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Review Article
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The Role of Prolactin in Men

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Abstract

The role of prolactin in women is quite documented while the man studies are conflicting. In this review we will study the structure, receptors, secretion factors, biological effects of prolactin in men. Previous studies in men associate hyper-prolactinemia with infertility, erectile dysfunction, reduced testosterone, decreased sexual desire as rarely galactorrhea. Originally had not been investigated low prolactin levels in the male but recent studies indicate that the hypo-prolactinaemia in men is associated with infertility, erectile dysfunction, hypo function of the seminal vesicles, oligospermia and asthenospermia. Recent studies indicated that 1 or 2 years after the bariatric surgery levels of the hormone prolactin reduced.

Keywords: Prolactin; Infertility; Erectile dysfunction

Introduction

Prolactin (PRL) was first discovered 80 years ago by Stricher and Giveter in 1928. It is a protein of molecular weight 23,000 D. Normally the values of the blood do not exceed 20-25 ng/ml. Secreted by mammotrofa cells of the anterior pituitary. The secretion is under increasing inhibition by inhibitory factor hypothalamic characterized as PIF [1-4]. Dopamine inhibits the synthesis and secretion of prolactin from mammotrofa inhibiting cAMP generating within a few minutes even. Mammotrofa cells show a large number of dopamine receptors. The gene of the PRL is expressed mainly in mammotropa cells of the anterior pituitary, but is expressed in many other places (endometrium, myometrium, brain, mammary gland, lymphocytes, spleen, thymus), and it is possible that there is a special gene regulation for each site production. Also described and several factor Prolactin secretion (PRFs), as release hormone Thyrotropin (TRH) and Vasoactive Intestinal Peptide (VIP). The role of prolactin in men has little effect especially on reproduction and homeostasis of the organism.

Chemical Structure of Prolactin

Pituitary is formed quite early in prenatally, from the combination of RATHKE sac (where front pituitary comes from) and a part of the abdominal brain (where rare pituitary comes from) [5]. Subsequently, gonadotropin cells are developed, the cells that produce the Growth Hormone (GH) and Prolactin (PRL). So, they form separate populations of somatotropin and lactotropin cells. The transcription factor PIT1 which belongs to the Pov-Homaiodomain family is produced in somatotropin, lactoprotin and thyroid cells [6]. Mutations of the PIT1 factor prevent the development of these cells and create hormone deficiency. This linear correlation might also be responsible for the fact that some tumors that produce the Growth Hormone (GH), also secrete PRL.

The hormone production from the front pituitary begins mainly on the 9th week of pregnancy. The lactotropin cells constitute the 15-25% of the front pituitary cells and are found scattered inside it. Estrogens stimulate the proliferation of the lactotropin cells so their number is bigger in women than in men [7-12]. During pregnancy, lactotropin cells constitute almost 70% of the pituitary cells. Prolactin is produced by the lactotropin cells of adenohypophysis, it shows similar chemical structure to the GH and Placental Lactogen Hormone (hPL).

Prolactin Gene

Prolactin gene in human genome is located on chromosome 6. It encodes for a pre-hormone of prolactin with 227 amino–acids. The 10 Kb sized prolactin gene consists of 5 exons and 4 introns (intron: the part of DNA inside a gene that does not recombine into proteins. – exon: it recombines into proteins [11-14].) The DNA consists of 914 nucleotides which encode into 227 amino acids of the prolactin pre-hormone. Next, the prolactin pre-hormone disintegrates into 28 amino acids (peptide sign) and into 199 prolactine amino acids.

Prolactin Structure

The prolactin molecule consists of 199 amino acids and its molecular weight is 23,000 D. 50% of the amino acids sequence is arranged in 4 long chains like propellers, with a similar structure to the GH (Figure 1). Three disulfide shackles form between 6 cysteine residues (Cys4-Cys11, Cys58-Cys174, Cys191-Cys199). Prolactin glycosylates in a small scale and the role of chains and sugars is not clear yet [15-19].

