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Invited review article

Prolactin and adipose tissue

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ABSTRACT

The pituitary lactogenic hormone prolactin (PRL) exerts various physiological actions in humans and rodents via its binding to a membrane receptor. Beside its role in lactation and reproduction, accumulating evidence suggests that PRL has a crucial impact on energy balance by acting on two key players, the pancreas and the adipose tissue. Adipose tissue is now recognized as an endocrine organ and its metabolic activity appears to play an important role in pathophysiology such as obesity and diabetes. White adipocytes store excess of energy in the form of triglycerides for future need while brown adipocytes metabolize lipids and glucose to produce heat, highlighting their different metabolic functionality. The plasticity of white adipose tissue, by the emergence of beige adipocytes, appears to be essential in energy homeostasis. PRL receptor deficient mice provided direct evidence that PRL signaling is involved in the regulation of adipogenesis affecting energy balance and metabolic adaptation most notably during development. Moreover, it was demonstrated that PRL signaling participates to brown adipose tissue differentiation and function, opening novel understanding of hormonal regulation of energy balance. This review summarizes our current knowledge about PRL signaling and its role on adipose tissue.

1. Introduction

Principally produced by the pituitary lactotroph cells, prolactin (PRL) can also be synthesized by other extra-pituitaries tissues. PRL is therefore recognized as acting like an endocrine, paracrine and autocrine factor. Its effects are produced by binding to a membrane receptor (PRLR) which is ubiquitously expressed, conferring to PRL a large potential of action. Indeed, roles of PRL are multiple and are divided into several categories: reproduction, osmoregulation, immunoregulation, growth and development and metabolism. We will focus this review on the metabolic role of PRL, in particular the one that it plays on adipose tissue.

2. Prolactin

2.1. Structure and regulation

Prolactin is a polypeptide hormone/cytokine identified more than 80 years ago as a pituitary factor that stimulates mammary gland development and lactation [1]. PRL is mainly secreted by lactotroph cells of the anterior pituitary but is also synthesized by a number of extra-pituitary sources including the mammary gland, the uterus, the lymphocytes and the adipose tissue in humans and rodents. A very recent finding provided the first demonstration that PI3K-Akt pathway regulated the synthesis and secretion of autocrine PRL in the mouse mammary gland [2]. However, the regulation of extrapituitary PRL release has been studied mainly in human cells and tissues since there are no suitable rodent models. Belonging to the PRL/growth hormone (GH)/placental lactogen (PL) family protein, PRL is considered as a cytokine on the basis of molecular and functional evidence [3].

The *prl* gene exists in all vertebrates and contains 5 exons and 4 introns for a length of 10 kb. At a transcriptional level, this gene is driven by two distinct promoters. A proximal one, described as the pituitary promoter, and another one, referred as the extra pituitary promoter containing the extra-non coding exon 1a. Depending on promoter usage, the mRNAs differ in length by 134 bp but both encode a prehormone of 227 amino acids (aa) including a signal peptide of 28 aa. It drives the expression of a 23 kDa mature polypeptide (199 aa) which can undergo posttranslational modifications [3].

PRL can be positively and negatively regulated at the transcriptional level but its secretion can also be controlled. Indeed, PRL secretion is affected by numerous factors provided by the environment and the internal milieu. The most important physiological

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stimuli that trigger pituitary PRL secretion are suckling, stress, pregnancy and increased levels of ovarian steroids, primarily estrogen. On the opposite, PRL release inhibition is mainly controlled by dopamine from hypothalamus acting through its D2 receptor present at lactotroph cells surface [4].

2.2. Prolactin receptor (PRLR)

PRL acts on cells by binding to its membrane receptor, the PRL receptor (PRLR) which belongs to the class I cytokine receptor superfamily. PRLR possesses three major structural domains, an extra-cellular (ligand binding) domain, a single-pass transmembrane chain and an intra-cellular domain (IC). Nevertheless, several isoforms of PRLR were identified with different length of IC domain in humans and rodents [5].

A unique gene containing several promoters for tissue-specific usage encodes PRLR. A differential RNA splicing or post-translational cleavage is at the origin of the different PRLR isoforms often identified as short, intermediate and long isoforms. A soluble isoform has also been identified but its role remains elusive [6].

The level of PRLR proteins and the different expressed isoforms vary since they are present in almost all tissues and in a number of cells along fetal life. The expression of all isoforms has been shown to vary as a function of the stage during life like lactation, pregnancy or estrous cycle [1,7]. It is important to note that PRLR not only binds PRL but it also binds the placental lactogens and the primate growth hormone. PRLRs lack enzymatic activity and they are therefore associated with a number of kinases.

