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Neuroendocrine Factors in the Regulation of Inflammation: Excessive Adiposity and Calorie Restriction

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Abstract

Acute inflammation is usually a self-limited life preserving response, triggered by pathogens and/or traumatic injuries. This transient response normally leads to removal of harmful agents and to healing of the damaged tissues. In contrast, unchecked or chronic inflammation can lead to persistent tissue and organ damage by activated leukocytes, cytokines, or collagen deposition. Excessive energy intake and adiposity cause systemic inflammation, whereas calorie restriction without malnutrition exerts a potent anti-inflammatory effect. As individuals accumulate fat and their adipocytes enlarge, adipose tissue undergoes molecular and cellular alterations, macrophages accumulate, and inflammation ensues. Overweight/obese subjects have significantly higher plasma concentrations of C-reactive protein and several cytokines, including IL-6, IL-8, IL-18, and TNF-alpha. Experimental animals on a chronic CR regimen, instead, have low levels of circulating inflammatory cytokines, low blood lymphocyte levels, reduced production of inflammatory cytokines by the white blood cells in response to stimulation, and cortisol levels in the high normal range. Recent data demonstrate that CR exerts a powerful anti-inflammatory effect also in non-human primates and humans. Multiple metabolic and neuroendocrine mechanisms are responsible for the CR-mediated anti-inflammatory effects, including reduced adiposity and secretion of pro-inflammatory adipokines, enhanced glucocorticoid production, reduced plasma glucose and advanced glycation end-product concentrations, increased parasympathetic tone, and increased ghrelin production. Measuring tissue specific effects of CR using genomic, proteomic and metabolomic techniques in humans will foster the understanding of the complex biological processes involved in the anti-inflammatory and anti-aging effects of CR.

Keywords

obesity; energy intake; adipocyte; adipokines; neuroendocrine

Introduction

Inflammation is a complex set of responses to cellular/tissue injuries triggered by pathogenic invaders and/or trauma. This well-orchestrated and tightly controlled process normally leads to elimination of noxious agents and to healing of the damaged tissues (Nathan 2002).

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Therefore, acute inflammation usually is a self-limited life preserving response, as reflected by the augmented risk of life-threatening infections in individuals with genetic deficits in some components of the inflammatory cascade (Arnaout 1990).

In contrast, chronic inflammation triggered, for example, by some viral or intra-cellular pathogens (e.g. Hepatitis B and C, Mycobacterium tuberculosis, etc.) can lead to persistent tissue damage by activated leukocytes, cytokines, and collagen deposition, and in some cases may even promote neoplastic transformation (Schottenfeld and Beebe-Dimmer 2006). In addition, chronic inflammation plays a central role in the pathogenesis of several age-associated chronic diseases (e.g. atherosclerosis, cancer, arthritis, dementia and osteoporosis) and in the aging process itself (Akiyama et al. 2000;Coussens and Werb 2002;Libby 2002).

Elevated cellular and circulating IL-6 levels have emerged to be a common characteristic of senescence among several species, including rodents, monkeys and humans (Ershler et al. 1993;Harris et al. 1999). Recently, it has been shown that excessive energy intake and adiposity, in particular visceral adiposity, cause a state of systemic chronic inflammation (Rajala and Scherer 2003;Visser et al. 1999;Fontana et al. 2007a). In contrast, calorie restriction (CR) without malnutrition, the most robust intervention to slow down aging and prevent/delay the occurrence of many chronic diseases, exerts a potent anti-inflammatory effect (Fontana and Klein 2007).

