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PI3K signaling: a molecular pathway associated with acute hypophagic response during inflammatory challenges

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Abstract

Energy balance has in the hypothalamus a central component of integration of food intake and energy expenditure. An accumulating body of evidence indicates that energy homeostasis is largely affected by inflammatory challenges. Severe undernutrition caused by exacerbated inflammatory response may lead to cachexia. On the other hand, prolonged low-grade inflammation such as that observed in obesity and metabolic syndrome, raises the risk for the development of diabetes and heart diseases. Changes in circulating insulin and cytokines such as leptin, interleukins and tumor necrosis factor, as well as changes in their action in the hypothalamus drive the inhibition of food consumption during inflammation. The molecular pathways associated with these responses have only started to be unraveled. One potential candidate is the PI3K signaling, an important player in distinct hypothalamic neurons that control food intake. This study presents an overview of the current knowledge about PI3K role on cytokines and insulin signaling in the hypothalamic regulation of feeding during inflammation.

Keywords

Inflammation; Hypothalamus; Metabolism

1- Introduction

Organism survival basically rests on the ability to store energy and to fight infection. For that reason, metabolic and immunological systems are the most elementary necessities common to a variety of species. Several hormones, signaling molecules, cytokines and transcription factors act in both metabolic and immune systems. Acute inflammatory states are often associated with a significant loss of appetite and body weight as a result of

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increased cytokine production [Socher et al., 1988; Grunfeld et al., 1989; Langhans 1996; Johnson, 1998; Borges et al., 2007; 2011]. Interleukin (IL) 1β, IL-6, and tumor necrosis factor-α (TNF-α) classically secreted by activated mononuclear myeloid cells, are found in the endocrine system and brain [Johnson, 1998]. Central or peripheral injection of these molecules inhibits food consumption whereas their antagonism abolishes the hypophagia induced by inflammatory stimuli [Socher et al., 1988; Grunfeld et al., 1989; Johnson, 1998]. Compelling evidence has demonstrated that these pro-inflammatory cytokines act on adipocytes and induce secretion of leptin [Grunfeld et al., 1996; Kurosawa et al., 2015]. Leptin is a cytokine-like protein whose activity to reduce food intake and increase energy expenditure is exerted primarily through the hypothalamus and potentially other brain sites [Scott et al., 2009].

The mechanisms regulating energy intake and expenditure during inflammation have being unveiled in studies using the lipopolysaccharide (LPS) component of the Gram-negative bacteria cell wall. LPS activates innate immune system and induces cytokine expression and secretion [Langhans 1996; Johnson, 1998]. Among the cytokines, leptin secretion is stimulated by LPS making it reasonable to hypothesize that leptin is an additional player in the inflammation-induced hypophagia [Sarraf et al., 1997; Berkowitz et al., 1998; Borges et al., 2011]. By utilizing a neutralizing antiserum against rat leptin, Sachot and coworkers [2004] found a reversal of LPS-induced appetite suppression and weight loss, in parallel with an inhibition of the LPS-induced IL-1β and IL-1 receptor (IL-1ra) mRNA expression in the hypothalamus. These findings pointed out to leptin as an adjuvant factor by which inflammatory peripheral anorexigenic signal is conveyed to appetite-regulating centers in the hypothalamus. Inflammatory cascades have also been shown to be linked to insulin secretion and the development of insulin resistance [Wellen and Hotamisligil, 2005; Konner and Bruning, 2010; Jia et al., 2014]. Increased insulin secretion by LPS and attenuation of LPS-induced hypophagia in insulin-deficient streptozotocin treated rats suggest a role for insulin in the endotoxemic suppression of food consumption [Kim et al., 2007].

Although independent, metabolic and immune pathways are closely linked, suggesting the existence of an integrator signal capable of ensuring the maintenance of energy homeostasis during metabolic or immunological challenges. In this regard, the phosphoinositide 3- kinase (PI3K) pathway, largely activated by the above mentioned players, emerges as a potential molecular integrator of metabolic and inflammatory signals in energy balance. The new findings supporting this model are highlighted in this review.

