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Hypothalamic inflammation and the central nervous system control of energy homeostasis

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ABSTRACT

The control of energy homeostasis relies on robust neuronal circuits that regulate food intake and energy expenditure. Although the physiology of these circuits is well understood, the molecular and cellular response of this program to chronic diseases is still largely unclear. Hypothalamic inflammation has emerged as a major driver of energy homeostasis dysfunction in both obesity and anorexia. Importantly, this inflammation disrupts the action of metabolic signals promoting anabolism or supporting catabolism. In this review, we address the evidence that favors hypothalamic inflammation as a factor that resets energy homeostasis in pathological states.

1. Introduction

In response to environmental variations, any physiological system strives to return to a previously established set point in a process described as homeostasis. This equilibrium is achieved through a robust net of signals that emanate from the endocrine and neural system. Appreciable advances have been made in our understanding of the cellular signaling mechanisms that control vital physiological programs, such as energy expenditure and blood pressure. In addition, distinct tissues have been identified as sensors of physiological state enabling rapid responses to changes in the environment. Although we have taken great strides to advance our knowledge of how this physiological balance is achieved, our understanding of the influence of modern human diseases and basic inflammatory processes on homeostasis is inadequate.

Interestingly, theories on the origin of inflammation were initially rooted in the concept of homeostasis, such that inflammation was seen as a means by which the tissue attempted to return to normal in response to infection or damage. However, we now know that the initiation of an inflammatory program often has deleterious consequences, (Tracey, 2007, 2002), which strongly correlate with the pathophysiology of diseases such as obesity and cancer where homeostatic processes are clearly disrupted (Scrivo et al., 2011; Nathan and Ding, 2010; Medzhitov, 2008; Tabas and Glass, 2013). These observations led inflammation to be viewed as a program evoked not to maintain homeostasis but rather to remove the initiating stimuli and boost host defense, regardless of antagonistic consequences to normal physiology (Okin and Medzhitov, 2012). Importantly, inflammation may therefore reset the homeostatic set points of the endocrine and neural systems to improve protection against noxious stimuli. In this review we will discuss the conspicuous effects of hypothalamic inflammation in the regulation of energy homeostasis.

2. Hypothalamic insulin and leptin signaling

Our current model for how the central nervous system orchestrates energy balance is profoundly influenced by the concept of stability of the 'interior environment' (the '*milieu intérieur*'), conceived more than a century ago by Claude Bernard. Bernard described that the vital organs functioned to serve a single purpose, which was to maintain the uniformity of the internal environment, a necessary action for a 'free and independent life' (Bernard, 1854). Subsequently, in 1938, the central nervous system (CNS) was linked to regulating energy homeostasis in seminal experiments conducted by W.R. Ingram's group, where they observed increased adiposity in monkeys and cats submitted to hypothalamic lesions (Ranson et al., 1938). Further investigations demonstrated that specific hypothalamic nuclei lesions could modulate energy balance in opposing directions (Anand and Brobeck, 1951; Teitelbaum and Stellar, 1954; Miller, 1957; Hervey, 1959). For example, lesion of the ventromedial nuclei (VMH) leads to hyperphagia, whilst lesions in the lateral hypothalamus (LHA) induce weight loss (Miller,

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1957). While these works conclusively demonstrated the role of the hypothalamus in centrally regulating energy homeostasis, it became apparent that signals from the periphery also influenced the maintenance of this balance. Specifically, pioneering parabiotic studies performed by Coleman et al. in the 1970's suggested the existence of an adipose tissue-derived hormone that could inform the hypothalamus of the metabolic state of the individual (Coleman and Hummel, 1973; Coleman, 1973). In 1994, this hormone was cloned by Friedman's group and coined 'leptin' (Zhang et al., 1994). Following a meal, leptin is released by adipocytes and enters the circulation to signal satiety and decrease feeding behavior. Importantly, leptin, much like insulin, circulates in levels that are proportional to body fat content and feeds information back to the CNS on the reservoirs of fat available for use in energy production (Bruning et al., 2000; Woods et al., 1979; Konner and Bruning, 2012).