Excessive adiposity, neuroendocrine alterations and inflammation

Excessive caloric intake, particularly in sedentary individuals, results in a chronic positive energy balance, increased abdominal adiposity and several metabolic and neuroendocrine alterations, including: (1) insulin resistance (Xu et al. 2003); (2) chronic inflammation (Rajala and Scherer 2003;Visser et al. 1999;Fontana et al. 2007a); (3) sympathetic nervous system and angiotensin system activation (Seals and Bell 2004;Engeli et al. 2000); (4) accumulation of advanced glycation end-products (Soldatos et al. 2005), (5) oxidative stress-induced protein, lipids and DNA damage (Furukawa et al. 2004), and (6) alterations in neuroendocrine systems (Smith et al. 2001). All these metabolic abnormalities are implicated in the pathogenesis of several age-associated chronic diseases, such as type 2 diabetes, atherosclerosis, cancer and arthritis, which can cause accelerated dysfunction and damage of various tissues and organs (Must et al. 1999).

Chronic inflammation, in particular, is one of the key metabolic alterations associated with excessive calorie intake and adiposity (Rajala and Scherer 2003;Visser et al. 1999;Fontana et al. 2007a). Data from epidemiological studies have clearly shown that obesity is associated with increased non-infectious chronic inflammation, manifested by an up-regulation of cytokine and chemokine production by adipose tissue, presumably from both adipocytes and infiltrated macrophages (Rajala and Scherer 2003;Wellen and Hotamisligil 2003). Weight (fat) loss, induced by a negative energy balance, reduces inflammation by decreasing the production of inflammatory cytokines and chemokines by adipose tissue (Esposito et al. 2003). In contrast, removal of large amounts of subcutaneous abdominal fat by liposuction does not improve inflammation or other cardiometabolic risk factors for cardiovascular disease (Klein et al. 2004).

Until rather recently, adipocytes were simply considered to be fat storage depots. Instead, it is now clear that adipose tissue is an endocrine organ that secretes several adipokines, which act as hormones as well as pro-inflammatory cytokines (Rajala and Scherer 2003). These include leptin, adiponectin, resistin, tumor necrosis factor (TNF), IL-6, MCP-1, and other cytokines and chemokines (Rajala and Scherer 2003). As individuals accumulate fat and their adipocytes enlarge, adipose tissue undergoes molecular and cellular alterations, macrophages accumulate, and inflammation ensues (Cancello et al. 2005;Weisberg et al. 2003). Infiltrated and activated

macrophages in adipose tissue of obese individuals are responsible for most of the cytokine production, in particular IL-6 and TNF-alpha (Cancello et al. 2005;Weisberg et al. 2003).

Plasma IL-6 concentrations are much higher in the portal vein, which drains visceral fat, than in peripheral artery blood in obese subjects, demonstrating that visceral fat is an important source of IL-6 production in obese persons (Fontana et al. 2007a). These data are consistent with previous ex vivo findings that IL-6 secretion is higher in omental than in subcutaneous adipose tissue (Fain et al. 2004). Moreover, portal vein IL-6 concentrations correlate directly with arterial CRP concentrations in obese subjects (Fontana et al. 2007a). Recently, IL-6 was shown to cause systemic insulin resistance (Cai et al. 2005). Elevated IL-6 and CRP concentrations are predictors for the development of type 2 diabetes and myocardial infarction (Fontana et al. 2007a;Xu et al. 2003;Sattar et al. 2003).

Calorie restriction and inflammation

Hundreds of studies have consistently shown that CR without malnutrition increases maximum lifespan and healthspan in different species, including yeast, flies, worms, fish, and rodents (Masoro 2000;Weindruch and Sohal 1997). Multiple overlapping mechanisms are responsible for the CR-mediated effects on aging-related diseases and aging itself in rodents, including decreased free radical-induced tissue damage, improved insulin sensitivity, decreased inflammation and several major neuroendocrine adaptative responses (Fontana and Klein 2007). In addition, CR enhances DNA repair processes, decreases protein glycation, and increases removal of damaged cellular proteins and oxidized lipids (Sell et al. 2003;Forster et al. 2000;Leeuwenburgh et al. 1997). Many of the effects of CR are likely mediated by regulation of gene expression, with 1) upregulation of genes involved in stress resistance, protection against oxidative damage, cellular repair and survival, and 2) downregulation of genes involved in mediating inflammation (Lee et al. 1999).