2 - Hypothalamic control of food intake during inflammation

The precise brain circuitry underlying innate immunity-central nervous system (CNS) interactions in the context of suppression of food intake during inflammation remains unsettled. Two key neuronal populations in the arcuate nucleus (ARC), comprised by the orexigenic neuropeptide Y (NPY)/Agouti-related peptide (AgRP) neurons and the anorexigenic proopiomelanocortin (POMC) neurons are targets of peripheral leptin and insulin [Elmquist et al., 1999; Schwatz, 2006; Flak and Myers, 2015]. Their actions result in different acute cellular reponses: leptin depolarizes POMC while hyperpolarizes NPY/AgRP neurons, and insulin hyperpolarizes both POMC and NPY/AgRP neurons [van den Top et

al., 2004; Konner et al., 2007; Hill et al., 2008; Williams et al., 2010; Gavello et al., 2016]. Although the metabolic control of energy balance by the ARC is well stablished, how the ARC neurons behave in response to immune challenge is still unclear. Upon binding to the Toll like receptor 4 (TLR4), LPS from invading pathogens promotes IL-1β and TNF-α secretion [Langhans, 1996]. However, the lack of evidence for TLR4 expression in ARC neurons in addition to the scarcity of conclusive studies on the direct effects of the endotoxin over hypothalamic neurons, precludes meaningful assumptions that LPS would directly act on neuronal populations to inhibit feeding. Microglial cells, known for a long time as central sentinels of brain injury, express TLR4 and produce cytokines under LPS stimulation [Milanski et al., 2009; Saijo and Glass, 2011; Borges et al., 2012; Fan et al., 2012]. These findings support the idea of microglia acting to inhibit food intake under endotoxin challenges. LPS would centrally stimulate cytokines secretion by microglia which in turn would act in hypothalamic neurons to suppress feeding. In line with this, a study defining the transcriptome of the hypothalamic leptin responsive neurons [Allison et al., 2015] describes the expression of *Il* and *Tnf* receptors genes in LepR neuronal population, suggesting that leptin responsive cells are also reactive to other proinflammatory cytokines and are likely to share intracellular signaling pathways.

In order to examine whether activated microglia alters ARC neuronal function, Reis et al. [2015] dissected the functional consequences of TLR4-mediated microglia activation on the firing activity of POMC and NPY/AgRP neurons. Interestingly, acute exposure to LPS evoked a predominantly excitatory response in POMC and an inhibitory response in NPY/AgRP neurons. The LPS effects in NPY/AgRP, but not in POMC neurons, were blocked when microglia function was inhibited. The inhibition of the orexigenic NPY/AgRP neurons evoked by the activation of ARC microglial TLR4 advocates for a likely role of microglia in the hypothalamic modulation of food intake in inflammation.

Recent chemo- and opto-genetic studies have emphasized the protagonism of NPY/AgRP neurons in the regulation of food intake [Atasoy et al., 2008; Krashes et al., 2011]. Activation of AgRP neurons rapidly stimulates vigorous feeding whereas its inhibition or ablation suppresses food consumption [Krashes et al., 2011, Liu et al., 2016]. Considering that central AgRP injection blunted the hypophagic effect of LPS [Sartin et al., 2008] it has been postulated that inflammatory hypophagia might be caused by lack of AgRP action. Using pharmacogenetics and the DREADD (designer receptors exclusively activated by designer drug) technique Liu and colleagues [2016] attempted to delineate the exact neural circuits linking LPS-induced hypophagia to the AgRP neuronal pathway. They assessed if activation of AgRP neurons attenuates LPS-induced hypophagia. Data from pharmacogenetically activated AgRP neurons in LPS-treated mice indicate that the absence of AgRP action is unlikely to play a role in inflammation-induced hypophagia, given that LPS similarly reduced food intake in both AgRP-DREADD negative or positive mice. Therefore, AgRP-DREADD neuronal activation is not sufficient to prevent LPS hypophagia in mice [Liu et al., 2016].