Prolactin secretion in men

Prolactin is produced in several tissues:

- Adenohypophysis: the lactotropin cells constitute the 20-50% of the cell population of adenohypophysis, based on the genre [20,21].
- Cerebrum/Brains: Flux was to found out that it is produced in the hypothalamus (in terminal neural axons), in cerebral cortex, in hippocampus, in amygdale, in the diaphragm, in caudate putamen, in cerebellum, in spinal cord and in choroid plexus.
- Mammary Gland: in which we also have production of an equally important isoform prolactin with molecular weight 16KD, which prevents the angiogenesis locally and that way it might also prevent the Ca breast creation-scope for research-! During pregnancy the prolactin levels, the estrogens, progesterone, thyroid hormones cortisol and insulin grow. The breast epithelium is stimulated for multiplication and the milk production induces. However, high levels of estrogens and progesterone prevent milk production during pregnancy. The sharp fall of these steroids after birth allows the lactation [22-25].
- Lymphocytes: they contain m-RNA of prolactin, despite the fact that the prolactin secretion control from the pituitary is different from the lymphocyte secretion. They also contain dopamine receptors.
- Spleen
- Thymus

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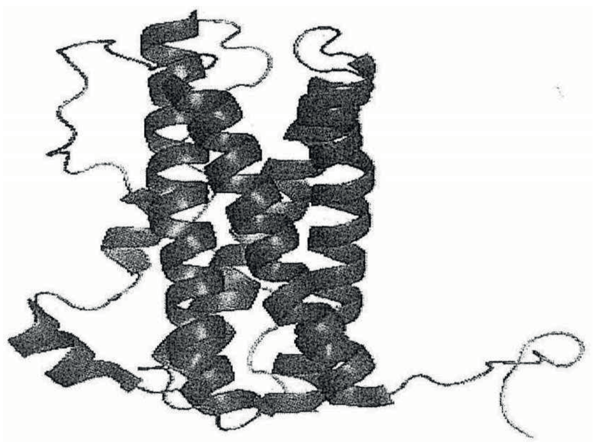

Figure 1: Amino acids sequence.

Prolactin receptors (PRLR)

They belong to the family of the class 1 cytokine receptors. Each receptor has 3 domains: an extracellular, a transmembrane and an intracellular. The gene that encodes the human PRLR is found in chromosome 5 and contains at least 10 exons. The transcriptional function of the gene PRLR is achieved by 3 different promoters:

Promoter 1 special for gonads; Promoter 2 for Liver; Promoter 3 for all tissues [26-30].

Extracellular Domain of the Receptor

It consists of 210 amino acids, and has similarities to other cytokine receptors. The extracellular domain is divided into: NH2 terminus that is called in a section inside the cell membrane called D2 [31,32]. The above extracellular domain resembles to the fibronectin molecule type 3. The part D1 consists of 2 pairs of disulfide bonds (between Cys-12 and Cys-22 and also Cys51 and Cys62) but the D2 as a "WS motif"- (Tpr-Ser-x-Trp-Ser). The disulfide bonds along with the WS-motif are essential for the folding and movement of the receptor [33,34]. D1 and D2 are essential for the right folding and formation of the receptor, even if they aren't responsible for the receptor-hormone fusion.

Trans Membrane and Intracellular Domain

The trans-membrane domain consists of 24 amino acids. Their role for the receptor activation is not particularly known. The intracellular domain of the receptor constitutes a main factor for the signal transduction mechanism of the PRLR receptor start up [35-42].

STEP 1: (Figure 2) the prolactin molecule contains 2 binding sites. The bonding of the prolactin to the extracellular domain of the receptor activates the receptor [42-47].

STEP 2: The interaction of the second binding site of the prolactin molecule with a second prolactin receptor induces. (homodimerization of the receptor) [48-50].

STEP 3: Activation of tyrosine kinase Jak2 which is found in box1. Jak2 phosphorylate between them and at the same time they phosphorylate the tyrosine in box1. Box1 (Figure 2) are rich in proline, which is essential for the Jak2 activation [51-59].

