfunction such as premature ejaculation, changes in seminal quality (oligozoospermia, asthenospermia), anxiety symptoms and the metabolic syndrome (73, 119). Hypoprolactinemia accompanied by lymphopenia and lymphoid depletion is observed in patients with severe sepsis (120).

Potential clinical importance for the pleiotropic actions of prolactin

Pleiotropic actions of PRL may be used in future in the treatment of selected autoimmunological or cardiovascular disorders. Novel drugs modulating PRL secretion and/or acting on its receptor and the signal transduction pathways in lymphocytes may be utilized. Moreover selected treatments directed on the use of modulation of PRL levels has already been introduced in cardiovascular practice. Decreasing of the PRL level using dopaminergic agonists (bromocriptine, cabergoline) is a new important method of therapy in cases of severe peripartum cardiomyopathy. This application has been documented in a few recent publications (94, 95) On the other hand, hyperprolactinemia stimulates both production of myelin and also the regeneration of the central nervous system (76-78). This effect may turn out to be critical for novel therapies of patients with degenerative diseases of the nervous system. The antiangiogenetic action of 16 kDa PRL and its application in the treatment of neoplasmatic tumors is being investigated now (16). The universal acceptance of a method of treatment which uses dopaminergic agonists in prevention of atherosclerosis in hyperprolacinemic patients is being widely discussed (97). In order to achieve this we need to further understand the exact molecular mechanisms and clinical importance of pleiotropic actions of prolactin, which seems to be holding a lot of promise for future medicine.

Conflict of interests: None declared.

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