In this regard, stimulation of the ARC POMC neurons could be considered a contributing factor to LPS-caused hypophagia. Nevertheless, studies found no detectable changes in LPS-induced c-Fos expression in POMC neurons [Gautron et al., 2005; Liu et al., 2016]. Previous

reports by our group and others have described no changes in POMC mRNA expression in the ARC of rats treated with LPS [Gautron et al., 2005; Borges et al., 2007]. Nonetheless, a higher number of cells expressing phosphorylated signal transduced and activator of transcription 3 (STAT3) in the ARC has been observed after LPS treatment [Borges et al., 2011]. STAT3 is an intracellular mediator linking inflammation and metabolism. In ARC cells, leptin and other inflammatory cytokines activate the Janus kinase (JAK)2/STAT3 signaling pathway, that induces the expression of POMC mRNA [Borges et al., 2011; Flak and Myers, 2015].

In a recent study, we have found LPS-induced pSTAT3 in ARC LepR neurons [Borges et al., 2016]. However, LPS failed to acutely (after 2 h) reduce food intake in leptin-deficient mice, although it did reduce food intake in later periods of endotoxemia [Borges et al., 2016]. As previously reported, body weight was similarly decreased in wild type and *ob/ob* mice [Faggioni et al., 1997]. Interestingly however, *ob/ob* mice presented a delayed LPS-induced pSTAT3 expression in the ARC, leading us to postulate that leptin-induced pSTAT3 expression in the ARC is not required for the initial LPS hypophagia. On the other hand, pSTAT3 likely induced by other inflammatory cytokines in the ARC may be important for the hypophagia over the course of the endotoxemia. Of note, IL-1β activates and depolarizes POMC neurons in the ARC, indicating that this cytokine participates in the hypophagia during inflammation by acting in ARC neurons [Scarlett et al., 2007]. The precise role of POMC neurons in LPS-induced hypophagia remains inconclusive and further studies are warranted.

The regulation of energy homeostasis by non-neuronal cell types has been described in several studies. Astrocytes, the most abundant cell type in the CNS, are activated in response to states of positive and negative energy balance, such as obesity and fasting, regulating neuronal activity by altering synaptic function [Buckman and Ellacott, 2014]. Under endotoxemia or high fat diet, astrocytes have essential role in the central innate immune response, where they undergo morphological and proliferative changes, in a process referred to as astrogliosis [Borges et al., 2012; Thaler et al., 2012; Buckman and Ellacott, 2014]. Studies have demonstrated that astrocytes express leptin receptors [Hsushou et al., 2009; Kim et al., 2014] and that leptin signaling in astrocytes plays a role in energy homeostasis [Kim et al., 2014; Wang et al., 2015]. Kim and coworkers [2014] utilizing a mouse model with tamoxifen- inducible deletion of leptin receptors from astrocytes demonstrated that time-specific ablation of leptin receptor led to altered astrocyte morphology and synaptic inputs onto hypothalamic neurons involved in feeding control. The ability of leptin to reduce food intake was partially inhibited following the loss of astrocytic leptin-receptor signaling, suggesting that these cells play an active role in hypothalamic synaptic remodeling and control of feeding by leptin. By combining chemo-genetic approach with cell-type-specific electrophysiology, pharmacology, and feeding assays, Yang et al., [2015] found that astrocyte activation depressed ghrelin-evoked hyperphagia, whereas it facilitated leptin-induced anorexia. On the other hand, astrocyte inactivation potentiated ghrelin-evoked feeding but blunted leptin- induced anorexia. Because of the inhibition of feeding by astrocytes activation, the authors focused on the effects of astrocytes on the firing rate of AgRP neurons. The main findings demonstrated that astrocyte activation negatively

regulates ghrelin-evoked feeding by inactivating AgRP neurons. Studies on the specific role of astrocytes in the suppression of food intake during endotoxemia has yet to be developed.

