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PERSPECTIVE

Stress and Obesity as Risk Factors in Cardiovascular Diseases: A Neuroimmune Perspective

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Abstract Obesity is now growing at an alarming rate reaching epidemic proportions worldwide thus increasing morbidity and mortality rates for chronic disease. But although we have ample information on the complications associated with obesity, precisely what causes obesity remains poorly understood. Some evidence attributes a major role to a low-grade chronic inflammatory state (neurogenic inflammation) induced in obesity by inflammatory mediators produced and secreted within the expanded activated adipocyte pool. Adipose tissue is an endocrine organ that secretes numerous adipose tissue-specific or enriched hormones, known as adipokines, cytokine-like molecules thought to play a pathogenic role in cardiovascular diseases. The imbalance between increased inflammatory stimuli and decreased anti-inflammatory mechanisms may depend on chronic stress. Hence the positive correlation found between stress, obesity and cardiovascular diseases. The chronic inflammatory state associated with insulin resistance and endothelial dysfunction is highly deleterious for vascular function. This review focuses on the proposed neuroimmunodulatory mechanisms linking chronic (psychological) stress, obesity and cardiovascular diseases.

Keywords Stress · Immune system · Obesity · Insulin · Adipokines · Cardiovascular diseases

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Introduction

Although ample consensus over the past century accepts that the mind influences physical well-being only far later did research develop a discipline investigating within the framework of psychosomatic medicine, a possible relationship between the mind and the body. In an innovative study, Ader and Cohen first coined the term psychoneuroimmunology (PNI) to indicate the relationships between stress, immune system (IS) and health outcomes (Ader and Cohen 1975), now known by the modern term neuroimmunomodulation (NIM). The International Society of NeuroImmunoModulation (ISNIM) states that "[…] of particular interest are the mechanisms by which local and systemic immune processes act upon the brain, and in turn, how the brain modulates the susceptibility and course of inflammatory, infectious, neoplastic, and autoimmune diseases via direct innervation and the release of hormones and neuropeptides. NIM is also intimately linked to physiological processes such as temperature regulation, sleep patterns, appetite control, energy metabolism, biological rhythms, and behavior, and to the effect of stress on immunity."(www.isnim.org).

An exciting field of current research studies whether environmental or psychosocial factors such as stress, affect the onset of disease and investigates the complex interactions linking the body's major control and sensory systems in health and disease. NIM also investigates how psychosocial factors influence the endocrine system (Brannon and Feist 2004; Ho et al. 2010). Accumulating evidence underlines the major role of chronic stress in accumulating visceral fat, secondary to altered eating behaviors (Siervo et al. 2009; Capuron et al. 2011). Increased abdominal obesity predisposes to the metabolic syndrome, diabetes and cardiovascular diseases (CVD) (Black 2006). Convincing evidence links the onset of visceral obesity to various stressors acting on the hypothalamic-pituitary-adrenal (HPA) axis and on the central and peripheral

sympathetic nervous systems (Dallman et al. 2006; Kyrou et al. 2006; Bose et al. 2009; Warne 2009). Because obesity and the metabolic syndrome have reached epidemic proportions in Western populations the World Health Organization (WHO) has predicted a "globesity epidemic" with more than 1 billion adults being overweight and at least 300 million of these being clinically obese (Hansen et al. 2010). In the United States approximately 65 % of adults are overweight or obese (Hedley et al. 2004; Heber 2010), and almost half of the population of Italian men and about 1 in 3 Italian women are overweight or obese (Micciolo et al. 2010). Having up-to-date information on the link between chronic (psychological) stress, obesity, low-grade inflammation, energy dysregulation (leptin-insulin resistance) and multifactorial diseases including the metabolic syndrome and CVD would help in developing strategies to combat the obesity epidemic.

The aim of this descriptive review is therefore to examine advances reported over the past 5 years on the relationships linking chronic stress, obesity, and progressive CVD and to investigate how NIM by regulating body energy could integrate these increasing worldwide social and psychosocial concerns in modern society.

Stress, allostasis, and allostatic load

The term psychosocial stress as used in this review includes various human stresses, including work-related stress (mobbing), family stress (divorce, mourning, solitude, poverty) and environmental stress (climate, traffic, and noise). The term "Stress" in general describes the effects induced by psychological and environmental factors on physical or mental well-being and the capacity and mechanisms to sustain and adjust to externally or internally challenging situations (Esch and Stefano 2010a). Stress implies a challenge (stimulus or stressor) that requires behavioral, psychological, and physiological changes (adaptations) to be successfully met, thereby inducing a state of hyperarousal initiating the necessary counteracting reactions (Esch et al. 2003; Stefano et al. 2005). This hyperarousal, alert state involves physiological mechanisms known as the stress/emergency response or fight-or-flight response. Alertness was first described by Walter Cannon almost 100 years ago (Cannon 1914, 1915).

The body's ability to restore a dynamic balance in response to environmental stressors is referred to as "allostasis" and stress as "allostatic load" (Sterling and Eyer 1988; McEwen and Wingfield 2003; McEwen and Gianaros 2010). Allostasis literally means "maintaining stability through change" (Esch and Stefano 2010a) i.e., adjusting physiological variables to the ever-shifting environmental conditions. "Allostatic load" refers to the wear and tear that the body experiences owing to repeated allostatic cycles (McEwen and Gianaros 2010).