Signal transducer and transcription activators are STAT proteins. They consist of 8 sub-units. The STAT1, STAT3, STAT5a, STAT5b,

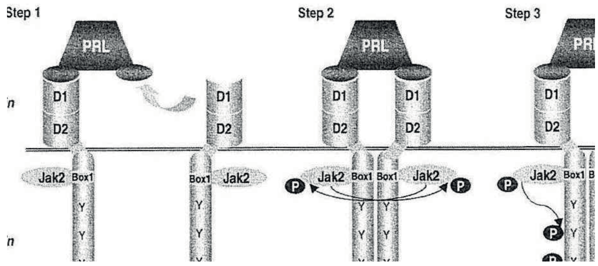

Figure 2: Activation of tyrosine kinase Jak2

have been characterized as signal transducers of PRLR. STAT have the following features:

a) -DNA binding domain

b) -SH3 like domain

c) -SH2 like domain

d) -NH_2 terminal transactivating domain

e) -COOH terminal transactivating domain

The signal transportation paths begin with the prolactin-receptor-prolactin – Jak/STAT path activation (Figure 3). Aphosphorylated tyrosine of a long isoform PRLR interacts with –SH2 area of STAT. The STAT phosphorylates from Jak-kinase. The STAT-P unshackles from the receptor and is homodimerized through phosphotyrosine residues with the –SH2 edge of another STAT-P [60-65]. The bilateral STAT is moved in the nucleus and activate a STAT-DNA binding motif in the promoter of the gene-target that is called Gas (G interferon activated sequence). The tyrosine inside a short form PRL doesn't phosphorylate from Jak2 [66-72].

MAPK: It's involved in the transcription activation factors. Phosphorylated tyrosine (long isoform) is used as a connection area for the proteins Shc/Grb2/SOS where they will connect the PRLR receptor with the Ras/Raf/MAPK [73-81]. There is a communication between JAK/STAT and MAPK signal paths.

The box1 of the prolactin receptor is involved in the activation of kinase of the tyrosine through K^+ and Ca^{++} ion channels. The – COOH terminal of the PRLR is involved in the creation of the intracellular messengers IP4 and IP6 where they open calcium channels. Prolactin also induces the SRC kinase and FYN activation which involve in the phosphorylation of the tyrosine of PI3k [82].

The Jak/STAT paths are suppressed by the Socs (suppressors of cytokine signaling) or the CIS which compete for the connection area of the prolactine receptor [83-85].

Allocation of the prolactin receptor

The prolactin receptors are found in several peripheral organs such as pituitary, heart, lungs, thymus, spleen, liver, pancreas, kidneys, adrenal glands, skeletal muscles, skin, uterine, but mainly in the mammary gland and the ovaries [86,87]. Glycosyliation of Asn35, Asn80, Asn108 of the extracellular domain is of great importance for the PRLR activation. Even if PRLR is a surface receptor, its glycosylized forms can accumulate in the Golgi system.

The Nitric oxide activates the N-acetyl-glucose-aminotransferase, which is responsible for these receptors and promotes their migration

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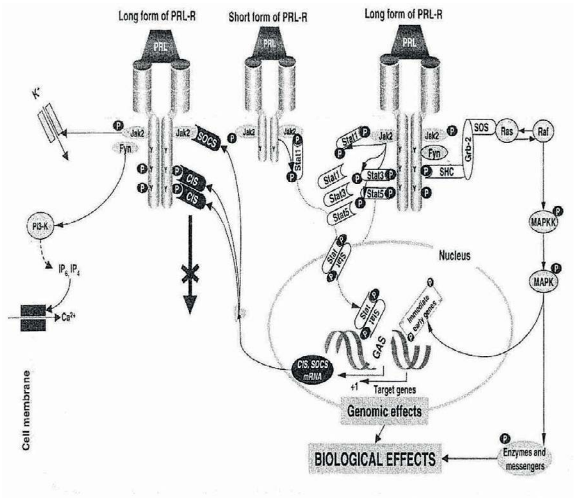

Figure 3: Jak/STAT path activation.

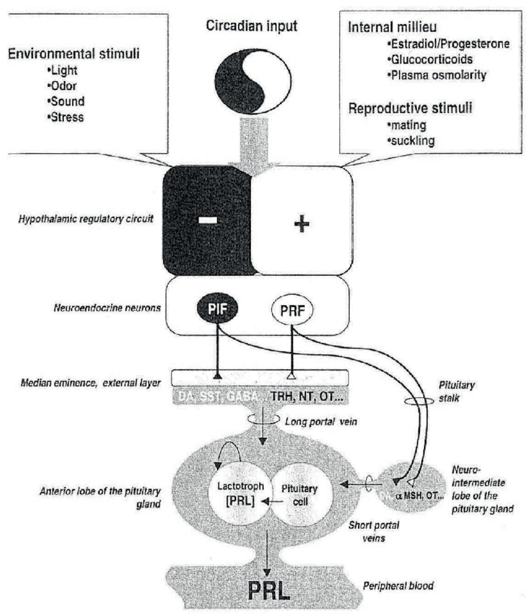

Figure 4: Regulatory factors of prolactin secretion.

