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Regulation of Energy Balance by Inflammation: Common Theme in Physiology and Pathology

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Abstract

Inflammation regulates energy metabolism in both physiological and pathological conditions. Pro-inflammatory cytokines involves in energy regulation in several conditions, such as obesity, aging (calorie restriction), sports (exercise), and cancer (cachexia). Here, we introduce a view of integrative physiology to understand pro-inflammatory cytokines in the control of energy expenditure. In obesity, chronic inflammation is derived from energy surplus that induces adipose tissue expansion and adipose tissue hypoxia. In addition to the detrimental effect on insulin sensitivity, pro-inflammatory cytokines also stimulate energy expenditure and facilitate adipose tissue remodeling. In caloric restriction (CR), inflammatory status is decreased by low energy intake that less energy supply to immune cells, which favors energy saving in the body under caloric restriction. During physical exercise, inflammatory status is elevated due to muscle production of pro-inflammatory cytokines, which promote fatty acid mobilization from adipose tissue to meet the muscle energy demand. In cancer cachexia, chronic inflammation is elevated by the immune response in the fight against cancer. The energy expenditure from chronic inflammation contributes to weight loss. Immune tolerant cancer cells gains more nutrients during the inflammation. In these conditions, inflammation coordinates energy distribution and energy demand between tissues. If the body lacks response to the pro-inflammatory cytokines (Inflammation Resistance), the energy metabolism will be impaired leading to an increased risk for obesity. In contrast, super-induction of the inflammation activity leads to weight loss and malnutrition in cancer cachexia. In summary, inflammation is a critical component in the maintenance of energy balance in the body. Literature is reviewed in above fields to support this view.

Keywords

Inflammation; caloric restriction; obesity; exercise physiology; cachexia; energy expenditure

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Introduction

In obesity, white adipose tissue together with other tissues (liver and brain hypothalamus) has a low-grade chronic inflammation (1-9). It is generally believed that the chronic inflammation contributes to the pathogenesis of systemic insulin resistance, which was originally developed from mouse models. The concept has been tested in patients of obesity and type 2 diabetes with anti-inflammatory medicines in many clinical trials. 70% of the studies failed to produce the expected improvement in insulin sensitivity although the concept continues to receive support from rodent studies (10-13). This status has been discussed in a couple of recent review articles including ours (14-16). Although there is no consensus yet about the cause of discrepancy, emerging evidence suggests that some inflammatory molecules are required for the maintenance of energy expenditure (EE) - which is called “beneficial activity” of inflammation by us (14). We suggest that the controversy is likely a result of poor understanding of inflammation activity in the regulation of energy metabolism. Here, we would like to extend the view by reviewing evidence in four different fields: obesity, aging, exercise physiology, and cancer cachexia. The aim is to understand why anti-inflammation therapies fail in the improvement of insulin sensitivity in type 2 diabetic patients. Insulin resistance is a result of energy surplus in the body (17).

Obesity

In obesity, energy (glucose and fatty acids) surplus leads to an increase in energy storage (triglycerides) in white adipose tissue. Accumulation of triglyceride leads to adipose tissue expansion, which is coupled with local chronic inflammation in the form of infiltration by immune cells. Several types of immune cells including macrophages, granulocytes, and lymphocytes have been reported in adipose tissue (Fig. 1). In consequence, expression of pro-inflammatory cytokine (TNF- α , IL-1, IL-6, etc) is elevated, and activation of inflammatory kinases (IKK β , JNK1, etc) is enhanced in adipose tissue. The inflammation occurs in the absence of bacteria/viral infection in obesity. Classically, inflammation is considered negative/detrimental in the regulation of metabolism, especially for inhibition of adipose tissue function and induction of insulin resistance. These negative effects have been extensively documented for pro-inflammatory cytokines in review articles (1,15,16,18). We will not reiterate the negative effects in this article. This review is devoted to the beneficial effects of pro-inflammatory cytokines in energy metabolism (14).

