Review

MOLECULAR METABOLISM

PI3K signaling: A key pathway in the control of sympathetic traffic and arterial pressure by leptin

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ABSTRACT

The adipocyte-derived hormone, leptin, is a master regulator of energy homeostasis. Leptin action in the central nervous system also contributes to arterial pressure regulation through its capacity to increase renal sympathetic outflow. The accumulating evidence pointing to a key role for leptin in the adverse sympathetic and cardiovascular consequences of excessive adiposity highlight the importance of understanding the mechanisms underlying the sympathetic and cardiovascular effects of leptin. The ability of the leptin receptor to stimulate various intracellular pathways allows leptin to regulate physiological processes in a specific manner. In this review, we examine the role of the PI3K pathway emanating from the leptin receptor in mediating the sympathetic and arterial pressure effects of leptin. We also discuss the relevance of PI3K signaling for obesity-induced hypertension through its role in mediating selective leptin resistance.

Keywords Leptin; PI3K; Autonomic nervous system; Cardiovascular function; Energy homeostasis

1. INTRODUCTION

The importance of the central nervous system (CNS) in maintaining homeostasis is now well recognized. The CNS influence on physiological processes occurs through efferent humoral and neural signals. For this, the brain controls the release of key hormones and the activity of the sympathetic and parasympathetic branches of the autonomic nervous system. In turn, the brain receives a myriad of information from peripheral tissues about their status. The adipocyte-derived hormone, leptin, is an example of the afferent input that informs the CNS about the status of body's energy reserves [1]. Plasma levels of leptin are proportional to fat stores and changes in circulating leptin levels are detected by the CNS which then adjusts energy intake and expenditure, the later mediated through the sympathetic nervous system [2]. Indeed, CNS action of leptin increases sympathetic activity of the nerves subserving various tissues involved in metabolic control such as brown adipose tissue (BAT), white fat pads, liver and skeletal muscle [3,4].

Besides its critical role in the control of energy homeostasis, leptin action in the CNS is implicated in the regulation of a number of physiological functions including glucose metabolism, sexual maturation and reproduction, the hypothalamic–pituitary–adrenal system, thyroid and growth hormone axes, angiogenesis and lipolysis, hematopoiesis, immune or pro-inflammatory responses, and bone remodeling [5–9]. Leptin also contributes to the regulation of arterial pressure with important pathophysiological implications in obesity-associated hypertension [3]. Leptin impacts arterial pressure through its ability to increase sympathetic nerve activity subserving cardiovascular organs such as the kidney. In addition, it is well established that leptin resistance, particularly with respect to its anorexigenic action, contributes to obesity development [2,9]. However, leptin's sympathetic/cardiovascular effects are preserved under obese conditions. This selectivity in leptin resistance appears to contribute to the obesity-associated sympathetic overdrive and hypertension [10,11]. In this review, we will discuss the molecular pathways triggered by leptin binding to its receptor and the importance of the PI3K signaling in mediating the sympathetic and cardiovascular actions of leptin in health and disease.

2. LEPTIN RECEPTOR (LEPR) SIGNALING

The leptin receptor belongs to the class 1 cytokine receptor family [12]. Despite the existence of many splice variants of the leptin receptor, the long LepRb isoform which is lacking in *db*/*db* mice is the most relevant for the physiological actions of leptin. A large number of signaling pathways have been associated with the LepRb. In the CNS, leptin binding to LepRb leads to the activation of at least four major signaling pathways. These four signaling pathways have been shown to be involved in mediating the effects of leptin on energy homeostasis (Figure 1).

Binding of leptin to LepRb triggers a conformational change in the receptor which promotes its activation by autophosphorylation through Janus kinase (Jak) 2 tyrosine kinase. Activated Jak2 then phosphorylates three tyrosine residues within the LepRb at position 1138, 1077 and 985. Each of these tyrosine residues mediates the activation of distinct downstream signaling pathways [13,14]. Phosphorylated Tyr_{1138} promotes the recruitment and phosphorylation of signal transducer and activator of transcription (STAT) 3, whereas phosphorylated Tyr_{1077} binds and phosphorylate STAT5 [15]. Activated STAT3 and STAT5 translocate to the nucleus to modulate gene transcriptional with implications for physiologic regulation [16]. Interestingly, these two transcription factors appear to be differentially

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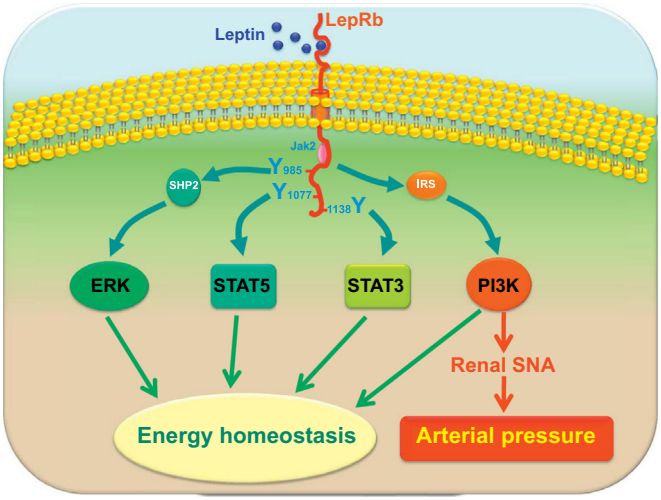