When the brain perceives an experience or stimulus as stressful, it initiates physiologic and behavioral stress-driven responses, leading to allostasis and adaptation. The goal is to restore balance, self-organize, and maintain autonomy under challenge, and ultimately to survive. As a result of this ongoing adaptation over time, a substantial allostatic load can accumulate causing stress. Overexposing the body to neural, endocrine, and immune stress mediators can have adverse effects on various organ systems, leading to the onset or progression of diseases such as metabolic disease or cognitive decline (Esch and Stefano 2010a; McEwen and Gianaros 2010).

Stressors activate the HPA axis or the sympathetic nervous system (SNS) by inducing the parvocellular neurons in the hypothalamic paraventricular nucleus to produce corticotropic releasing hormone (CRH). CRH then stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) targeting to the zona fasciculata in the adrenal cortex to produce glucocorticoids. Together with the HPA axis, the SNS is the major pathway involved in the cross-talk between the brain and the immune system (Elenkov et al. 2000). Peripheral norepinephrine/epinephrine (NE/E) act by increasing glycogenolysis in liver and muscle, lipolysis in adipose tissue, and modulating insulin secretion (Marino and Cosentino 2011) thus inducing metabolic disorders, such as obesity. Ample data now show that obesity is characterized by SNS predominance in the baseline state and reduced SNS responsiveness after various sympathetic stimuli (Marino and Cosentino 2011). SNS activity is associated with the metabolic syndrome and energy balance. Sympathomimetic medications decrease food intake, increase resting metabolic rate, and thermogenic responses, whereas SNS blockers exert the opposite effect (Tentolouris et al. 2006). The SNS contributes little to daily energy expenditure, only about 5 % in healthy subjects consuming a diet intended for weight maintenance. Fasting suppresses SNS activity, whereas meal ingestion induces it. In obesity, a reduced SNS responsiveness after various sympathetic stimuli is observed and also a weight loss reduces SNS overactivity (Tentolouris et al. 2006).

In the sympathetic nerve terminals neuropeptide Y (NPY) is co-stored with NE, and upon sympathetic system activation is co-released with this neurotransmitter. NPY and catecholamines (NE/E), as SNS end products, and glucocorticoids , as HPA axis end products, are major homeostatic regulators but also the main components in the peripheral stress system. Hence some evidence associates acute or subacute stress with a differential increase in catecholamines, NPY and glucocorticoids, depending on the type and intensity of stressors, whereas chronic stress preferentially increases NYP levels and glucocorticoids. Stress exaggerates diet-induced obesity through a peripheral NPY-mediated mechanism in the abdominal white adipose tissue (Kuo et al. 2007). The frequency with which NPY and other

stress reactants are released into the fat, as well as the amplitude of release may critically contribute to the risk for metabolic syndrome (McEwen 2012). Chronic, repeated, stress pathway activation (allostatic load) leads not only to the metabolic syndrome but also to CVD.

Stress, neuroimmune activation and disease

The main stress response mediators are the catecholamines (NE/E) and cortisol. The catecholamines act through adrenergic receptors and cortisol acts through glucocorticoid receptors. The presence of these receptors in various immune cells clearly shows and reinforces the link between stress, and inflammation due to neuroimmune activation. For this reason immune-mediated mechanisms may stimulate the onset of several chronic diseases, because, as Blalock hypothesized, the immune system may function as a "sixth sensory organ" intended to recognize those stimuli that the neuroendocrine system cannot recognize, and transmit the information to the CNS via immune-derived soluble mediators (hormones, neuropeptides, cytokines) (Blalock 1984). In a later study, Besedovsky et al. (1985) further suggested that the CNS acquires information not only about the type of immune response through the immune system-derived soluble mediators, but also on the localized ongoing immune response through the soluble factors released from nerve fibers located within the lymphoid organs.

Changes taking place in the immune system or the endocrine system during development and throughout life can profoundly influence immune homeostasis and hence the allostatic load that induces various diseases (Negrao et al. 2000). Interactions between neuroendocrine hormones and the immune system are undoubtedly involved in regulating normal immunity but also have a pathogenetic role in various immune-mediated diseases such as autoimmunity, cancer, aging, and various physical and psychological stress-induced diseases in which inflammation plays a major role (McEwen 1998). Besides, stress can impair an organism's ability to cope, weaken neuroendocrine responses and thus impair immune function. For example, circumstances and external forces, such as financial or economic crises, are responsible for the psychosocial stress that individuals perceive as a threat, related to demographic, socioeconomic or environmental degradation. Individual behavior and resources are nevertheless of importance for stress resilience and relief (Stefano et al. 2005; Esch and Stefano 2010a). Consequently, traumatic events may dysregulate the HPA axis and SNS, increasing severe, life-threatening illnesses including CVD (Kendall-Tackett 2009). Chronic stress activates the immune system thus consuming energy. In this way many apparently unrelated metabolic diseases arise because other organs receive no energy-rich fuels from storage organs. Changes in metabolic pathways lead to objective symptoms associated with those very conditions: cachectic obesity, insulin resistance and hyperinsulinemia, dyslipidemia, adipose tissue increase in inflamed tissues, hypertension and osteopenia (Straub et al. 2010; Straub 2011, 2012). Increasing evidence therefore underlines the pathogenetic relationships between stress, obesity and metabolic disease through neuroimmune activation.