Mechanistically, leptin acts through the long form of its receptor, a type 1 cytokine receptor, which is abundantly expressed in the arcuate (ARC), paraventricular, and VMH of the hypothalamus (Tartaglia et al., 1995; Schwartz et al., 1996, Mercer et al., 1996; Woods and Stock, 1996). Binding of leptin to its receptor leads to activation of the Janus kinase-2 (JAK2)/signal transducer and activator of transcription-3 (STAT3) (Vaisse et al., 1996; Ghilardi et al., 1996; Ghilardi and Skoda, 1997), phosphatidylinositol 3-kinase (PI3K) (Kellerer et al., 1997; Bjorbaek et al., 1997) and Src homology-2 containing protein-tyrosine-phosphatase extracellular-signal regulated kinase (SHP2/ERK) signaling pathways (Bjorbaek et al., 2001; Myers et al., 2008). Importantly, insulin not only shares the same leptin intracellular signaling proteins but also amplifies leptin-induced signal-transduction cascades in the hypothalamus to decrease food intake and increase energy expenditure. Specifically, insulin induces tyrosine phosphorylation of JAK2, which potentiates leptin-induced activation of JAK2-STAT3 pathway (Carvalheira et al., 2001; Carvalheira et al., 2005).

Although leptin activation of JAK2/STAT3 signaling pathway was the first to be documented, downstream mediators of PI3K, such as AMPK and mTOR, have emerged as relevant molecules, which mediate leptin effects on energy balance (Cota et al., 2006; Ropelle et al., 2008; Ropelle et al., 2010). It should be noted that AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) have primarily opposing roles, such that leptin mediates inhibition of AMPK activity through mTOR mediated serine$^{485/491}$ phosphorylation of AMPKα2 while AMPK impairs mTOR activity by phosphorylating and activating tuberous sclerosis 2 (TSC2) (Dagon et al., 2012; Inoki et al., 2003). Importantly, beyond its role in coordinating hormonal homeostatic signals, the hypothalamus also directly senses nutritional signals through the mTOR/AMPK axis, (Lage et al., 2008; Martinez de Morentin et al., 2014; Hardie et al., 2012). More recently, both AMPK and mTOR were discovered to be central for the orexigenic effects of thyroid hormone and ghrelin as well as the anorexigenic effects of cytokines observed in cancer and exercise (Ropelle et al., 2010; Lopez et al., 2010; Martins et al., 2012; Lopez et al., 2008; Varela et al., 2012; Laviano et al., 2003). Thus, in aggregate, these studies have identified AMPK/mTOR axis as key sensor for the integration of energy homeostasis.

3. Obesity-induced insulin and leptin resistance

Loss of tightly controlled homeostatic systems such as blood pressure and core body temperature results in life threatening conditions, such as hypertensive emergency/hypotension and hyperthermia/hypothermia, responses that have defined upper and lower limits. In contrast, energy homeostasis in humans has developed without clear environmental pressure to define an upper limit for body fat content, which was hypothesized to be extinguished millions of years ago with the removal of predatory risk – reviewed by (Speakman, 2007). While normal homeostatic mechanisms strive to balance food intake and fat storage with energy output, the lack of a clear upper limit permits excess fat storage. Therefore, in a world with easy access to highly palatable, dense hypercaloric food, and an environment that encourages reduced physical activity, obesity has become a pandemic that originated in developed countries and has rapidly spread to developing ones (Hossain et al., 2007; Zheng et al., 2011; Tobias et al., 2014). Although not associated with acute morbid conditions, obesity is now a major health burden as it is a risk factor for numerous chronic non-communicable diseases, such as type 2 diabetes mellitus, cardiovascular disease and certain cancers (Hossain et al., 2007; Tobias et al., 2014; Pal et al., 2012; Park et al., 2010; Yoshimoto et al., 2013; Flores et al., 2012; Osório-Costa and Carvalheira, 2013).