Figure 1: Intracellular signaling pathways regulated by the leptin receptor (LepRb) in the central nervous system. Four primary intracellular signaling pathways emanates from LepRb: signal transducer and activator of transcription (STAT) 3 and STAT5 proteins, the extracellular signal-related kinase (ERK) and phosphoinositol-3 kinase (PI3K). Each pathway is activated by phosphorylation of specific tyrosine residues in ObRb. The four signaling pathways are implicated in leptin regulation of energy homeostasis. In contrast, leptin control of renal sympathetic nerve activity (SNA) and arterial pressure occur through PI3K signaling.

engaged by leptin to control physiological processes. Indeed, mice carrying a mutation at Tyr_{1138} of ObRb, which disrupts leptin-induced STAT3 activation, are severely obese and hyperphagic, but in contrast to the mice lacking leptin or LepRb these mice remain fertile and are less diabetic [6]. Conversely, knock-in mice bearing a mutation at Tyr_{1077} of LepRb, which disrupts leptin-induced STAT5 signaling were found to have impaired reproductive function, but exhibited only a modest increase in adiposity [58].

The phosphorylated Tyr_{985} of LepRb leads to the recruitment and binding of the COOH-terminal SH2 domain of the tyrosine phosphatase, SHP2, leading to the activation of extracellular signal-related kinase (ERK) pathway [13,14,17,18]. Tyrosine phosphorylation sites on Jak2 also appears to contribute to leptin-induced ERK activation independent from LepRb phosphorylation [13]. Tyr_{985} (and perhaps Tyr_{1077}) also binds suppressor of cytokine signaling-3 (SOCS3) which act as a negative regulator to inhibit STAT3 signaling. Protein tyrosine phosphatase 1B is another negative regulator of LepRb through a direct action to dephosphorylate Jak2 [9,19].

Stimulation of LepRb also promotes the activation of phosphatidylinositol-3 kinase (PI3K) pathway. A role for the PI3K pathway in transducing leptin action was initially identified in vitro using various cell types and confirmed later in vivo. For instance, in C_2C_{12} myotubules, leptin stimulation of glucose transport was shown to be dependent on PI3K pathway [20]. In primary rat hepatocytes leptin was also found to activate PI3K [21]. Moreover, in CRI-G1 insulinoma cells, modulation of K_{ATP} channels activity by leptin was demonstrated to require PI3K signaling [22]. In hypothalamic brain slices, leptin evoked depolarization of proopiomelanocortin (POMC) neurons in a PI3K-dependent manner [23]. Thus, PI3K signaling has been implicated in mediating leptin action in various cell types. The exact mechanism by which LepRb activates PI3K signaling remains unclear, although this appears to involve the insulin receptor substrates [14].

Several downstream mechanisms that would explain the involvement of PI3K signaling in mediating the metabolic effects of leptin have been suggested, including its activation of phosphodiesterase-3B which can then interact with STAT3 [24] or through inactivation of FoxO-1 transcription factor that stimulate POMC neurons while inhibiting Agouti-related peptide (AgRP) neurons [25,26].

3. PI3K SIGNALING AND LEPTIN REGULATION OF ENERGY BALANCE

A number of studies have demonstrated the relevance of PI3K as an underlying mechanism of leptin actions in vivo [24,27]. In rats, peripheral leptin administration was found to activate PI3K in the hypothalamus, a region of the brain known to be critical for the metabolic effects of leptin [27]. Moreover, pre-treatment with inhibitors of PI3K abolished the anorectic response induced by leptin [27,28].

The use of genetically modified mouse models has been critical in establishing the importance of PI3K signaling in the long-term regulation of energy homeostasis and in mediating the metabolic effects of leptin. In addition, the genetically engineered mouse models allowed the identification of the neuronal populations and brain regions where PI3K mediates leptin effects. For instance, a conditional knockout mouse model in which PI3K activity was enhanced specifically in LepRb-expressing cells exhibited increased energy expenditure leading to less adiposity provided strong evidence regarding the metabolic consequences of chronic enhancement of PI3K in LepRb-containing neurons [25]. Other studies used loss of function approach to assess the importance of PI3K signaling in specific neuronal populations of the hypothalamus. Such approach revealed that targeted disruption of PI3K signaling in POMC neurons altered the ability of leptin to decrease food intake in mice [23]. On the other hand, disrupting PI3K in the AgRP neurons rendered the mice leptin-sensitive, lean and resistant to diet-induced obesity [29]. Together, these findings demonstrate that interference with PI3K pathway in a subset of hypothalamic arcuate nucleus neurons alters the ability of leptin to regulate food intake and energy homeostasis. These obsertvations are also consistent with the differential effects of leptin on PI3K activity in POMC and AgRP neurons. Indeed, in POMC neurons leptin stimulate PI3K activity whereas leptin action in AgRP neurons inhibits PI3K activity [30].

A recent study demonstrated the importance of PI3K signaling in the ventromedial hypothalamic nucleus and its involvement in the long-term effects of leptin on energy homeostasis. Indeed, mice with specific reduction in PI3K activity in the ventromedial hypothalamic neurons exhibited resistance to the anorectic effects of leptin associated with