3 - Cytokines activate the PI3K signaling pathway

Upon binding to TLR4, LPS recruits a diverse array of intracellular signaling pathways. One of these pathways engages in the activation of the PI3K enzyme [Guha and Mackman, 2002; Schabbauer et al., 2004; Borges et al., 2016]. The heterodimeric enzyme PI3K consists of a regulatory (p85) and a catalytic (p110) subunit [Cantley, 2002] and its activation results in the conversion of phosphatidylinositol 4, 5 bisphosphate (PIP2) into phosphatidylinositol 3, 4, 5 triphosphate (PIP3). PIP3 allows for the recruitment and activation of downstream molecules such as AKT, that in turn participates in several cellular responses including cell survival, proliferation and metabolism, regulation of gene expression and cytoskeletal rearrangements [Cantley, 2002]. PI3K/AKT pathway negatively regulates LPS actions in monocytes and macrophages due to inhibition of the expression of inflammatory mediators [Schabbauer et al., 2004; Luyendyk et al., 2007; Weichhart and Saemann, 2008]. Both pharmacological and genetic approaches have shown that blockade of PI3K promotes loss of downstream targets activated by LPS, such as phosphorylation of AKT [Guha and Mackman, 2002; Schabbauer et al., 2004]. In human monocytic cells and macrophages, PI3K inhibition enhances LPS-induced TNF-α expression [Guha and Mackman, 2002; Luyendyk et al., 2007].

One of the main downstream targets of the PI3K/AKT pathway is the mammalian target of rapamycin (mTOR). Studies have identified that mTOR complex 1 (mTORC1) is involved in the regulation of the levels of pro- and anti-inflammatory cytokines produced by innate immune cells. These effects result in inhibition of the pro-inflammatory and stimulation of the anti-inflammatory pathways [Weichhart and Saemann, 2008].

Another crucial PI3K/AKT downstream substrate is the transcription factor forkhead box class O1 (FoxO1), known to inhibit the transcription of targeted genes. PI3K/AKT inhibits FoxO1 via phosphorylation and subsequent nuclear exclusion that in turn releases the expression of targeted genes [Matsumoto and Accili, 2005]. LPS-induced IL-6 and TNF-α production are blunted by the FoxO1-specific siRNA in microglial cell culture, indicating that LPS-triggered inflammatory signaling depends in part on FoxO1 [Dong et al., 2014].

4 - PI3K pathway in the hypothalamus participates in Leptin, Insulin and LPS inhibition of food intake

PI3K signaling has emerged as one of the main pathways through which leptin and insulin alter neuronal excitability in the hypothalamus [Xu et al., 2005; Donato et al., 2010; Gavello et al., 2016; Kwon et al., 2016]. Targeted deletion of PI3K from POMC neurons blunted leptin-induced neuronal activation as well as acute suppression of food intake [Hill et al., 2008; Hill et al., 2009]. Interestingly, a study by Williams et al. [2010] showed both histological and electrophysiological evidence that leptin and insulin act differentially in segregated groups of ARC POMC cells. In agreement, leptin and insulin action to reduce food intake is prevented by PI3K inhibitors, suggesting that the crosstalk between leptin and

insulin in modulating food intake lies in part on PI3K signaling. Whether this crosstalk occurs within a network of cells or within individual neurons still needs to be directly demonstrated [Niswender et al., 2001; Niswender et al., 2003; Schwartz, 2006; Williams et al., 2010].

Studies have shown that the PI3K/AKT downstream molecules FoxO1 and mTOR are cellular fuel sensors whose hypothalamic activity are tied to the regulation of energy homeostasis [Kim et al., 2006; Weichhart and Saemann, 2008]. Under negative energy balance condition, FoxO1 inhibits POMC expression, while stimulates AgRP in the ARC. In response to leptin, FoxO1 is phosphorylated and translocate from the nucleus to the cytoplasm, stimulating POMC expression and inhibiting AgRP, leading to a reduction of the food intake [Kitamura et al., 2006; Kwon et al., 2016]. In turn, activation of mTOR signaling suppresses food intake whereas hypothalamic mTOR inhibition markedly increases food intake [Weichhart and Saemann, 2008]. Of note, mTOR inhibitor attenuates leptin-induced hypophagia and weight loss [Cota et al., 2006]. Investigating how these hypothalamic pathways respond to LPS, Yue et al. [2016] recently found that LPS phosphorylates both mTOR and FoxO1 in the ARC. Central blockade of mTOR pathway with rapamycin attenuated both LPS-induced hypophagia and LPS-induced phosphorylation of FoxO1. These data reinforce the likely role of PI3K pathway in the hypophagia during inflammatory states.