[88-92]. We can also have a transposition of the PRLR receptor inside the nucleus, that is accompanied by nuclear reaction such as PKC stimulation.

Biological reactions of prolactin in men

•Prolactin is of great importance:

~ In reproduction (there is negative correlation between sperm and prolactin levels). In increased secretion of prolactin situations hyperprolactinaemia acts suspensory in secretion of gonadotropin affecting the testes function [93]. Prolactin and receptors also express in the cellular epithelium of prostate. Their levels grow after a therapy with androgens. So, having autocrine or paracrine action they act like a growth factor or protective factor for the prostate epithelium cells [94]. In a study that concerned men's fertility, there are a 20% percentage of prolactin receptors in sterile men. This is not happening due to the couple's relationship, while in the 2 subsequent studies, the first one had no prolactin effect in fertility and the other showed that the receptors of prolactin are found in 10% of sterile men [95-100]. From the fertile I only 40% had possibility for a successful first pregnancy.

~ The role of prolactin in paternal care has been studied mainly on fish and birds but not so extensively on mammals, but it is not the only factor [101-106]. Men that use a bromocriptine therapy reducing the inside production of prolactin show decreased paternal care in contrast with the witnesses, at the same time they showed a level of reproduction success. Men parents have higher concentrations of prolactin than men who aren't parents. This fact is confirmed by the fact that there is an increasing trend of prolactin two weeks before the birth [107-109].

~ In the homeostasis of inner environment via effects on the immune system, the osmotic balance and angiogenesis [110]. Prolactin is a common hormonal mediator of nervous, endocrine and immune systems. Nagy and Berczi after studies found waning of immunity (cellular and lymphatic), after suppression of prolactin secretion by bromocriptine or in hypophysectomized animals [111-115].

Prolactin plays an active role in the transport of liquid and electrolytes through the intestinal mucosa (gut epithelial cells). The blood vessel growth is inhibited by prolactin 16KD. Capillary endothelial cells are found high-affinity receptor with prolactin 16-KD [116-119].

Of course, recently was found that human prolactin has antigenic properties. Although a normal interpretation has not been attributed to these opposing studies, they appear to have a significant therapeutic use as a local inhibitor of tumourigenesis or vice versa, a pathological effect on vascularization failure [120,121]. The secretion of prolactin in cellular levels introduced sexual dimorphism. The men secreted elapsed (discontinuous standard secretion). Increased concentration is the plasma prolactin during sleep. Men present a lesser extent prolactin secretion (amplitude) than women [122-125].

Factors that Regulate the Secretion of Prolactin

Figure 4 shows the main regulatory factors of prolactin secretion. External stimuli such as light, sound, odor, affect the secretion of prolactin, reducing it. The secretion is increased in bed and after any emotional or organic stress [126-129].

Secretion is inhibited by dopamine, which acts through receptors D2 in lactogen cells. Receptors D2 is connected to a protein G inhibiting the stimulation of adenylate cyclase and thus inhibiting the production of cAMP [130-135].

On the contrary, the biosynthesis of prolactin is stimulated not only from the hypothalamus peptides TRH and VIP but also the angiotensin 2 [136-139]. VIP acts through the receptors that increase the cAMP. It is located in the pituitary, involving in autocrine and paracrine action in the production of prolactin. Medicine that reduces the action and the secretion of dopamine stimulates the secretion of prolactin.

Conclusion

Prolactin is present in men but has not yet got a clear role. It is a field for investigation. Hypersecretion of prolactin in men has been associated with decreased sexual desire, infertility, reduction of testosterone and erectile dysfunction. But recent studies have also correlated low levels of prolactin in men with sexual disorders and psychological fluctuations.

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