In obesity, the energy surplus triggers the chronic inflammation through a hypoxia response in adipose tissue, which is a consequence of adipose tissue expansion (19,20). In addition, metabolites of fatty acids and glucose (diacylglyceride, ceramide, and reactive oxygen species, etc) contributes to the inflammation by activation of serine kinases (PKCs, JNKs and IKKs) in cells (21), which may involve activation of cell membrane receptors (TLR4, CD36 or GPR) (22-25). Induction of endoplasmic reticulum (ER) stress also contributes to activation of JNK and IKK (10,26). Fatty acid and glucose also promote pro-inflammatory response through induction of oxidative stress during production of ATP in mitochondria. These lines of evidence suggest that energy surplus is a risk factor for chronic inflammation.

Hypoxia has indirect and indirect effects in the induction of inflammation. Directly, hypoxia activates transcription factors (NF- κ B and HIF-1) in adipocytes and immune cells (27). Indirectly, hypoxia induces stress responses in adipocytes, such as oxidative stress and ER stress, to promote adipocyte death, which activates macrophages (19,20,28,29). The hypoxia is a result of insufficient blood supply and increased oxygen demand locally in adipose tissue (11,27). The hypoxia response provides a mechanism for most abnormalities in adipose tissue in obesity, such as chronic inflammation, ER stress, oxidative stress, cell death, leptin expression and adiponectin reduction, etc (14).

The inflammation is proposed as a feedback signal to resolve the hypoxia condition (14). The inflammation is a result of disbalance between cells (adipocytes and immune cells) and extracellular matrix in adipose tissue, which leads to the hypoxia response. The inflammation acts in a couple ways to facilitate restoration of the balance. Inflammation inhibits adipocyte expansion and adipocyte differentiation to slow down the tissue expansion (30). In metabolism, inflammatory cytokines (TNF- α , IL-1 and IL-6, etc.) induce lipolysis, and inhibit TAG synthesis in adipocytes. In signaling, inflammation suppresses the insulin signaling pathway and PPAR γ activity in adipocytes (31). The inflammation-induced lipolysis promotes release of energy from adipocytes in mobilization of energy reserve during physical exercise.

In addition, the inflammation stimulates angiogenesis and vessel dilation to enhance blood supply in adipose tissue (32,33), which is required for tissue remodeling. As a major type of inflammatory cells, macrophages produce angiogenic factors, such as PDGF (34), HGF (35,36), and TGF- β (27,36). Macrophages are required for adipose tissue growth in lean mice (37,38) and obese mice (34). Production of the angiogenic factors and vessel dilators (NO) is a part of the macrophage function (34). Macrophage malfunction is associated with angiogenic deficiency in adipose tissue, which was observed in SIRT^{-/-} mice (36). Adipocytes express a high level of angiogenic factors such as VEGF, which induces endothelial cell proliferation and differentiation. VEGF expression is induced by insulin, adipogenesis and hypoxia through activation of HIF-1 (39). Inhibition of the angiogenic activity may inhibit adipose tissue growth in the treatment of obesity (40).

Inflammation enhances energy expenditure and reduce energy intake in direct and indirectly manner. In the indirect pathway, induction of leptin expression represents a molecular mechanism of the inflammatory activity (Fig. 1). Leptin is an adipokine that inhibits appetite and induces energy expenditure (41). Leptin is not an pro-inflammatory cytokine by definition. However, we propose leptin to be a pro-inflammatory cytokine for following reasons: (a) Leptin is a member of superfamily of pro-inflammatory cytokines in terms of protein structure (42); (b) Leptin expression is increased in adipose tissue by inflammation. Leptin transcription is induced by hypoxia (19,43) and inflammatory mediators (44-46). (c) Inflammation enhances expression of leptin receptor. Leptin receptor expression is induced by TNF- α (47), which provides a mechanism by which pro-inflammatory cytokines enhance leptin activity for energy expenditure. (d) Leptin enhances inflammatory response. Leptin induces expression of pro-inflammatory cytokines in macrophages and T-cells (48-50), and stimulates macrophage phagocytosis and monocyte proliferation (49,51). (e) Leptin activates the JAK/STAT3, and MAPKs (mitogen-activated protein kinases p38 and ERK) signaling

pathways through its cell membrane receptor (52,53). These signaling pathways are well known for pro-inflammation reaction in immune cells. Leptin has a strong activity in the induction of energy expenditure in the maintenance of body temperature (54). The leptin deficiency leads to hypothermia in ob/ob mice. We propose that leptin is an excellent example of pro-inflammatory cytokine with an established activity in the induction of energy metabolism. Leptin resistance in obesity is a type of “inflammation resistance”. In obesity, leptin resistance occurs in the central nervous system for hyperphagia and insulin resistance. Leptin resistance makes leptin unable to promote energy expenditure in obesity. Although leptin exhibits the activity in pro-inflammatory response as discussed above, leptin is not required for the chronic inflammation in obesity. ob/ob mice exhibit comparable chronic inflammation to wild type obese mice (27).