We recently assessed if leptin-mediated PI3K signaling plays a role in LPS-induced hypophagia. PI3K inhibitor prevented hypophagia in mice exposed to endotoxin [Borges et al., 2016]. We further investigated whether genetic deletion of PI3K catalytic subunits in LepR cells has the same effect as the global inhibition. Mice lacking both PI3K p110α and p110β subunits, but not only p110α, selectively in LepR cells showed blunted suppression of food intake by endotoxin [Borges et al., 2016]. Our findings indicate that PI3K via p110β catalytic subunit in LepR expressing cells is required for the acute hypothagic response induced by endotoxemia. LPS-induced AKT phosphorylation in LepR cells in the ARC was attenuated by targeted deletion of PI3K catalytic subunits. Additionally, LPS failed to phosphorylate AKT in the ARC of leptin-deficient mice [Borges et al., 2016]. Taken together, these data demonstrate that the suppression of food intake during an inflammatory challenge depends on PI3K/AKT pathway activated by cytokines and leptin in hypothalamic neurons (Figure 1).

Obesity is considered a state of chronic low-grade inflammation, featured by increased expression of TNF-α and IL-6 from adipocytes in the periphery [Konner and Bruning, 2010], as well as an increase in these cytokines in the CNS [Milanski et al., 2009; Thaler et al., 2012]. TNF-α and IL-6 inhibit serine phosphorylation in the insulin receptor substrate-1 (IRS-1), disrupting insulin signaling transduction and causing insulin resistance [Wellen and Hotamisligil, 2005]. Animal models of obesity induced by high-fat diet show elevated plasma levels of LPS originated from the gut microbiome. These increased levels are sufficient to induce an inflammatory response [Cani et al., 2007]. Given that central and peripheral inflammation are key components in the development of leptin and insulin resistance in obese subjects, studies focusing on the role of PI3K in low-grade inflammation during obesity will potentially constitute an important advance in human's health. At

present, the role of insulin in PI3K-mediated LPS hypophagia has not been investigated and future studies designed to address this topic are invaluable.

5 -PIP3 phosphatase PTEN and downregulation of PI3K pathway in inflammation

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a tyrosine phosphatase engaged in dephosphorylation of PIP_3 into PIP_2 [Tsou and Bence, 2013]. PTEN acts as a downstream negative regulator of both leptin and insulin signaling by directly counteracting PI3K function. Taking advantage of the genetic mouse models of conditional gene deletion, studies have shown that LepR-specific deletion of PTEN results in decreased body weight, adiposity and adipocyte size in mice, in spite of unchanged food intake and energy expenditure [Plum et al., 2007]. However, LepR-specific overexpression of PTEN does not result in obese phenotype in mice. POMC neuron-specific PTEN deletion results in a diet-sensitive increase in body weight and hyperphagia, in a sexual dimorphic dependent mechanism [Plum et al., 2006]. Intriguingly, POMC neuron-specific PI3K deletion results in hyperphagia as well [Hill et al., 2009]. These data suggest that PTEN regulates the activity of the PI3K pathway by triggering multiple effects on energy homeostasis. To determine the effect of genetically increased activation of the PI3K/AKT pathway on LPS-induced cytokine expression, Luyendyk et al. [2008] used endotoxemic mice with PTEN deletion in macrophages. LPS induction of TNF-α and IL-6 expression was reduced in mice with PTEN-deficient macrophages, confirming that activation of the PI3K/AKT pathway inhibits LPS effects on cytokine production. Despite a clearly defined intracellular role for PTEN opposing leptin- or insulin-stimulated PI3K signaling, its ability to regulate metabolism during inflammatory challenges remains to be addressed.