The lack of a clearly defined upper limit with regard to body fat content allows for built-in checkpoints, such as leptin to be easily over-ridden. The development of leptin resistance and the inability of obese individuals to respond to leptin treatment are key characteristics associated with obesity (Heymsfield et al., 1999). Notably, it is still debatable whether leptin resistance is a cause or consequence of obesity, more recent evidence points to the former. For example, intervention with less palatable chow attenuates further weight gain in diet-induced obesity (DIO) mice restoring leptin sensitivity (Myers et al., 2010). Interestingly, different animal models of obesity such as Zucker obese rats, and genetically obese mice, which present with leptin signaling defects, also develop hypothalamic insulin resistance, while high-fat diet (HFD) fed mice concomitantly develop insulin and leptin resistance (Ropelle et al., 2010; Phillips et al., 1996; Carvalheira et al., 2003; De Souza et al., 2005). Furthermore, hypothalamic insulin resistance is an early event in western diet fed mice, again pointing to cause rather than consequence (Prada et al., 2005). Thus, whatever the cause, obesity is linked with hypothalamic hormonal resistance, suggesting that the major role of this resistance is to reset the energy homeostatic sensors for a period where food is abundant. This serves as an anticipatory measure guaranteeing the host energy reservoirs for periods of caloric deprivation.

Mechanistically, hypothalamic insulin and leptin resistance are mediated by signals that may be grouped into the following functional categories: serine kinases, protein tyrosine phosphatases and suppressors of cytokine signaling. Serine kinases phosphorylate insulin receptor substrates (IRSs), blocking signal transduction by reducing the docking capability of these proteins to recruit PI3K (Konner and Bruning, 2012; Xu et al., 2005; Niswender et al., 2004; Zabolotny et al., 2002). The tyrosine phosphatases, in turn, reduce the level of tyrosine phosphorylation of IRSs and JAK2, which is associated with decreased IRSs recruitment of PI3K and JAK2 tyrosine kinase activity, respectively (Konner and Bruning, 2012). Finally, suppressor cytokine signaling 3 (SOCS3) inhibits phosphorylation of the leptin receptor (Bjorbak et al., 2000; Kievit et al., 2006), decreases IRSs tyrosine phosphorylation and decreases total IRS levels by inducing its proteosomal degradation (Emanuelli et al., 2001; Senn et al., 2003; Ueki et al., 2004; Shi et al., 2004).

4. Cellular and molecular mechanisms of obesity-mediated inflammation

Work over the last few decades has established a firm link between obesity and low-grade inflammation (Hotamisligil et al., 1993; Odegaard and Chawla, 2013a, b; Hotamisligil, 2006; Saberi et al., 2009). Although the exact sequence of events and the signals that establish obesity-mediated inflammation are still unclear,

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recent evidence indicates that the adipocyte plays an important role in deflagrating the recruitment of immune cells by either acting as an antigen presenting cell to both T lymphocytes and invariant natural killer T (iNKT) cells (Iyer et al., 2010; Carvalheira et al., 2013; Sell et al., 2012) or by secreting chemotactic factors, such as C–C chemokine ligand (Ccl) 2, 5, 8, which mediate the recruitment of monocytes to white adipose tissue (WAT) (Weisberg et al., 2006). These events promote an increase in the WAT inflammatory timbre, which is cardinally characterized by the infiltration of macrophages and the switch of macrophage functionality from the alternative M2 phenotype (characterized by expression of CD206, Arginase 1, CD301) observed in lean individuals to the classic pro-inflammatory M1 phenotype (characterized by production of tumor necrosis factor (TNF), inducible nitric oxide synthase (iNOS), interleukin-1 beta (IL-1β)) (Lumeng et al., 2007; Weisberg et al., 2003; Olefsky and Glass, 2010). Besides macrophages, a long list of other leukocytes, comprised of cells from both the innate and adaptive arms of immunity, also contribute to WAT inflammation. To study the complex interaction between the different subsets of immune cells that infiltrate the WAT it is convenient, for didactic reasons, to divide the cells in functional categories. The first group consists of the WAT resident cells whose primary role it is to maintain the normalcy of lean WAT, whilst in the second group are the infiltrating immune cells that increase the inflammatory tone of obese adipose tissue – reviewed by (Carvalheira et al., 2013).