One of the most important mechanisms for the CR-mediated retardation of aging and prevention/delay of chronic diseases is the reduction in chronic systemic inflammation (Ershler et al. 1993). It is important to note that the CR-induced lower inflammatory state does not occur passively from an absence of inflammatory stimuli, but from positive actions of specific metabolic, hormonal and gene expression products that repress reactions to potential inflammatory stimuli that do not demand a full response (Higami et al. 2003;Lamas et al. 2003;Matsuzaki et al. 2001;Spaulding et al. 1997a).

Studies on animals have consistently shown that chronic CR results in low levels of circulating inflammatory cytokines, low blood lymphocyte levels, reduced production of inflammatory cytokines by the white blood cells in response to stimulation, and cortisol levels in the high normal range (Higami et al. 2003;Lamas et al. 2003;Matsuzaki et al. 2001;Spaulding et al. 1997a;Sabatino et al. 1991;Spaulding et al. 1997b;Tsuchiya et al. 2005). Furthermore, chronic CR enhances the ability to cope with intense inflammatory stressors. The inflammatory response to an injection of carageenan toxin into the footpad is attenuated in mice on a CR regimen (Klebanov et al. 1995). In addition, CR protects against aging-associated deterioration in immune function, including reduced immune response capacities, thymic involution, and shifts in leukocyte and lymphocyte subsets (Spaulding et al. 1997b;Poetschke et al. 2000;Weindruch et al. 1997;Messaoudi et al. 2006). CR also reduces the production of prostanoids (e.g. TXA2, PGI2, and PGE2) that occurs in sites of disease and inflammation (Kim et al. 2004).

Recent data show that CR also exerts a powerful anti-inflammatory effect in non-human primates and humans (Mascarucci et al. 2002). In monkeys CR attenuates the age-associated increase in IL-6 protein production by peripheral mononuclear cells (Mascarucci et al. 1999;Kim et al. 1997). Data from self-imposed CR, and from short-term CR intervention

studies have shown that CR in humans results in a reduction of markers of inflammation and pro-inflammatory cytokines. In non-obese, sedentary humans, a randomized clinical study demonstrated that a 20% reduction in calorie intake for 12 months decreases visceral fat mass, improves insulin sensitivity, increases plasma adiponectin concentration, reduces circulating inflammatory markers, decreases plasma T3 levels, and reverses some of the age-related deterioration in cardiac diastolic function (Fontana et al. 2007b;Racette et al. 2006;Weiss et al. 2006).

Information regarding the long-term effects of CR is coming from studies conducted in members of the Calorie Restriction Society, who practice self-imposed CR in the belief that CR will extend their lifespan (Fontana et al. 2004;Holloszy and Fontana 2007;Meyer et al. 2006). The CR Society members designed their diets to consist primarily of micronutrient-dense foods, supplying more than 100% of the Recommended Daily Intake (RDI) for all of the essential nutrients, while minimizing energy-dense foods and thus total energy content. These individuals have been eating ~ 30% fewer calories for an average of ~ 7 yr than age- and sex-matched, control subjects consuming a typical Western diet (1770±350 kcal/d and 2490±479 kcal/d, respectively).

The CR practitioners show many of the same alterations in metabolic and organ function that have been reported in CR rodents, including a low percent total body and truncal fat, low blood pressure, enhanced insulin sensitivity and lipid profile, and low serum T3 concentration (Fontana et al. 2004;Fontana et al. 2006). Also like mice and rats, middle-aged humans on CR have very low levels of chronic inflammation as reflected in remarkably low levels of C-reactive protein of ~0.3 mg/L compared to values in the 1.5 to 2mg/L range in healthy age matched controls (Fontana et al. 2004;Holloszy and Fontana 2007;Meyer et al. 2006). Serum tumor necrosis factor-α (TNF-α) levels are also low in humans on long-term CR, with values approximately 50% lower than those of age-matched controls (Fontana et al. 2006;Meyer et al. 2006).