Stress and inflammation

Reactions to stress: eating as a neuroendocrine reward response

Allostasis, but especially allostatic load, arises through several inflammatory cytokines that target the HPA axis and SNS but also influence cognition and emotion (Businaro et al. 2012a; Peters and McEwen 2012). Long-term exposure to glucocorticoids stimulates the brain reward system (Heber and Carpenter 2011) thus encourages the search for "comfort food" (high fat and sugar content) (Adam and Epel 2007) and clearly ranging from depression to anxiety illustrates the close relationship between stress, inflammation and obesity (Hill et al. 2010).

Stress induces various neuroimmune responses. A crucial component in CNS reward and motivation circuitries are the brain ventral tegmental area neurons. These dopaminergic cells send projections to target regions in the frontal brain, notably to a structure lying deep beneath the frontal cortex, i.e. the nucleus accumbens (Nestler 2001; Nestler et al. 2001). The brain reward systems distinctly differ in animals and humans. The animal dopamine system is a phylogenetically old though highly effective component in motivational physiology and behavior. The human reward circuit is more complex, and is integrated with several other brain regions. The amygdala, for instance, is closely related to primitive emotions such as fear, but the brain is integrated with other pathways, those enriching and experiencing emotion, driving individual responses or reward behavior toward sex, social interaction and especially, food (Esch et al. 2004; Esch and Stefano 2010b).

By encouraging the search for palatable food (sweets and fatty foods), stress stimulates endogenous opioid release. Consuming highly palatable food increases mu-opioid receptor binding and precipitates opioid withdrawal symptoms (Wardle et al. 2000). People may choose calorie-rich foods to blunt their stress response or reduce anxiety. Calorie intake can increase also in response to the elevated cortisol levels commonly found during chronic stress. Under steady-state conditions, glucocorticoids and insulin regulate metabolism in opposite ways. During chronic stress this balance becomes completely disrupted. Some evidence associates the role of increased glucocorticoid concentrations related to insulin resistance, as well as to

leptin resistance, in desensitizing satiety signals and inducing weight gain (Adam and Epel 2007; Heber and Carpenter 2011). Ample evidence therefore documents overeating as a neuroendocrine reward response.

Stress, eating behavior and obesity

Obesity has a well-known multifactorial origin comprising genetic, environmental, socio-economic, behavioral or psychological causes or both, and a relative increase in both morbidity and mortality (Flegal et al. 2007). Obesity is the ultimate consequence of a chronic positive energy balance, regulated by a complex signalling network that links the endocrine system and CNS in search of food as reward (Adam and Epel 2007). In research investigating NIM, Heber and Carpenter (2011) reported that in overweight and obese subjects the same brain reward circuits activated in drug abuse intervene in hedonic urges for foods both in animals and in humans, via dopamine and other neurotransmitters that increase motivation for food intake. Hence surprisingly reduced brain D2 levels in obese individuals are inversely related to body weight.

Humans react to stress in different ways. Stress may be interpreted as "challenge" or a "threat". (Adam and Epel 2007).The body responds to a challenge mainly by activating the adrenergic system in the *locus ceruleus.* Conversely, the body responds to a threat in a more serious and harmful way by activating the HPA axis thereby increasing circulating cortisol, in turn increasing blood insulin and leptin (Adam and Epel 2007). Hence the pathways underlying the relationship between stress, cortisol, and the feeding stimulator NPY resemble those regulating the search for food or substances of abuse, such as opioids (Esch and Stefano 2010b). These behavioral differences depend on the fact that stress stimuli such as overnutrition, physical inactivity, and aging result in cytokine hypersecretion and eventually lead to insulin resistance and type 2 diabetes in genetically or metabolically predisposed individuals (Adam and Epel 2007). Alternatively, resistance to insulin's anti-inflammatory actions enhances circulating levels of pro-inflammatory cytokines giving rise to persistent low-grade inflammation (Huffman and Barzilai 2009). Chronic stress, via the NPY-Y2R pathway, amplifies and accelerates diet-induced obesity and the metabolic syndrome (Kuo et al. 2008). Accordingly, longitudinal studies show that chronic life stress favors a preference for energy-rich and nutrient-dense foods, particularly high in sugar and fat, causally linked to weight gain (Torres and Nowson 2007). Hormones released in response to stress affect appetite in opposite ways: NE suppresses appetite during acute stress whereas cortisol stimulates it (Halford 2001; Takeda et al. 2004). Cortisol may dysregulate feeding behavior by continually activating NPY and blocking the leptin pathway (leptin resistance) (Bjorntorp 2001). Overall these findings confirm that chronic stress triggers the search for comfort food thus causing obesity, low-grade inflammation, energy dysregulation and leptin/insulin resistance. Our review identified many studies confirming that as an appetite stimulant, cortisol along with the HPA axis are responsible for altering the balance between hunger and satiety (Bjorntorp 2001; Adam and Epel 2007; Chrousos 2009; Capuron et al. 2011).

Cytokines in NIM interactions: role of adipose tissue

Research over many years has helped to understand how chronic HPA axis stimulation favors circulating cytokine release thus influencing the relationship between the CNS and IS (Ramírez et al. 1996; McEwen and Gianaros 2010). Studies in more recent years have introduced a third actor, adipose tissue, involved in energy regulation but also in immunomodulation by regulatory T cells (Treg) and T helper (Th1/Th17) cells (Matarese and La Cava 2004; Curotto de Lafaille and Lafaille 2009; Galgani and Matarese 2010). These immunological findings prompted us to extend current knowledge on the metabolic pathways underlying stress-induced obesity and related disease, especially CVD, to NIM.