In addition to leptin, the pro-inflammatory cytokines may induce energy expenditure regulation of GLP-1 (Fig. 1). IL-6 is reported to promote GLP-1 secretion in gut in response to endotoxin (55). GLP-1 enhances energy expenditure and reduces food intake in addition to promotion of glucose-dependent insulin secretion (56). GLP-1 is reported to enhance heat production in brown fat in a study of GLP-1 agonists (57). The mechanism is related to activation of AMPK in the hypothalamic. The increased serum GLP-1 in subjects of bariatric surgery is proposed to account for the metabolic effects of the surgery (56). Although GLP-1 contributes to the metabolic effects of bypass surgery, the surgery effects remain intact in the absence of GLP-1 activity in several studies (58-60).

Pro-inflammatory cytokines act through cell membrane receptors in the brain or peripheral tissues to induce energy expenditure. The classical pro-inflammatory cytokines (TNF- α , IL-1, and IL-6) share activities with leptin in the induction of energy expenditure (61-65) (Fig. 1). In the peripheral tissue, induction of white fat browning is a mechanism by which inflammation promotes energy expenditure. In this case, IL-6 and PDGF have been reported recently to induce beige cell formation in white fat (66,67). Induction of pro-inflammatory cytokines by over-expression of IKK or NF- κ B p65 (RelA) in the fat tissue induces energy expenditure in mice (70,71). Interferon regulatory factor 4 (IRF4) is reported to promote heat production by brown fat through interaction with PGC-1 α (68). Type 2 macrophages and eosinophils contribute to beige cell formation through secretion of IL-4 and IL-13 (12). The pro-inflammatory cytokines also inhibits food intake to prevent hyperphagia (63,69).

Inhibition of pro-inflammatory response by gene overexpression or knockout consistently supports that lack of inflammation leads to a higher risk of obesity, which may involve induction of hyperphagia and inhibition of energy expenditure. This conclusion is supported by the genetic studies of IL-1 (14), IL-6 (14), IL-15 (72), IL-18 (14), TNF- α (14) and COX-2 (73). The conclusion is also supported by pharmacological studies, in which anti-inflammatory medicines induce weight gain and fat accumulation. The medicines include salsalate (74), celecoxib (73), anti-TNF- α (75), and anti-IL-6 (76). In addition to these non-sterol anti-inflammation medicines, glucocorticoids are well known anti-inflammation drugs that induce weight gain and obesity. In these models, food intake (14) and energy expenditure (73) were examined in some studies. The mechanism remains to be investigated in most of the models of anti-inflammatory medicine.

Above evidence suggests that pro-inflammatory cytokine is an important component in the control of energy metabolism. In the physiological condition, the cytokines are required for maintenance of body temperature in response to environment changes. In obesity, inflammation is a feedback response in the fight against energy over supply. Lack of the inflammatory response increases the risk of obesity.

Caloric restriction (CR)

CR promotes longevity, in which aging-related processes, such as chronic inflammation, oxidative damage, and insulin resistance are inhibited. Reduction of energy intake leads to reduced inflammatory response in CR (77,78). CR is an excellent example for low energy supply in the control of inflammation. It is known that the low energy intake contributes to the low energy expenditure. However, it is not known if the low energy expenditure is a consequence of reduced inflammation.

