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Review

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.

Contents

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).

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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, 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.