2.3. Mechanism of action

The first experiments described an activation of PRLR triggered by its dimerization which was ligand-dependent. Under these conditions, proximity of two receptors allowed the tyrosine Janus Kinase 2 (JAK-2) transphosphorylation of the IC domain, starting point of signaling pathways. More recently, the PRLR, as many cytokine receptors (if not all), was described as present in a pre-assembled form at the cellular plasma membrane. Indeed, it was shown that PRLR was constitutively homodimerized at the membrane (or heterodimerized when long and short isoforms were co-expressed in the same cell). Mutational and structural studies of PRL have identified two binding sites, each able to interact with one receptor chain [8]. Thus, the activation of PRLR involves the two sites 1 and 2 of the hormone which bind to two PRLR molecules and induce a conformational change in the IC region triggering intracellular signaling. It remains possible that PRLR activation occurs through both mechanisms [6,9]. These two hypotheses support the role of the IC domain as the key player in the initiation of the signal transduction. Indeed, the proximal region of IC domain is constitutively associated with JAK2 and ligand binding to the receptors triggers the merge of the two JAK2 molecules. JAK2 transphosphorylation occurs and phosphorylates PRLR on tyrosine residues located on the cytoplasmic tail [4].

2.4. Signaling pathways

Phospho-tyrosines of the C-terminal part of PRLR are required for signaling pathways because they are potential binding sites for transducer molecules containing SH2 domain. Several signaling cascades are associated with PRLR activation (Fig. 1). The classical pathway described is the JAK/Signal Transducer and Activator of Transcription (STAT) one. Among eight members in the STAT family, four have been identified as PRLR transducer proteins, STAT1, 3, 5a and 5b. SH2 domain of STATs binds to PRLR phospho-tyrosines and then STAT molecules are phosphorylated by JAK2 associated to PRLR. The phosphorylated STATs dissociate from the receptors and dimerize with another phosphorylated STAT. Finally, the STAT dimer translocates to the nucleus where it activates transcription of the PRL target genes.

Other pathways are described to occur after PRLR activation as the mitogen-activated protein kinase (MAPK) pathway. Docking proteins are recruited to phospho-tyrosines via their SH2 domain and then adapter proteins allow the recruitment of the Ras/Raf/MAPK cascade. It has also been shown that PRL could activate other kinases pathways such as members of Src kinase family like c-src and Fyn. This pathway might drive the recruitment and the phosphorylation of IRS1 to induce PI3K cascade [4].

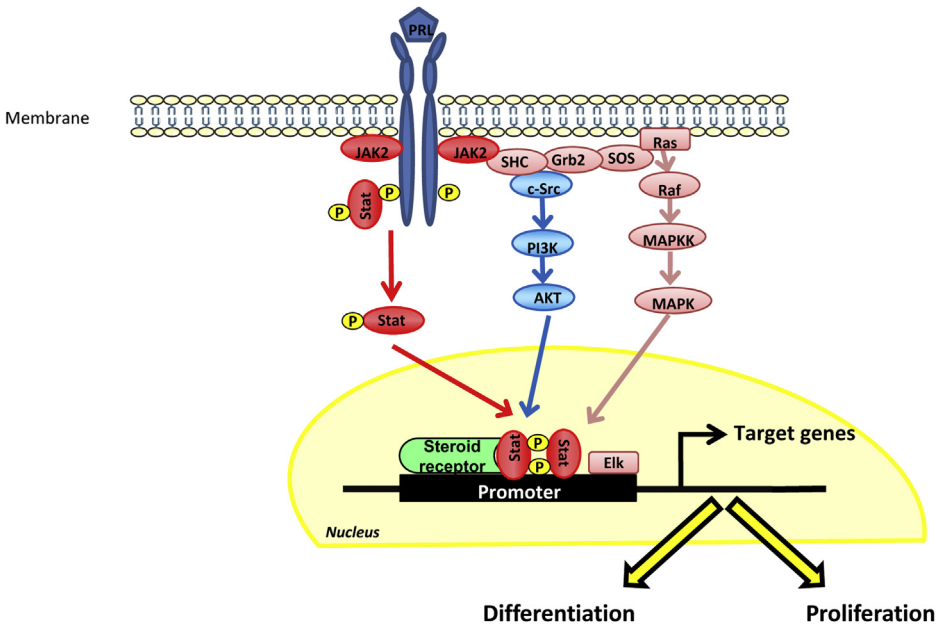

Fig. 1. Prolactin signaling pathways. Ligand binding induces activation of the PRLR triggering several signaling cascades. The main pathway involves the tyrosine kinase Jak2, which in turn activates members of the Stat family (Stat1, 3 or 5a/b). The MAPK and PI3K pathways are other important cascades activated by the PRL.

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