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Review

Hypothalamic inflammation and energy homeostasis: Resolving the paradox

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ABSTRACT

Determining the effect of hypothalamic inflammatory signals on energy balance presents a paradox. On the one hand, a large body of work has identified inflammatory signaling in the hypothalamus as an essential mediator of the sickness response – the anorexia, cachexia, fever, inactivity, lethargy, anhedonia and adipsia that are triggered by systemic inflammatory stimuli and promote negative energy balance. On the other hand, numerous recent studies implicate inflammatory activation within the hypothalamus as a key factor whereby high-fat diets – and saturated fats in particular – cause central leptin and insulin resistance and thereby promote the defense of elevated body weight.

This paradox will likely remain unresolved until several issues have been addressed. Firstly, the hypothalamus – unlike many peripheral inflamed tissues – is an extremely heterogeneous tissue comprised of astrocytes, oligodendrocytes, microglia, endothelial cells, ependymal cells as well as numerous neuronal subgroups. Determining exactly which cells activate defined inflammatory signals in response to a particular stimulus – i.e. sepsis vs. nutrient excess – may yield critical clues. Secondly, for the sake of simplicity many studies evaluate inflammation as an on/off phenomenon. More realistically, inflammatory signaling occurs as a cascade or cycle that changes and progresses over time. Accordingly, even within the same cell type, the low-grade, chronic signal induced by nutrient excess may invoke a different cascade of signals than a strong, acute signal such as sepsis. In addition, because tolerance can develop to certain inflammatory mediators, physiological outcomes may not correlate with early biochemical markers. Lastly, the neuroanatomical location, magnitude, and duration of the inflammatory stimulus can undoubtedly influence the net CNS response. Rigorously evaluating the progression of the inflammatory signaling cascade within specific hypothalamic cell types is a key next step towards resolving the paradox surrounding the effect of inflammatory signaling on energy homeostasis.

1. Inflammation in the CNS

Although the brain is considered an *immuno-privileged* organ – since the blood brain barrier restricts access of immune cells and mediators from the blood – this distinction is most relevant in limiting the adaptive immune response (i.e. antigen presentation, T and B cell activation, antibody production). In contrast, innate immune activation can occur throughout the brain in response to both local and systemic inflammatory stimuli [32]. Most CNS cells have pattern recognition receptors (e.g. Toll-like receptors, TLR) that respond to both pathogen-associated products and endogenous mediators, are capable of activating the master inflammatory transcription factor Nuclear Factor kappa B (NFκB), produce cytokines and/or chemokines and are capable of responding to autocrine, paracrine or even endocrine immune signals. To date studies elucidating the role of innate immune signaling in the brain have been focused primarily on neurodegenerative diseases and cerebrovascular injury, and this work has begun to unravel the complexity of immune communication between neurons and surrounding glial cells. Identifying the specific role of individual cytokines in the CNS is made difficult by the fact that numerous cytokines can be either pro-inflammatory or anti-inflammatory depending on their cellular source, the state of their cellular target and the phase of the immune response. For example, IL6 can trigger either neuronal toxicity or neuronal protection depending on whether its action initially targets glia or neurons [13]. Thus, although CNS inflammation can in some instances cause or exacerbate a deleterious process, activation of immune signaling is as critical to neuroprotection, repair and regeneration (i.e. IL10, TGFβ), as it is to neurotoxicity and cell death [17]. Moreover, it is also important to recognize that CNS cytokines (IL1β, TNFα) may also participate in physiological – rather than pathophysiological – processes related to regulation of food intake [60], sleep [43] and thermoregulation [36], and that these cytokines may be regulated by diurnal variation in glucocorticoid signaling [19]. The potent anti-inflammatory effect of glucocorticoids also highlights the

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fact that communication between neuronal and glial signaling is bidirectional not only at the cellular level, but also systemically where CNS control of the HPA axis, among other hormonal mediators, can have profound effects on both peripheral and central immunity.

2. CNS inflammation and negative energy balance

Systemic infectious or inflammatory conditions induce a syndrome referred to as the sickness response, comprised of characteristic behavioral and autonomic alterations that cause net negative energy balance (Table 1). Food intake is limited by anorexia while fat and muscle breakdown are accelerated by – among other factors – the extraordinary energetic costs of increasing body temperature and expanding the immune response. In the last 30 years, numerous cytokines have been shown to cause negative energy balance when administered either peripherally or centrally, including IL1β, TNFα, IL6, IFNγ, CNTF, GMCSF and leptin [46,26,53,56]. However, the redundant nature of the cytokine cascade has undermined pharmacological and genetic efforts to implicate any single cytokine as an essential factor in causing negative energy balance and weight loss [25,8,30,49,47]. Although the majority of these studies have focused on the role of inflammation in the hypothalamus, important effects of immune signaling have also been demonstrated in the brainstem [11,15], suggesting that inflammation may regulate energy balance in multiple brain regions.