Metabolic pathways influence the host immune system through hormone release that regulates the magnitude and specific direction (deviation) taken by innate as well as adaptive immune responses (Eskandari and Sternberg 2002; Steinman 2004; Brogden et al. 2005). When the brain perceives changes in the peripheral environment (stressors), it mounts a neuroendocrine response matching the immune system response to bacterial antigens (Blalock 1994). Within the immune system, homeostasis depends largely on the proper interplay between intricate networks throughout the organism that include cytokines, differential co-stimulatory molecule expression and regulatory cell activities (Besedovsky et al. 1985). New studies now underline that psychological and behavioral factors such as depressive disorder, negative emotion and social isolation, modulate and activate immune system functions (Lichtman et al. 2008; Saab et al. 2009; Lim et al. 2011; Ricci et al. 2012). By giving rise to cytokine release and chronic inflammation these immune system changes may trigger the metabolic syndrome and CVD (Eckel et al. 2005; Capuron et al. 2008).

Inflammation: from obesity to CVD

Adipose tissue, adipokines and inflammation

Adipocytes produce and secrete numerous cytokines (adipokines) first discovered in immunocompetent cells and acting as hormones in regulating energy metabolism

and catabolism: tumor necrosis factor-alpha (TNF−α), leptin, interleukin-6 (IL-6), interleukin-8 (IL-8), angiotensinogen, plasminogen activator inhibitor-1 (PAI-1), transforming growth factor-beta (TGF-β), adiponectin, and resistin (Matarese and La Cava 2004; Yang et al. 2007). The adipokine *inflammatory marker,* resistin, induces insulin resistance and is produced by macrophages as well as adipocytes in humans. Resistin is associated with increased pro-inflammatory cytokine production, mediated through NF-kB activation (Yang et al. 2007), and decreased anti-inflammatory cytokine production. The adipokine family also includes interferon-gamma (INF-γ) and chemokines such as monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-1(MIP-1), proteins known to elicit endothelial dysfunction. Each of these adipokines plays an important role in inflammation and atherosclerosis and extensive evidence confirms that obesity favors a pro-inflammatory state (Businaro et al. 2012a, b). In a study conducted on male mice C57BL/6 fed a standard diet low in fat until the age of 6 weeks and then switched to a high fat diet for the following 15 or 21 weeks to induce obesity, macrophage concentrations in visceral adipose tissue were higher in obese mice than in lean mice (Rocha et al. 2008). Hence they implicate pro-inflammatory molecules produced by adipose tissue as active participants in the obesity-related development of insulin resistance and increased risk of CVD (Fantuzzi and Mazzone 2007). In vivo chronic stress in experimental animals, fed with a high-fat, high sugar diet, led to NPY release and NPY receptor Y2R expression in visceral fat, increasing its growth by 50 % in 2 weeks, followed 3 months later by the onset of metabolic syndrome-like symptoms, including abdominal obesity, inflammation, hyperlipidemia, hyperinsulinemia, glucose intolerance, and hypertension (Kuo et al. 2008). In the presence of psychological chronic stress, increased cortisol leads to overeating and to obesity despite elevated circulating leptin concentrations. Increased cortisol inhibits lipid mobilization and promotes adipocyte differentiation and proliferation (Alonzo-Alonzo and Pascual-Leone 2007). Many of these adipokines especially leptin, TNF-α, IL-6, heparin-binding epidermal growth factor , and vascular endothelial growth factor may aggravate many clinical conditions by promoting angiogenesis, chronic inflammation, cell proliferation, and insulin resistance (Huffman and Barzilai 2009).

Among adipokines pathogenetically involved in obesity-related disease, the most harmful is TNF-α because it promotes lipolysis and free fatty acid (FFA) release. In the presence of circulating FFA, TNF-α induces visceral adipose tissue (VAT or "sick fat") thus blocking physiological adipogenesis in subcutaneous adipose tissue (SAT) (Eckel et al. 2005). Under these conditions, the subsequent IL-6 release induces inflammation in ectopic adipose tissue and increases circulating triglyceride levels. FFA sends endocrine signals on insulin sensitivity and causes type 2 diabetes (Breitling 2009; Gustafson 2010). This increased expression of key adipokines, working independently and together, creates insulin resistance and chronic sympathetic overactivity (Smith and Minson 2012). Psychological stress, by activating the HPA axis and inducing cortisol release, stimulates macrophages and adipocytes in VAT to secrete numerous pro-inflammatory cytokines/adipokines. Because VAT expresses higher cortisol receptor concentrations than SAT in response to chronic stress it maintains low-grade inflammation (Yamasu et al. 1992; Huffman and Barzilai 2009).

Individual stress systems, personality and disease

Modern perspectives reappraising NIM, conceptualize psychological stress as a "social pollutant" that when "breathed into the body" alters several physiological processes, just as environmental pollutants, chemical or physical processes can increase allergy risk (Wright et al. 2005; Wright 2012) and also possibly affect responses to immunomodulating therapies (Ippoliti et al. 2006). The development of psychological inadequacy also depends on cultural factors such as personality. Variations from normal weight are usually associated with internalized behavioral issues and discomfort, but not with externalized attitudes (Raison et al. 2006; Capuron et al. 2008). Hence high body mass index (BMI) values are associated with introversion potentially inducing depression and anxiety in the most vulnerable persons (Hu et al. 2007; Capuron et al. 2008).