In the lean state, the resident immune cells, innate lymphoid cell-2 (ILC-2) cells, eosinophils and Tregs, cooperate to maintain the alternatively activated state of adipose tissue associated macrophages (ATM), which secrete IL-10 to promote insulin sensitivity. Specifically, ILC-2 cells recruit and activate eosinophils promoting their production of IL-4 and IL-13, whilst Tregs cells secrete IL-10, which not only support M2 polarization but also directly acts on WAT to promote insulin sensitivity (Carvalheira et al., 2013; Nguyen et al., 2011; Odegaard and Chawla, 2013a, b). DIO disrupts this anti-inflammatory program by recruiting and activating inflammatory monocytes ($Ly6C^{hi}$), that ultimately differentiate into M1 inflammatory macrophages, Th1 lymphocytes, $CD8^{+}$ T cells, B cells, neutrophils and mast cells that produce inflammatory cytokines such as TNF, IL-1β and IL-6, to promote insulin resistance (Odegaard and Chawla, 2013a, b; Olefsky and Glass, 2010; Ferrante, 2007). Importantly; obesity-induced inflammation is not restricted to WAT but targets other metabolic organs (i.e. muscle and liver), as well as the brain, contributing to systemic insulin resistance and disturbances in glucose homeostasis.

Not surprisingly, these newly recruited inflammatory immune cells up-regulate and increase the activity of a surfeit of pro-inflammatory signaling molecules such as, inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) (Lumeng et al., 2007; Cai et al., 2005; Arkan et al., 2005), IKKε, janus kinase (JNK) (Solinas et al., 2007; Schneider et al., 2006; Han et al., 2013; Holzer et al., 2011; Hirosumi et al., 2002), mitogen-activated protein kinases (MAPK) (Wu et al., 2006), double-stranded RNA-dependent protein kinase (PKR) (Nakamura et al., 2010) and iNOS (Carvalheira et al., 2005; Ropelle et al., 2013; Foster et al., 2003) in metabolic tissues. Importantly, these pro-inflammatory molecules have been associated with activation of protein tyrosine phosphatase 1B (PTP1B), SOCS3 or in altering the ability of IRS-1 to be tyrosine phosphorylated, ultimately leading to insulin resistance. Specifically, TNF knockout mice placed on a HFD present with decreased PTP1B activity in multiple metabolic tissues (Zabolotny et al., 2008), whilst pro-inflammatory cytokines promote SOCS3 expression (Ehlting et al., 2007; Bode et al., 1999). On the other hand, serine kinases, such as IKK, JNK, MAPK, PKR, induce serine phosphorylation of IRSs and iNOS to promote nitrosation of these proteins, diminishing their capability to be tyrosine phosphorylated (Carvalho-Filho et al., 2005; Ropelle et al., 2013; Marshall et al., 2004; Stamler and Hess, 2010; Reynaert et al., 2004) (Fig. 1).

In addition to the recruitment of inflammatory immune cells, inflammation and insulin resistance can also be regulated via the direct activation of toll-like receptors (TLRs). These receptors primarily recognize pathogen-associated molecular patterns (PAMPs) and are activated by pathogens and aseptic injury to trigger an innate immune response (Takeda and Akira, 2004). Interestingly, two receptors of the TLR family were implicated in the genesis of insulin resistance in obesity. TLR2 and TLR4 are both activated by free fatty acids (FFA), which through myeloid differentiation factor 88 (MyD88) activates JNK and IKKβ leading to serine phosphorylation IRS-1 and insulin resistance (Tsukumo et al., 2007; Caricilli et al., 2011; Ehses et al., 2010; Shi et al., 2006). Moreover, FFA can classically activate macrophage through TLR-2/4 and JNK signaling pathway, therefore TLRs also promotes inflammation/insulin resistance via activation of immune cells (Solinas et al., 2007; Nguyen et al., 2007).