6 – Estrogen and PI3K pathway in the hypothalamus: a potential crosstalk between leptin and inflammatory signals

Among the numerous signals that affect the glia-neuron crosstalk, gonadal hormones have received singular attention. Gonadal steroids, known to regulate reproduction, are found to play a role in neuroprotection, energy homeostasis and regulation of diverse cellular, molecular and functional parameters in both neurons and astrocytes [Zhu et al, 2015; Acaz-Fonseca et al., 2014; 2016]. Central inflammatory responses are influenced by sex steroids. For example, microglial cells isolated from male, but not female rats, exhibit an enhanced mRNA expression of IL-1βb after exposure to LPS [Loram et al., 2012]. Sexual dimorphisms regarding the number and morphology of astrocytes have also been reported [Kuo et al., 2010]. Estrogen-induced synaptic remodeling is characterized by morphological changes in ARC astrocytes [Acaz-Fonseca et al., 2016], which may modulate the activity of ARC neurons.

In a recent report, Zhu et al. [2015] demonstrated that estrogen acts upon estrogen receptor α (ERα) to inhibit feeding in female mice, and the anorexigenic effects of estrogens are blunted in mice with selective deletion of ERα in POMC neurons. Treatment with ERα agonist stimulated PI3K pathway specifically in POMC neurons. In turn, mice with deletion

of PI3K pathway in POMC neurons show attenuated ERα agonist-induced activation of POMC neurons, as well as attenuated estrogen-induced inhibition of food intake. Taken together, these data indicate that an ERα -PI3K cascade in POMC neurons mediates the hypothalamic suppression of food intake.

Obesity affects both men and women, however premenopausal women are less susceptible to development of obesity-associated metabolic disturbances than males. Moreover, the incidence of obesity increases significantly following menopause [Shi et al, 2009]. Taking advantage of the high fat diet (HFD) experimental model to induce obesity, Morselli et al. [2014] analyzed the sexual dimorphic response in male and female mice. Although males and females showed similar weight gain after HFD, male mice presented higher levels of TNF-α, IL-1β and IL-6 in the hypothalamus than female mice. There was an inverse correlation between ERα and proinflammatory cytokine levels, suggesting a protective role of estrogen against central inflammation during obesity. It is possible that the protective effects of estrogen against central inflammation have an impact on food intake during inflammatory challenges other than obesity, but these responses remain to be addressed

7 - Concluding remarks

Molecules such as IL-1β, TNF-α, leptin and insulin have a role in both immunological and metabolic systems, which are clearly cohesive. Due to their potential crosstalk, the PI3K pathway emerges as an important integrative component for their action in the hypothalamus. PI3K/AKT/mTOR/FoxO1 pathways, widely associated with TLR4 actions in the immune system, are now found to be equally important for the metabolic control during infection/inflammation. The present review aimed to highlight the role of PI3K pathway to better understand the mechanisms underlying energy balance regulation in states of chronic low-grade inflammation such as in obesity or during cachexia, characterized by excessive immune response. Inhibition of severe acute hypophagia (mediated in part by PI3K) may contribute to the prevention of harmful undernutrition during bacterial infections and to warrant organism survival.

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Highlights

- PI3K pathway is commonly activated by leptin, insulin and endotoxin in the hypothalamus
- Inhibition of PI3K reverses the hypophagia induced by leptin, insulin and endotoxin
- PI3K is a potential integrator of the metabolic and immunological responses to suppress food intake