As we understand more about the natural history and pathophysiology of these disorders and the neurobiology underlying stress vulnerability evidence linking psychological stress to chronic disease has increased. (Chrousos and Kino 2009; Wright 2012). Stress starts surprisingly early. Maternal stress in utero may influence programming of brain neurotransmitter systems and the HPA axis, which in turn may alter neural regulation of immune function. Programming early neural-immune processes may depend fundamentally on epigenetic dysregulation (Wright 2012).

Because stress systems develop in various ways in different individuals, personality constructs vary in a similar manner (Chrousos and Kino 2009). The personality construct is closely associated with morbidity and mortality for CVD as an independent predictor, especially the type D personality construct (Pedersen et al. 2007). This personality type, characterized by the tendency to experience negative emotions and social inhibition, was first noticed in European patients with ischemic heart disease (Denollet et al. 1995). These findings again underline increasing evidence that in obese individuals, inflammatory status depending on cytokine release aggravates emotional distress and individual psychological features linked to the personality construct (Black 2006; Raison et al. 2006; Capuron et al. 2011; Wright 2012).

Our review expands current knowledge on the influential role played by psychological stress in immune responses

and explains why some patients receive no benefit from traditional CVD therapies. Epidemiological research over the past two decades has shown that distress through depression, hostility, social isolation, lower socioeconomic status, or job- related problems, is associated with an increased risk of CHD and a poorer prognosis (Hemingway and Marmot 1999; Rosengren et al. 2004).

Chronically stressed patients are not only at increased risk of dying from cardiovascular-related causes post myocardial infarction, they also have a higher suicide risk. These findings support the American Heart Association and American Psychiatric Association recommendations to screen all post myocardial infarction patients for depression and suicidal ideation (Larsen et al. 2010; Redford and Williams 2010). Primary care physicians therefore need to be familiar with the mechanisms underlying NIM and to understand the relationship between stress and disease, so that they can identify strategies for managing stress, help patients change their lifestyle and cope better with the day-today problems responsible for their clinical condition. For example, the patient can learn biofeedback techniques and become more assertive in limiting the impact of stressful events and negative emotional repression, reducing the risk of disease progression or relapse or both events (Chrousos 2009; Chrousos and Kino 2009; Esch and Stefano 2010a, b; Redford and Williams 2010; Ricci et al. 2012).

Stress, obesity and Co-morbidities

Our review again underlines that the major obesity-related problems are the co-morbidities, such as type 2 diabetes, CVD, stroke, and certain types of cancers (WHO 1998; National Task Force on the Prevention and Treatment of Obesity 2000). Convincing evidence now shows that VAT and SAT fat accumulation are differentially distributed in disease (Wajchenberg 2000). VAT conditions and determines central obesity strongly associated with the metabolic syndrome and with high cardiovascular morbidity and mortality (Tentolouris et al. 2006; Winter et al. 2008). Cortisol-induced SNS inhibition is mediated indirectly by CRH suppression and directly by the inhibitory effect on noradrenergic neurons. Reduced SNS activity may be involved in the development of obesity. Conversely, increased sympathetic drive contributes to hypertension and increases cardiovascular risk in obese individuals (Tentolouris et al. 2006).

Plasticity of the adipose organ

Plasticity in adipose tissue may manifest in various ways. Environmental stressors and eating disorders alter adipose tissue anatomy and physiology, fat distribution and function patterns, though changes in plasticity. Previous work supports the notion that VAT and SAT both contain white and brown adipose tissue, collectively forming a multi-depot organ called the “adipose organ”. White adipocyte tissue contains adipocytes that exhibit stable and intrinsic differences in gene expression and adipokine secretion (Gesta et al. 2006; Perrini et al. 2008). These genetic-epigenetic differences imply that multiple types of white adipocytes exist in mammals and contribute in different ways to maintain energy balance (Gupta et al. 2012a). These adipose tissue locations undergo plasticity changes (reversible transdifferentiation). For example a physical stressor such as chronic cold exposure turns white adipocytes into brown adipocytes to enhance heat production, whereas exposure to an obesogenic environment turns brown adipocytes into white adipocytes, to increase energy storage capacity (Cinti 2009; Caesar et al. 2010a, b; Vitali et al. 2012). These new findings may explain why in more advanced societies, the risk of obesity is higher owing not only to the prolonged motivation for food intake but perhaps also to more efficient household heating and higher environmental temperatures.

Plasticity in adipose tissue linked to external and internal factors modulates organ endocrine functions. Adipokines or FFA released from adipocytes also affect metabolic function in surrounding tissues (Li and Renier 2007). The interaction between blood vessels and perivascular adipose tissue regulates blood vessel function, releasing vasoconstrictive as well as vasorelaxing factors. Adipocytes activate the local immune system by releasing adipokines that interact with lymphocytes from adjacent lymph nodes. Perinodal adipocytes are rich in FFA released from adipocytes in response to local lipolytic signals and help to maintain low-grade inflammation (Tran et al. 2012).

Another well-documented plasticity feature is preadipocyte transformation in the adipose tissue. This physiological change may reflect an intrinsic ability of adipocytes to reprogram their gene expression and transform into various cell types related to stress and food intake: body fat deposits undergo dramatic physiological changes (De Matteis et al. 2009).