5. Inflammation orchestrates hypothalamic set-point adaptation

The constant adaptation of our bodies to the variability of our external environments is essential for survival. This constant fight compels organisms to develop coordinated physiological responses to more effectively deal with external variability. Interestingly, energy homeostasis and the immune system have a number of coordinated responses. For example, the sickness syndrome is an old coordinated response by which the brain helps the immune system cope with an infection. Archetypically, the symptoms of this syndrome: fever, anorexia, achiness and sleepiness; serve to amplify the body's response. First, the rise in core body temperature (i.e. fever) improves immune cell function to eliminate the infectious agent; second, sleepiness and achiness decreases energy expenditure by decreasing locomotor activity; and third, anorexia decreases the supply of glucose to the infectious agent – reviewed in (Saper et al., 2012). Conversely, increased food intake fuels regenerative processes (ex. muscle regeneration), though often accompanied by low-grade inflammation (Radley-Crabb et al., 2014). Moreover, hypothalamic activity is associated with increased regeneration such that a direct lesion of the hypothalamic VMH nucleus improves liver regeneration through increased vagal outflow (Lee et al., 2011; Kiba et al., 1992).

It should be noted that chronic diseases, such as obesity and cancer, subvert these very primitive and coordinated responses. For instance, central sensors of energy homeostasis rapidly adopt a status associated with increased energy expenditure and decreased food intake in cancer-mediated anorexia. This maladaptive response is an attempt to reduce glucose supplies to cancer cells, which is ineffective as rapidly proliferating cancer cells lose oxidative glycolysis capabilities, and in turn instigates a chronic state of malnutrition (O'Neill and Hardie, 2013; Faubert et al., 2013; Warburg, 1956; Hanahan and Weinberg, 2011). On the other hand, obesity-induced inflammation, which resembles the low-grade inflammation observed in regenerative programs, prompts the CNS to increase food intake and reduce energy expenditure therefore supplying more nutrients to an expanding adipose tissue (Ropelle et al., 2010; De Souza et al., 2005; Zhang et al., 2008; Thaler et al., 2012; Thaler and Schwartz, 2010) (Fig. 2).

5.1. Hypothalamic inflammation in obesity

The low-grade inflammatory response in obese WAT spreads not only to tissues involved in glucose homeostasis, such as muscle and liver, but also to the hypothalamus. Although IRS-1 serine

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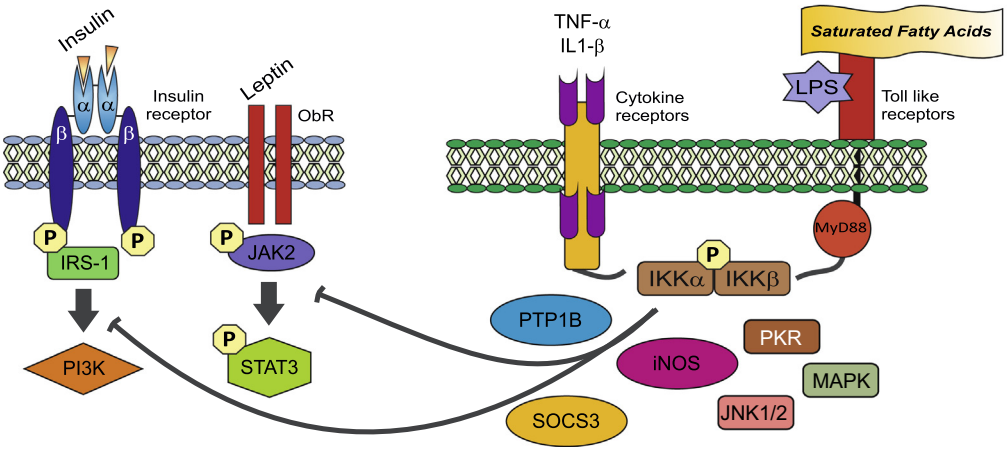

Fig. 1. Inflammation disrupts insulin and leptin signaling pathways. Insulin and leptin receptors catalyze the phosphorylation of intracellular proteins, such as JAK2 and IRSs, which activate PI3K and STAT3. These signaling pathways regulate food intake and energy expenditure regulating energy homeostasis. Increased cytokine levels promote increased levels of SOCS3, PTP1B and iNOSs, as well as serine kinases, such as JNK and IKK, that ultimately leads to hypothalamic inflammation and impair insulin and leptin signaling. IL1-β: interleukin 1 beta; JNK1/2: c-Jun N-terminal protein kinase 1 and 2; IKKα: inhibitor of nuclear factor kappa-B kinase subunit alpha; IKKβ: inhibitor of nuclear factor kappa-B kinase subunit beta; iNOS: inducible nitric oxide synthase; IRAK: IL-1 receptor-associated kinase-4; LPS: lipopolysaccharide; MyD88: myeloid differentiation primary response gene 88; PI3K: phosphatidylinositol-3 kinase; JAK2: janus kinase 2; PTP1B: protein tyrosine phosphatase 1B; SOCS3: suppressors of cytokine signaling; STAT3: signal transducer and activator of transcription 3.