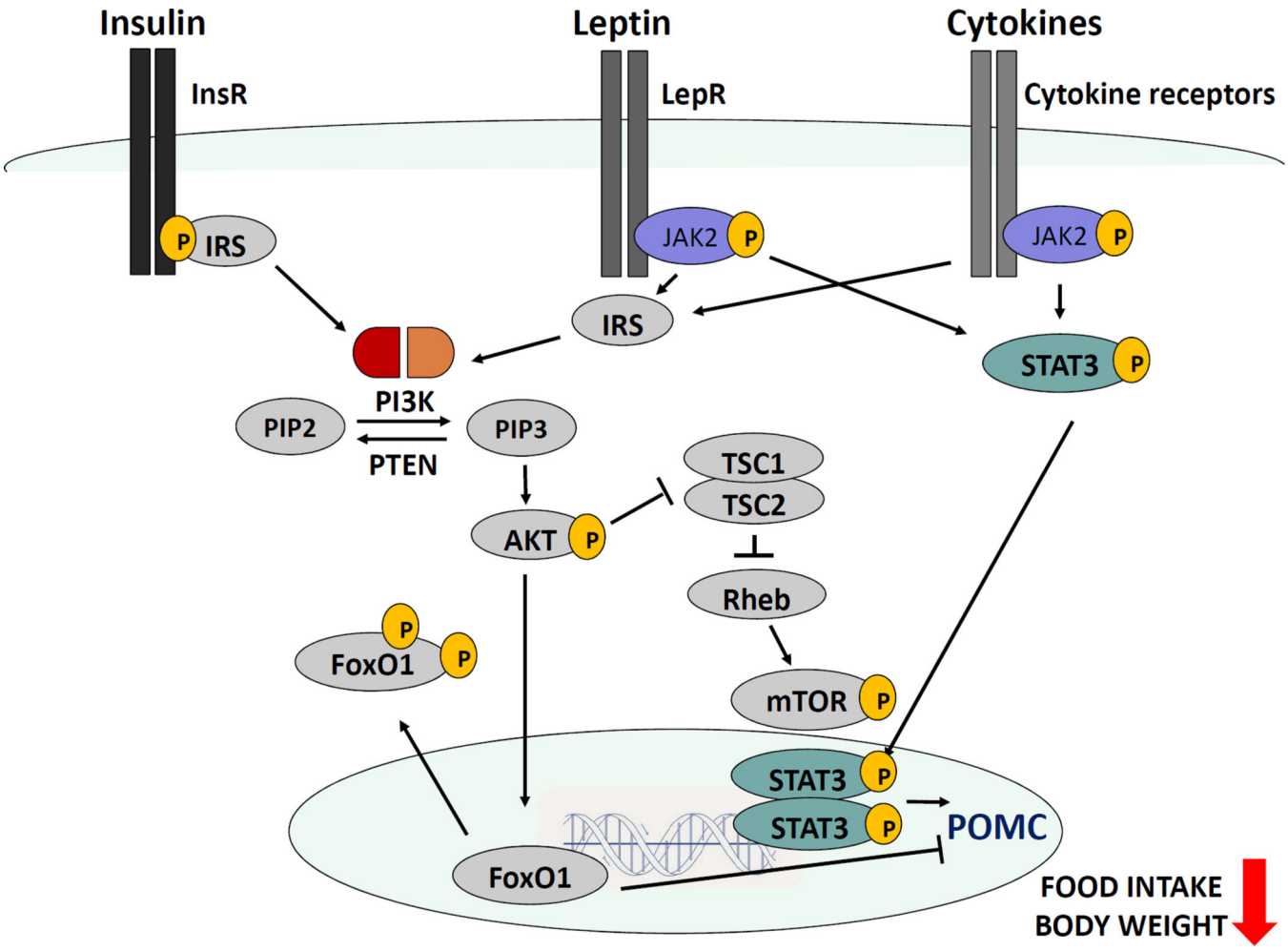

Figure 1. Proposed model for PI3K regulation of food intake and body weight in hypothalamic cells during endotoxemia

LPS stimulates insulin and leptin secretion in peripheral tissues as well as secretion of other pro-inflammatory cytokines in microglial cells and periphery. Insulin, leptin and cytokines bind to their receptors in hypothalamic neurons in the arcuate nucleus (ARC) and acutely activate the PI3K/AKT/mTOR/FoxO1 pathway. Simultaneously, leptin and other cytokines trigger the activation of JAK-STAT3 pathway. The final step in both pathways is the stimulation of transcription of POMC, which in turn inhibits food intake and promotes a reduction of the body weight. Abbreviations: InsR: insulin receptor, Lepr: leptin receptor, IRS: insulin receptor substrate, JAK2: Janus kinase 2, STAT3: signal transducer and activator of transcription 3, POMC: proopiomelanocortin, PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase, PIP3: Phosphatidylinositol 3,4,5-trisphosphate, PIP2: Phosphatidylinositol 4,5-bisphosphate, PTEN: phosphatase and tensin homolog deleted on chromosome 10, AKT: protein kinase B, FoxO1: transcription factor forkhead box class O1, TSC1/2: Tuberous sclerosis proteins 1 and 2, Rheb: Ras homolog enriched in brain, mTOR: mammalian target of rapamycin.