Perivascular adipose tissue (PAT) and vasocrine signals

Perivascular adipose tissue (PAT) seems to be implicated in regulating vasomotor function. Virtually all arteries are surrounded by PAT, which increases during obesity (Guzik et al. 2007; Gustafson 2010). The short distance (<100 μm) between PAT and the adventitial blood vessel layer allows adipocyte-derived products, such as adipokines and ROS, to alter vascular function (Vachharajani and Granger 2009). Whereas adiponectin is known to relax vascular smooth muscle and produce vasodilation, leptin, resistin, TNF-α and other adipokines impair endothelium-dependent vasodilation in small and large arteries, probably by activating

NADPH-oxidase and enhancing superoxide production thus inactivating the endothelium-dependent vasodilator, nitric oxide (NO) (Guzik et al. 2007). Other mediators released from the expanded and activated adipocyte pool in obese subjects increase endothelial cell sensitivity in the microvasculature (arterioles, capillaries, venules).

Only VAT responds to obesity in a manner that is consistent with active inflammation whereas no such changes are detected in microvessels from subcutaneous fat or skeletal muscle (Vachharajani and Granger 2009). Arterioles, the primary site of microvascular resistance to blood flow, undergo a large reduction in blood flow velocity and the reduction in perfusion is sufficient to induce a hypoxic state and resulting ischemia (Nishimura et al. 2008). The relation between angiogenesis and adipose tissue was described also by Gealekman et al. (2011) showing that subcutaneous capillary density and angiogenic capacity decrease with morbid obesity, and subcutaneous, but not visceral, adipose tissue angiogenic capacity correlates negatively with insulin sensitivity. Studies in animal models suggest that adipose tissue expansion requires angiogenesis, a normal process that is impaired not only in obese rodents but also in obese patients (Silha et al. 2005; Nishimura et al. 2007, 2008; Gealekman et al. 2011). Thus excess calories enlarge PAT depots with unfavorable consequences (Gustafson 2010). Overproduction of adipokines from PAT depots to arteries, and outside-to-inside signaling, lead to inflammation and ensuing atherosclerosis (Gustafson 2010).

Because plasticity differs in VAT and SAT, obesity manifests with various severe or less severe clinical features (Huffman and Barzilai 2009). VAT and SAT differ in their cellular composition, molecular properties and role in regulating metabolism (Ibrahim 2010): whereas increases in VAT contribute to metabolic disease, SAT is considered a weaker risk factor, and in some cases has a protective effect (Libby et al. 2010) although SAT capillary density and angiogenic potential decreases with increasing BMI leading to hypoxia (Gealekman et al. 2011).

Energy-rich foods increase SAT. When SAT saturates and adipocytes can no longer proliferate or expand, impaired adipose tissue expandability may lead to ectopic lipid accumulation in VAT, liver, muscle and pericardial cells. Energy dysregulation favors insulin resistance and metabolic disease (Capeau et al. 2005; Reaven 2011). Hence the risk of diabetes and coronary artery disease correlates strongly with relative visceral adiposity, rather than with BMI per se (Hu et al. 2007).

Poorly vascularized visceral adipose tissue could also induce hypoxia, and impaired antiinflammatory adipokine secretion (Gealekman et al. 2011). This deleterious effect depends on cytokines synthesized by VAT and released into the portal circulation, thereby reaching the liver, where they can trigger a series of events, including further FFA and glycerol release (Bjorntorp 1990; Kim et al. 2009; Zuo et al. 2010). A clinically important finding is that VAT secretes more proinflammatory cytokines than SAT. Hence waist circumference or waist-to-hip ratio or both diagnostic measurements are better than BMI as a proxy to prevent metabolic disease and CVD (Rebuffe-Scrive et al. 1985).

Central role of leptin in stress-immune system cross-talk

Cortisol, leptin, feeding behavior and energy metabolism

Psychological stress induces prolonged cortisol release thus causing leptin resistance. Although leptin is major anorexigen hormone, leptin overproduction is paradoxically emerging as a leading cause of obesity, weight loss difficulty and age-related weight gain. Despite elevated blood leptin concentrations in obesity, when psychological stress is prolonged in time and the body feels it has insufficient resources to combat it, the stress response activates the HPA axis and induces excessive cortisol release leading to overeating and to leptin resistant obesity. In up-regulating serum leptin concentrations, cortisol and insulin interact (Zakrzerwska et al. 1997; Dickerson et al. 2004). In humans, increased insulin and cortisol are concurrently dependent on the preference for "comfort food" and this food urge leads to excessive visceral fat accumulation and insulin resistance, dyslipidemia, hypertension, and impaired glucose tolerance with all the early signs of cardiovascular events (Bjorntorp 2001; Ibrahim 2010).

The relationship between stress and food intake in humans may also involve cortisol-induced changes in NPY, CRH, leptin as well as opioids. Leptin resistance acts as an impaired "brake" that in part explains the "globesity" epidemic, namely eating without metabolic need (Figlewicz 2003; Adam and Epel 2007; Hansen et al. 2010).

Stress-induced cortisol may impair right prefrontal cortex activity, thus impeding the more reflective cognitive control over eating. These cortisol-induced changes abolish leptin's main function, namely to transmit to the brain regions responsible for regulating food intake information on the extent of fat deposits. Hence food intake becomes uncontrolled, VAT increases and obesity and CVD develop.