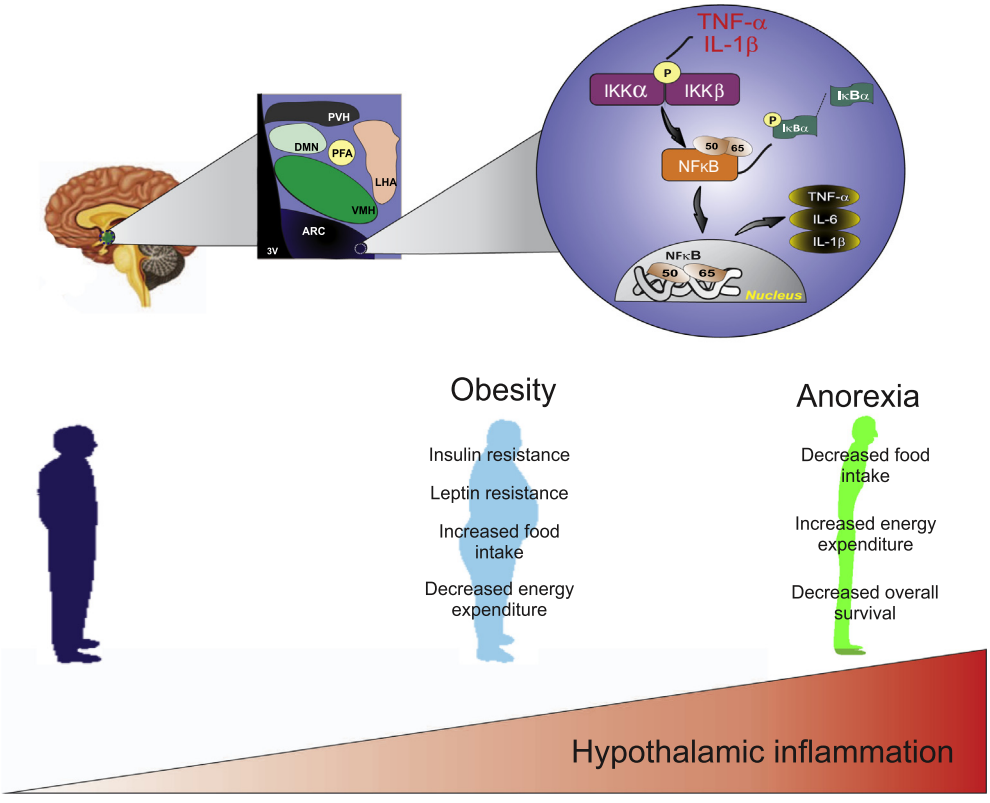

Fig. 2. Schematic representation of the consequences of hypothalamic inflammation on energy homeostasis. Hypothalamic low-grade inflammation promotes the activation of intracellular signaling pathways that suppress insulin and leptin signaling to promote obesity. Whereas, high-grade inflammation, such as that which occurs in cancer, directly induces anorexia. Notably, the same inflammatory mediators that are associated with obesogenesis are also involved in the development of anorexia. However, the exact hypothalamic inflammation threshold that makes the central nervous system change from a program that induces obesity to one that elicits anorexia is still unclear. ARC: arcuate nucleus; DMN: dorsomedial nucleus; IκB: inhibitor of nuclear transcription factor; LHA: lateral nucleus; NFκB: nuclear factor-kappaB; PVH: paraventricular nucleus; VMH: ventromedial nucleus.