According to the nature of inflammation, we propose that the reduced inflammation may contribute to the low energy expenditure in CR (Fig. 2). CR decreases the circulating levels of inflammatory cytokines and cuts down pro-inflammatory response in a variety of tissues (77,78). Animals on a CR regimen exhibit a low level of inflammatory cytokines in circulation, and the white blood cells express less inflammatory cytokines in response to stimuli. The anti-inflammatory effects are observed in non-human primates and humans. The anti-inflammatory effects involve in multiple mechanisms including reduced adiposity, enhanced glucocorticoid production, reduced glucose, decreased advanced glycation end-products, increased parasympathetic tone, and more ghrelin secretion. Visceral fat and ectopic fat are the major sources of pro-inflammatory cytokines in obesity (79-81). A reduction in visceral fat from CR contributes to the low inflammatory status. A reduction in inflammation will favor energy saving by reducing energy expenditure. As discussed above, in transgenic studies, inhibition of pro-inflammatory cytokines (IL-6, IL-15 and IL-18) by gene knockout increases the risk for obesity in adult mice (14,72). Suppression of pro-inflammatory response by anti-inflammatory medicines induces weight gain and fat accumulation. In these examples, a reduction in energy expenditure is a key to understand the risk of obesity from anti-inflammatory medicines. The medicines also increase food intake after inhibition of inflammation. CR has beneficial effects in non-obese humans as well (82,83). The benefit of CA may apply to both obese and non-obese conditions.

Exercise

Physical exercise enhances energy expenditure through muscle contraction, in which energy (glucose and fatty acids) is used to generate mechanical forces and heat in muscle. The muscles secrete myokines, which are cytokines or peptides released by muscle fibers (Fig. 3) (84). Myokines exert autocrine, paracrine or endocrine effects. Identified myokines include IL-6, IL-7, myostatin, LIF, BDNF, IGF-1, FGF-2, FSTL-1 and irisin (85). Some of them (IL-6 and IL-7) are classical pro-inflammatory cytokines. Myokines have many activities in the regulation of muscle function. One of them is to maintain energy supply in muscle cells through autocrine and endocrine activities as being reviewed (84,86,87). IL-6 is produced by muscle cells during contraction, especially after glycogen depletion in muscle, suggesting

that IL-6 acts as an energy sensor within the muscle cells. During exercise, IL-6 protein is increased in hundred folds in the muscle tissue and 3 or more folds in the circulation. Several mechanisms are used by IL-6 to provide energy to muscle cells (86,87) (Fig. 3): (a) Inducing lipolysis in adipocytes and myocytes (88); (b) Inducing gluconeogenesis in liver (84). (c) Stimulating fatty acid oxidation in muscle cells in ATP production (88). These activities favor energy supply in muscle, and enhance energy expenditure. In addition, IL-6 induces heat production in white fat and brown fat through induction of white fat browning (67), which is another mechanism of IL-6 action in physical exercise. The elevated inflammatory cytokines use these approaches to promote energy expenditure during physical exercise. In addition, it also triggers expression of IL-10 and IL-1Ra in the anti-inflammatory system (87), which help to control the inflammatory response after physical exercise (85,89). In this case, IL-6 has an anti-inflammatory activity.

It is common that retired athletes gain weight rapidly leading to an increased risk of obesity. This issue has been a concern in most retired athletes. A decrease in energy expenditure is an important factor in the weight gain, but an increase in food is another obvious factor. Mechanism of the two events remains unknown. However, a reduction in the inflammation activity may provide an answer to the changes that contribute to the weight gain in the retired athletes. Inflammation response occurs during physical exercise, which increase energy expenditure and suppresses food intake. When the inflammatory activities are decreased in the retired athletes due to reduced physical exercise, energy expenditure is decreased and appetite is increased. Inflammation inhibits appetite through the central action.

Cachexia

Cancer cachexia and obesity represents two extreme conditions in terms of energy balance. Cachexia is a status of negative energy balance due to the increased energy expenditure and reduced food intake. In contrast, obesity represents a positive energy balance with energy intake overriding energy expenditure. However, the common character in the two statues is chronic inflammation. In cachexia, the inflammation (IL-6 and TNF- α) is strong enough to trigger an obvious increase in energy expenditure with fever and muscle loss (90). In obesity, although pro-inflammatory cytokines are elevated, the increase is not sufficient to induce fever or muscle loss. In the two statues, although inflammation is at different degrees, the role of chronic inflammation remains identical in the induction of energy expenditure.