As well as increasing circulating leptin, excessive food intake, aggravated by inflammation related to psychological stress, may activate mTOR (the mammalian target of rapamycin pathway) (Procaccini et al. 2010). Energy metabolism may depend on the leptin/mTOR signalling pathway. mTOR (serine/threonine kinase) controls growth and metabolism, and its deregulation underlies the pathogenesis of many diseases, including cancer, neurodegeneration, and diabetes (Efeyan et al. 2012). mTOR pathways induce adverse effects on stress-related diseases also by inhibiting

liver lipophagia, a condition that contributes to steatosis and lipid accumulation in VAT (Singh 2011). Within this context, some evidence suggests that leptin might act as an endogenous "sensing" factor which activates mTOR behaving as a critical link between environment (availability of nutrients), metabolism, and immune responses (Matarese and La Cava 2004).

Given the established link between inflammation and thrombosis, leptin hardly surprisingly also promotes a prothrombotic phenotype in the vasculature (Beltowski 2006; Vachharajani and Granger 2009). Accordingly, leptin has now emerged as a major candidate for the link between obesity and the proinflammatory state. Specifically, leptin modulates T-helper (Th) cells toward a Th1 /Th17 phenotype, secreting proinflammatory cytokines (Tedgui and Mallat 2006). In obese children, a shift to a Th1-cytokine profile dominated by IFN-γ production is related to insulin/leptin resistance. The prevalent Th1 pattern exhibited by secreted cytokines may be regarded as a mechanism contributing to inflammation in infant obesity (Pacifico et al. 2006).

Neurogenic inflammation and immune dysregulation in obesity

The proinflammatory activity of leptin that potentiates Th1 immune responses reflects decreased T-regulatory (Treg) cell proliferation (De Rosa et al. 2007). A link between energy metabolism and Treg cell responsiveness may be the leptin/ mTOR signalling pathway itself. If Treg cells have a high metabolic state, high ATP and high mTOR activity, they may become unresponsive to regulatory action in neuroimmune /inflammatory responses (neurogenic inflammation) (Procaccini et al. 2010, 2012).

When macrophage-induced inflammation damages the vascular endothelium, low-density lipoprotein cholesterol accumulates in the artery wall. Over time plaque build-up in the arterial wall leads to atherosclerosis. Although leptin can favor survival in adverse conditions such as fasting, it may induce immune alterations by blocking the Treg precursor thus favoring the Th-17 clone. In this way, adipocyte-derived IL-17 plays a crucial role in the development of atherosclerosis (Galgani and Matarese 2010). This pathogenetic role of Th-17 cells can be seen in atheromas from symptomatic patients, characterized by a highly activated inflammatory milieu, owing to abnormally high IL-17 expression levels (de Boer et al. 2010; Erbel et al. 2011). Similarly, in patients with acute coronary syndrome, peripheral Th-17 cells, Th-17-related cytokines (IL-17, IL-6, IL-23) increase and Treg numbers decrease (Cheng et al. 2008) because the Th-17/Treg balance controls inflammation and may be pathogenetically important in destabilizing plaque. Human Treg express mRNA for adrenergic receptors thus putatively mediating (aggravating) the concurrent stress-induced effects on Treg cells (Cosentino et al. 2007). These immunological findings show the central role of leptin in stress-immune system cross-talk and stress, leptin and feeding behavior.

In obese patients leptin and TNF-α induce endothelial dysfunction and oxidative stress associated with leptin binding to the receptor site on vascular endothelial cells: in this way leukocytes and platelets appear to activate cells thus increasing reactive oxygen species (ROS) production, endothelial cell adhesion molecules and their ability to recruit immune cells (Katagiri et al. 2007). Also in experimental mice, leptin-induced platelet aggregation enhances platelet adhesion to extracellular matrix (ECM) proteins, and can induce thrombosis (Esmon 2004).

In summary, stress-induced overnutrition and obesity lead to hyperleptinemia and leptin resistance, a metabolic state now considered responsible for mTOR pathway hyperstimulation and IL-17 production in peripheral blood, as detected by enzyme-linked immunoassay (ELISA) (Pini and Fantuzzi 2010; Coupé et al. 2012).

Little is known about the stress mechanism through which adipose cells recruit immune cells thereby causing low-grade systemic inflammation. When adipocytes produce cytokines and cytokine-related substances and release them locally, adipose tissue recruits immune cells, including monocytes and T-lymphocytes in large numbers. A major molecule mediating monocyte recruitment into adipose tissue is monocyte chemotactic protein-1 (MCP-1). MCP expression is significantly higher in VAT than in SAT. Other adipocyte-derived molecules implicated in macrophage recruitment/activation in adipose tissue include FFA and lipoprotein lipase (Li and Renier 2007).

The function of adipose tissue-resident macrophages remains unclear. Some evidence suggests that macrophages clear dead cells by acting as apoptotic adipocyte scavengers. Hence, adipocytes undergoing necrosis secondary to hypertrophy may activate macrophages thereby releasing inflammatory mediators via Toll-like receptor 4 (TLR4) (Cinti et al. 2005). Adipocyte hypertrophy can alter folding in newly synthesized proteins, cause lipid droplet formation and impair cholesterol sensing in the endoplasmic reticulum (ER).