phosphorylation (used as a surrogate marker of hypothalamic insulin resistance) may suggest hypothalamic inflammation due to obesity (Carvalheira et al., 2003), definitive data demonstrating that hypothalamic inflammation is relevant for the pathogenesis of obesity comes from hypothalamic pharmacological manipulation of HFD fed rats. Interestingly, treatment of obese rats with a specific inhibitor of JNK was able to revert hypothalamic inflammation/insulin resistance and restore energy homeostasis (De Souza

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et al., 2005). These studies paved the way in recognizing that pro-inflammatory mediators classically involved in WAT inflammation, such as IKKβ, TNF and TLRs, played a significant role in hypothalamic inflammation (De Souza et al., 2005; Zhang et al., 2008; Posey et al., 2009; Milanski et al., 2009; Arruda et al., 2011). Interestingly, non-canonical inducers of inflammatory signaling, such as impaired autophagy, were also associated with increased IKK signaling in mediobasal hypothalamus and higher food intake, as well as reduced energy expenditure (Meng and Cai, 2011). Consistent with a crucial role of hypothalamic inflammation in the control of energy homeostasis, the reversion of hypothalamic inflammation with physical exercise promotes hypothalamic leptin and insulin sensitivity and decreases food intake (Ropelle et al., 2010; Yi et al., 2012).

It should be noted that the sequence of events during obesogenesis indicate that inflammation and insulin resistance in hypothalamus is an early onset event, suggesting that neuronal cells are more sensitive to HFD circulating mediators of inflammation than WAT (Prada et al., 2005). Moreover, maternal consumption of a diet rich in saturated fatty acids during gestation and lactation, an animal model used to assess predisposition to obesity, promotes hypothalamic inflammation through enhanced expression of TLR4, IKK and JNK as early as 21 days postnatal (Rother et al., 2012; Pimentel et al., 2012). Accordingly, short term intracerebroventricular (ICV) administration of stearic, arachidic and behenic fatty acids promote TLR activation and expression of endoplasmic reticulum (ER stress)-related proteins, indicating that saturated fatty acids play a main role in hypothalamic inflammation (Milanski et al., 2009). In striking contrast, treatment with unsaturated fatty acids attenuated the inflammatory response (Milanski et al., 2009).

Overfeeding induces pro-inflammatory activity directly in neuronal cells of the ARC, promoting increased food intake and reduced energy expenditure (Zhang et al., 2008). Moreover, HFD promotes hypothalamic inflammation in proopiomelanocortin (POMC) neurons of the mediobasal hypothalamus, which leads increased blood pressure (Purkayastha et al., 2011). In addition, the recent observation of increased CD68 and F4/80 expression in the hypothalamus of HFD fed rats suggested that HFD not only induces inflammation in neuronal cells but also activates the microglia to promote hypothalamic inflammation (Thaler et al., 2012).

The inflammatory response, if sustained for a long period, ultimately results in bystander tissue destruction (Medzhitov, 2008). Importantly, recent evidence suggests that obesity mediated inflammation in hypothalamus causes definitive neuronal injury that promotes obesity. Along this line, neuronal apoptosis is detected in hypothalamic nuclei in HFD fed rodents and in mHypoE-44 neurons cell treated with fatty acids (Mayer and Belsham, 2010; Moraes et al., 2009). Moreover, animal models of obesity display hypothalamic neuronal remodeling dysfunction (McNay et al., 2012) and increased gliosis levels in ARC nucleus (Thaler et al., 2012). Interestingly, inflammation mediated hypothalamic dysfunction was also linked to the control of glucose homeostasis. For example, inhibition of the fatty acid synthase in the hypothalamus improved insulin sensitivity in the liver of rodents fed a HFD, by decreasing TNF and IL-6 levels (Chakravarthy et al., 2009). In addition, ICV infusion of TNF-α leads to loss of peripheral insulin sensitivity and increased pro-*apoptotic* bcl-2-family protein (BAX) expression in pancreatic islets (Calegari et al., 2011). Furthermore, inhibition of hypothalamic TLR4 and TNF not only improved hypothalamic leptin and insulin sensitivity but also directly improved insulin sensitivity in the liver (Milanski et al., 2012).