The resting energy expenditure is enhanced in cachexia. Chronic inflammation contributes to the energy expenditure, in which inflammation induces heat production from fever and white fat browning. The chronic inflammation is a result of tumor growth that triggers mobilization of nutrient from adipose tissue and muscle. Cancer cells have a high demand on energy and nutrients due to rapid proliferation. Inflammatory cytokines are the signals from cancer tissue to induce catabolic responses in adipose and muscular tissues. IL-6 and TNF- α are examples in the tumor-initiated inflammation in cancer cachexia (90). Elevation of these cytokines in the circulation results from two sources: (a) cancer cells and (b) immune cells. Some cancer cells directly produce the cytokine, such as IL-6 by pancreatic

cancer (91). Alternatively, cancer triggers immune cells to produce the cytokines. Inside the solid tumor, a hypoxia response from relatively insufficient blood supply induces chronic inflammation, which includes macrophage infiltration and expression of pro-inflammatory cytokines (92).

The pro-inflammatory cytokines act locally and systemically to regulate energy metabolism (Fig. 4). They act through a couple of mechanisms. Locally, the cytokines inhibit or kill host cells, which favor cancer cells in the competition for energy and nutrient supplies.

Systemically, the cytokines act in brain, fat and muscle tissues. In the brain, the inflammatory mediators inhibit energy/food intake through suppression of appetite, which involves inhibition of the hypothalamus (93). As a result, host has to use the reserves in adipose tissue and skeletal muscle to meet the demand of cancer growth. The cytokines induce lipolysis in fat tissue to mobilize fatty acids into the circulation. Cancer cells use fatty acids in the synthesis of lipid proteins, lipid signaling molecules and ATP. The cytokine also induces white fat browning to increase heat production as recently reported in cachexia models (67). In muscle, the cytokines induce protein breakdown to release amino acids. Amino acids are used in protein synthesis in cancer cells, or in production of glucose by gluconeogenic organs (liver, kidney and intestine) (17). The glucose will support cancer growth through glycolysis, which provides ATP (Warburg effect) as mitochondrial function is usually decreased in cancer cells (94). Glycolysis also provides building materials in the synthesis of nucleotides and lipids. Fat loss usually happens first in cachexia with decreased food intake, which is followed by muscle loss. When fat is not sufficient to provide the energy support to cancer, muscle will be called in to provide the support through release of amino acids. At the end stage, both fat and muscle are decreased in cancer cachexia. In the brain, the cytokines are well known to change body temperature setting to induce fever in cachexia as well being documented.

In the treatment of cancer cachexia, the strategy is to stop weight loss and induce weight gain, which is opposite to the treatment of obesity. In the multimodal approach, dietary supplementation of nutrition is not sufficient to block the weight loss. Inhibition of the inflammatory response has shown promise. Anti-IL-6 antibody has been shown to increase body weight in lung cancer patients (95), which is consistent with weight gain in patients treated with anti-IL-6 for rheumatic disorders (76). Anti-TNF- α antibody was tested in lung cancer patients, but no effect was observed in the treatment of cancer cachexia (96).

However, anti-TNF- α antibody increased body weight in the treatment of psoriasis patients (75). These data suggest that IL-6 may be more important than TNF- α in cancer cachexia.

Summary

Inflammation is the common theme in obesity, caloric restriction, exercise and cachexia. In this review, we explain the inflammation activity in the regulation of energy metabolism in these conditions (Fig. 5). Multiple lines of evidence consistently suggest that inflammation is a key component in the regulation of energy expenditure. It senses energy surplus and deficiency in the body to coordinate energy metabolism. Inflammation induces energy mobilization and energy expenditure in addition to the inhibition of energy storage and food intake. Although there is abundant literature to support these activities of inflammation, the

view of beneficial effects of pro-inflammation remains under appreciated in obesity. In the treatment of obesity, CR is an ideal approach, but is hard to practice in most obese patients. It is worth to consider inflammation-associated energy expenditure in the control of obesity. “Inflammation resistance” prevents the beneficial effects of the inflammation in obesity. Physical exercise may break the inflammation resistance to promote energy expenditure. Pro-inflammatory response in physical exercise is the best example of a self-resolved inflammation that fine tunes the inflammation system to promote energy expenditure. Uncontrolled inflammation is not recommended as it may generate more damage than benefits, such as cancer cachexia.

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Fig. 1. Inflammation in obesity

Fig. 2. Inflammation in CR

Fig. 3. Inflammation in exercise

Fig. 4. Inflammation in cachexia

Fig. 5. Inflammation in physiology