Given the behavioral nature of many sickness characteristics, logic dictates that to cause sickness, peripheral inflammatory factors must ultimately alter neuronal signaling, but the mechanism whereby this occurs remains unsettled. A wide variety of peripheral inflammatory conditions have been shown to increase production and release of cytokines within the CNS [24,34,16], and several lines of evidence suggest that the presence of inflammatory cytokines in the CNS is crucial for the sickness response to develop [35,48]. However, the origin of these cytokines remains controversial as peripheral cytokines can both enter the brain directly [1,50] and be produced locally by microglia – the resident immune cells in the CNS – as well as by neurons [52,31].

Two recent studies suggest that in response to lipopolysaccharide (LPS), a potent inflammatory component of the gram-negative bacterial cell wall, it is central rather than peripheral cytokine signaling that is essential for CNS inflammation and negative energy balance to occur. The first study used bone marrow transplantation (BMT) of wild-type donor cells into LPS-resistant hosts to restore the peripheral immune response to LPS. This intervention normalized the acute peripheral cytokine response to LPS, and yet CNS expression of Nuclear Factor kappa B (NFκB) target genes was markedly attenuated at 2 h – and no different from control 6 h following LPS exposure [6]. A second study used a similar BMT strategy in mutant mice lacking MyD88, a key intracellular protein linking TLR4 signaling (which mediates the LPS response) to activation of inflammatory signals. As before, transplantation of wild-type donor cells into MyD88-deficient hosts normalized the peripheral cytokine response to LPS, but failed to increase CNS cytokine mRNA expression – in this study, specifically in the hypothalamus. More importantly, these animals demonstrated only very transient, mild anorexia after LPS administration such that food intake and body weight were comparable to vehicle-injected animals within 6 h. In stark contrast, wild-type hosts transplanted with MyD88-deficient donor cells displayed intact hypothalamic cytokine mRNA expression and sickness responses to LPS despite dramatically impaired peripheral cytokine responses to LPS [62]. In addition, a recent BMT study demonstrated that HPA axis activation, another sickness characteristic, is also dependent on central rather than peripheral inflammatory signaling [18].

Together these data suggest that multiple circulating cytokines and inflammatory mediators can trigger CNS immune signaling, but are themselves insufficient to cause sustained hypothalamic inflammation or sickness behavior. Rather it appears that activation of inflammatory signals within one or more CNS cell types is essential to allow a wide variety of peripheral mediators to cause the characteristic sickness response (Fig. 1). However, these studies have yet to identify either the inflamed cell critical to sickness or the brain region(s) where inflammatory signals cause negative energy balance – leaving open the possibility that inflammation in different cell types or brain regions can have different effects on the control of energy balance.

Table 1
The effect on energy balance of characteristic behavioral and autonomic alterations associated with infectious and inflammatory conditions, and inducible by the administration of cytokines.

Sickness response characteristics and their effect on energy balance	
Negative	Positive
Fever	Reduced activity
Anorexia	Reduced socialization
Cachexia	Anhedonia
Adipsia	Pain sensitivity
HPA axis activation	Sleepiness
Autonomic overactivity	

3. Hypothalamic inflammation and positive energy balance

The connection between hypothalamic inflammation and diet-induced obesity (DIO) is a relatively recent finding, though the foundation for this work is built on two well-established areas of research. First, obesity in both human subjects [42] and animal models [27] is associated with increased circulating inflammatory markers such as Tumor Necrosis Factor-α and Interleukin-6, and adipose tissue becomes infiltrated by macrophages as obesity progresses [58]. Second, circulating cytokines [22] – as well as nutrient excess in the form of exposure to glucose or fatty acids in amounts that exceed energy needs [27,28] – activate intracellular inflammatory pathways in a variety of target cells. In these cells – including liver, muscle, adipocytes and endothelial cells – inflammation can arise from any of several mechanisms, including mitochondrial dysfunction, reactive oxygen species, and endoplasmic reticulum stress and the associated unfolded protein response. A key cellular consequence of this inflammation includes resistance to both insulin and leptin [22].

In the wake of these studies involving peripheral tissues is a series of reports showing that during DIO inflammation occurs in the hypothalamus of rats and mice, just as in peripheral tissues [9,51,41,65,44]. Moreover, experimental interventions that block hypothalamic inflammation (e.g., inhibition of hypothalamic Inhibitor of Kappa Kinase-β (IKKβ) signaling by either a pharmacological approach or preventing neuronal IKKβ signaling by a gene therapy approach) reduce food intake and lower body weight in animals made obese by high-fat (HF) feeding, but not in controls fed a low-fat (LF) diet [51,41,65]. The mechanism whereby hypothalamic inflammation favors weight gain is strongly linked to the induction of resistance to leptin [65,44,10] and other humoral inputs to the hypothalamus, including insulin [9,51,65].

These observations provide direct support for the hypothesis that hypothalamic inflammation induced by HF feeding favors the defense of elevated body weight, as is characteristic of DIO. Two of these recent studies have attempted to link hypothalamic induction of specific cytokines (IL1β, TNFα, IL6 and IL10) in response to either DIO or intraventricular administration of