In addition, left ventricular (LV) diastolic function (i.e. parameters of viscoelasticity and stiffness) in these CR subjects were similar to normal sex-matched subjects who were approximately 16 yr younger (Meyer et al. 2006). This finding suggests that CR might influence primary aging in humans, because aging results in a progressive increase in LV stiffness and impaired LV diastolic function (Kitzman et al. 1991), and is similar to the cardiac effects of CR observed in mice (Taffet et al. 1997). The mechanism for this beneficial effect on LV function is not known, but could represent decreased connective tissue accumulation and myocardial fibrosis caused by the effects of CR on inflammatory/fibrogenic mediators, such as TNF-α and transforming growth factor β1 (TGFβ1) (Sivasubramanian et al. 2001) (Border and Ruoslahti 1992).

Anti-inflammatory mechanisms/pathways triggered by chronic calorie restriction

Reduced adiposity and circulating adipokines

Excessive adiposity is associated with a state of low grade chronic inflammation as reflected in significant higher circulating levels of IL-6, IL-8, IL-18, TNF-alpha, MCP-1, fibrinogen and C-reactive protein (Rajala and Scherer 2003;Visser et al. 1999;Fontana et al. 2007a). Weight loss induced by CR or exercise reduces macrophage activation and infiltration in adipose tissue, and systemic inflammation (Clement et al. 2004;Esposito et al. 2003;Xydakis et al. 2004). The weight-loss mediated reduction in inflammatory markers is also related to improvements in insulin resistance, and serum adipokine concentrations. Weight loss reduces circulating levels of resistin, a proinflammatory molecule (Bokarewa et al. 2005), and increases adiponectin, an

insulin sensitizer and potent anti-inflammatory hormone produced by adipocytes (Engeli et al. 2003;Xydakis et al. 2004). In addition, weight loss reduces leptin, an adipokine with multiple biological effects in modulating inflammation and autoimmune reactivity. Leptin induces T cell proliferation, promotes Th1 cell differentiation and induces pro-inflammatory cytokine production (Fantuzzi and Faggioni 2000).

Enhanced glucocorticoids production

Another mechanism by which CR may selectively exert it's anti-inflammatory effects is via enhanced endogenous corticosteroid production (Sabatino et al. 1991). Chronic CR potentiates the diurnal elevation of plasma corticosterone. CR mice and rats have "moderately" but significantly higher daily mean plasma free corticosterone concentration than mice fed "ad libitum" throughout their lifespan. This moderate increase in corticosterone does not, however, reflect increased hypothalamic-pituitary activity, as plasma ACTH concentration is lower in CR than in "ad libitum" fed rodents (Han et al. 2001). The elevated free corticosterone is due to an enhanced response of the adrenal gland to ACTH (Han et al. 2001).

It is well known that the hypothalamic–pituitary–adrenal axis and glucocorticoids in particular are essential in limiting and resolving the inflammatory process (Sapolsky et al. 2000). Glucocorticoids have pleiotropic inhibitory effects on the immune system and inflammatory gene expression (Rhen and Cidlowski 2005). In addition, treatment with pharmacological doses of exogenous glucocorticoids has been used to block many inflammatory and autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, thyroiditis, glomerulonephritis, multiple sclerosis, and psoriasis.

Reduced glycemia and advanced glycation end-products

Hyperglycemia and the accumulation of advanced glycation end products (AGE) have been shown to exert pro-inflammatory effects. Hyperglycemia, a major metabolic disorder associated with excessive adiposity and insulin resistance, has been shown to upregulate the expression of several genes involved in inflammation (e.g. activator protein-1, nuclear factor-kB, and early growth response), and the secretion of inflammatory cytokines in several cell types both *in vitro* and *ex vivo* (Nareika et al. 2006;Morohoshi et al. 1996).

Moreover, it has been shown that hyperglycemic spikes acutely increase plasma IL-6, TNF-α, and IL-18 concentrations, probably through an oxidative mechanism, in patients with impaired glucose tolerance as well as in healthy control subjects (Esposito et al. 2002). Finally, the interaction of the receptors for advanced glycation end products (RAGE) with AGE results in activation of signal transduction pathways that mediate diverse responses in a wide array of cell types, including induction of oxidative stress, increased extracellular matrix permeability, release of inflammatory cytokines and growth factors, and the increased expression of adhesion molecules and chemokines (Hofmann et al. 1999).