5.2. Hypothalamic inflammation in anorexia

Studies over the last decades have underscored a crucial role for pro-inflammatory cytokines, such as TNF, IL-1β and IL-6, in the control of energy homeostasis in anorexia–cachexia syndrome. The cytokines are directly released into circulation by inflammatory immune cells and subsequently transported to the brain through the blood brain barrier, or directly produced by neurons and glial cells in the CNS (Hopkins and Rothwell, 1995; Rothwell and Hopkins, 1995; Licinio and Wong, 1997; Sternberg, 1997; Mantovani et al., 1998; Haslett, 1998). Of note, in the context of systemic diseases such as cancer, the influence of cytokines on the hypothalamus is independent of the location of cytokine secretion due to its expression of a high density of cytokine receptors (Hopkins and Rothwell, 1995). Interestingly, chronic administration of cytokines reproduces the different characteristics of anorexia–cachexia syndrome (Mantovani et al., 1998; Gelin et al., 1991; Moldawer et al., 1992; Matthys and Billiau, 1997; Tisdale, 1997) while antibody neutralization of TNF inhibits the development of this syndrome (Matthys and Billiau, 1997; Sherry et al., 1989; Noguchi et al., 1996). Furthermore, administration of an IL-β receptor antagonist suppresses anorexia in animal models of cancer (Laviano et al., 2000).

The neural circuit by which cytokines elicit anorexia involves activation of the IL-1 receptor expressing POMC neurons in the ARC of the hypothalamus (Scarlett et al., 2007) while, TNF-induced levels of thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH) promotes energy expenditure through β3-adrenergic signaling to the brown adipose tissue (Arruda et al., 2011). Importantly, a number of different approaches aimed at attenuating inflammation concomitantly results in the reduction of hypothalamic inflammation and prevents weight loss in animal models of anorexia. For example, hypothalamic inhibition of AMPK not only reduces hypothalamic inflammation and increases food intake in cancer-induced anorexia but also decreases splenomegaly and increases overall survival (Ropelle et al., 2007). Second, physical exercise suppresses hypothalamic inflammation in tumor-bearing rats (Lira et al., 2011). Third, ghrelin treatment reduces IL1-β expression and increases food intake (DeBoer et al., 2007).

It should be noted that the CNS also modulates systemic inflammation through a cholinergic anti-inflammatory pathway; the efferent arc of this neural circuit, conducted by the vagus nerve, promotes acetylcholine release by T cells, which inhibits cytokine secretion from splenic macrophages that express the α7 subunit of the nicotinic acetylcholine receptor (nAChR) (Tracey, 2002). Moreover, activation of this circuit has been implicated in the reduction of tissue injury evoked by acute diseases such as sepsis, hemorrhagic shock and intestinal inflammation (Tracey, 2002). Much less is known, however, about the effects of this neural circuit on chronic diseases such as cancer and obesity. Interestingly, activation of nAChR diminishes lung and hepatic metastasis, an effect that is blunted by vagotomy (Erin et al., 2012). In addition, recent studies have shown that brain-derived neurotrophic factor (BDNF)-mediated reduction of hypothalamic inflammation and increased sympathetic neural activation was associated with suppression of cancer growth rate (Liu et al., 2014; Cao et al., 2010). In aggregate, the studies support the hypothesis that the hypothalamus senses metabolic and inflammatory signals and makes fine-tune adjustments to not only energy homeostasis but also to the systemic inflammatory timbre.

6. Conclusion

The last few decades have witnessed an incredible expansion in our understanding of the cellular and molecular mechanisms that orchestrate energy homeostasis. We now understand that hypothalamic inflammation has a prominent role in resetting the neural circuits involved in energy homeostasis in pathological states such as obesity and anorexia. Although better strategies are required to effectively target the brain, we can envision a

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scenario in which blocking hypothalamic inflammation restrains the vicious circle leading to the pathogenesis of disease. As such, the hypothalamus represents an attractive drug target that could potentially ameliorate some of the most prevalent diseases we are faced with today.

Authors' contributions

G.D.P. wrote the initial drafts of the manuscript; K.G. and J.B.C.C. revised the manuscript.

Conflicts of Interests

The authors declare that they have no competing interests.

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