Chronic CR improves insulin sensitivity and reduces serum glucose and AGEs concentrations (Masoro et al. 1989;Cefalu et al. 1995). Moreover, CR significantly reduces AGE accumulation in several tissues of experimental animals, including kidney, aorta and skin (Cefalu et al. 1995;Sell et al. 2003;Teillet et al. 2000).

Sympatholitic activity and increased parasympathetic tone

The two principal branches of the autonomic nervous system (parasympathetic and sympathetic pathways) control heart rate, blood pressure, and respiratory rate, gastrointestinal motility, and other essential life functions such as the innate immune system (Tracey 2007). Rodents maintained on a CR diet have lower resting heart rate and higher heart and blood pressure

variability than rodents on ad libitum diet, suggesting that CR decreases sympathetic activity and augments parasympathetic or vagal tone (Mager et al. 2006).

Interestingly, vagus nerve stimulation has been shown to effectively suppress cytokine-mediated inflammation and damage in several pathological conditions, including endotoxemia, ischemia reperfusion injury, sepsis, and arthritis (Borovikova et al. 2000). In contrast, vagotomy aggravates cytokine responses to inflammatory stimuli and sensitizes animals to the lethal effects of endotoxin (Borovikova et al. 2000). The neurotransmitter acetylcholine is released by firing efferent vagus nerve endings, binds to nicotinic-α7 receptors on resident macrophages, and thus prevents the release of TNF, IL-1, and IL-18 (Wang et al. 2003). Data from experimental animal studies indicate that the threshold of vagus nerve activity that stimulates the vagal anti-inflammatory pathway is significantly lower than that required to change heart rate variability.

Increased ghrelin production

Ghrelin is a circulating orexigenic peptide secreted predominantly from stomach cells (Lee et al. 2002). Ghrelin modulates growth hormone release, energy homeostasis and central feeding regulation. Ghrelin levels increase following fasting and chronic food deprivation (Lee et al. 2002). Chronic CR significantly increases plasma ghrelin concentration as well as total ghrelin production in the stomach of rodents (Yang et al. 2007).

Chronic ghrelin administration potently stimulates food intake, and increases body weight and adiposity in rodents (Tschop et al. 2000). Intravenous ghrelin infusion enhances appetite and increases food intake in humans, too (Wren et al. 2001). In addition, ghrelin exerts potent anti-inflammatory effects (Li et al. 2004). It has been shown that ghrelin, via the functional cell surface growth hormone secretagogue receptor (GHS-R), inhibits proinflammatory cytokine production, cell binding, and nuclear factor-kappaB activation in a wide variety of cells in vitro (Dixit et al. 2004). Further, ghrelin attenuates endotoxin-induced cytokine production in a murine cytokine-induced anorexia model. Interestingly, ghrelin and leptin exert mutually antagonistic effects on food intake and immune function (Dixit et al. 2004).

CONCLUSIONS

The neuroendocrine system and inflammation are deeply involved in the pathogenesis of many age-related diseases and in the biology of the aging process itself. Calorie intake and adiposity, and their associated metabolic and neuroendocrine alterations, are important determinants of inflammation in experimental animals and humans.

Excessive calorie intake and adiposity up-regulate the expression of several genes and proteins involved in mediating inflammation in many tissues and organs. In contrast, CR with adequate nutrition, a robust life extending intervention, prevents or attenuates local and systemic inflammation via multiple metabolic and neuroendocrine mechanisms. Recent data indicate that CR exerts a powerful anti-inflammatory effect also in non-human primates and humans. Measuring tissue specific effects of CR using genomic, proteomic and metabolomic techniques in humans will promote an understanding of the complex biological processes involved in the anti-inflammatory and anti-aging effects of CR.

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