When unfolded proteins accumulate in adipocyte cytosol FFA release and inflammatory mediators in muscle, liver and adipose cells increase thus promoting insulin resistance (Vachharajani and Granger 2009). The physiological energy-rich fuel allocation in SAT (adipocytes) is widely disturbed. Impaired lipid storage in the adipose tissue increases obesity and increased visceral obesity promotes chronic systemic inflammation (Xu et al. 2003; Fantuzzi 2005; Straub et al. 2010). The cross-talk between macrophage/lymphocytes and adipocytes reinforces the notion that "energy (dys) regulation" can reflect an 'energy appeal reaction' in an activated immune system (Straub et al. 2010).

This cross-talk probably ultimately amplifies and perpetuates the inflammatory macrophage phenotype induced by the expanding body fat mass mostly in VAT (Moller and Kaufman 2005; Vachharajani and Granger 2009). Abdominal adipocyte hypertrophy with increased triglyceride lipolysis, results in raised circulating FFA levels particularly in the portal system. This deleterious metabolic pathway causes ectopic fat to accumulate in the liver and leads to pancreatic β-cell dysfunction thereby inhibiting insulin production (Breitling 2009). The adipose tissue has become a central focus in the pathogenesis of obesity-mediated cardiovascular and metabolic disease. Various stress conditions stimulate sphingomyelin catabolism to produce ceramide. In a study investigating metabolism in genetically obese (ob/ob) mice, Samad et al. (2006) demonstrate altered adipose sphingolipid metabolism in cultured adipocytes, ceramide, sphingosine, TNF-α, monocyte chemoattractant protein-1, IL-6, and keratinocyte-derived chemokine. Collectively, these results in an experimental mouse model identify a novel role for sphingolipids in contributing to the prothrombotic and proinflammatory phenotype in obese adipose tissue currently believed to play a major role in the pathogenesis of obesity-mediated cardiovascular and metabolic disease (Samad et al. 2006). Lipid research has focused on how aberrant production of bioactive lipids contributes pathophysiological changes associated with obesity in turn causing insulin resistance. Emerging data support a role for sphingolipids also in other metabolic diseases including obesity, type 2 diabetes, atherosclerosis and metabolic syndrome (Cowart 2009). Elevated plasma FFA promotes aberrant sphingolipid production and composition thus inducing systemic inflammation in various tissues including skeletal muscle, pancreas and adipocytes.

Macrophages, ECM and toll-like receptors

Macrophage cells are ubiquitously infiltrated within the ECM in numerous organs. They control diverse metabolic routes, participate in inducing and conserving immunity through both innate and acquired immune responses and modulate inflammatory reactions by releasing a wide set of proinflammatory and anti-inflammatory cytokines and by expressing membrane receptors for numerous inhibitory neurotransmitters (Elenkov 2004; Steinman 2004). Hence macrophages are a key element in the bidirectional cross-talk between the human immune and nervous systems (Elenkov et al. 2000).

Current research already provides a detailed insight into how stress influences the innate immune system, in particular by activating TLR-4, the receptor involved in signalling the neurogenic inflammatory response (Caso et al. 2008). TLRs play essential roles in generating innate immune responses and specifically recognize the conserved microbial structural motifs referred to as pathogen-associated molecular patterns (Janeway and Medzhitov 2002). Ligand recognition by TLRs activates signalling cascades that ultimately transcribe many proinflammatory genes that encode cytokines, chemokines, and enzymes such as cyclo-oxygenase or inducible nitrous oxide synthase and other inflammatory mediators. In a clinical study, Farb et al. (2012) suggest that the visceral microenvironment may be intrinsically toxic to arterial health thus providing a potential mechanism linking the visceral adiposity burden to atherosclerotic vascular disease. VAT exhibited intense expression of proinflammatory and proangiogenic genes, and increased activated macrophage populations, and cytokine production. Adipose tissue quality and quantity may both play significant roles in shaping cardiovascular risk in human obesity (Farb et al. 2012). A possible link exists also between neurogenic inflammation and the adipose tissue anatomically associated with lymph nodes, myocardium and large arteries (Vachharajani and Granger 2009). Two reports propose a relationship between epicardial adipose tissue and myocardial tissue in high-risk cardiac patients undergoing coronary artery bypass grafting (Mazurek et al. 2003; Baker et al. 2006). Increased macrophage accumulation in epicardial adipose tissue may account for the enhanced inflammatory potential described in these reports thereby raising the possibility that locally generated adipokines may be a predisposing factor for coronary artery disease. A detrimental role for epicardial fat receives further support from reports describing the ability of TNF-α, leptin and other adipokines to reduce myocardial contractility (Baker et al. 2006).

Another event underlining the relationships linking chronic stress, obesity, and progressive CVD comes from research showing that TNF-α induces cells to produce lipid mediators, proteolytic enzymes and free radicals (ROS) all directly responsible for the noxious effects leading to pathological processes (Koedel et al. 2007; Pérez-Nievas et al. 2007). During times of environmental stress, ROS levels can increase dramatically. This may result in significant damage to cell structures (Devasagayam et al. 2004). Overnutrition (high circulating glucose and FFA levels) is the predominant pathogenic factor inducing central metabolic inflammation. Excessive nutrients transported into cells can pose severe stresses on cellular metabolic machinery, affecting organelles such as mitochondria and ER. Mitochondria are responsible for nutrient oxidation and the ER is responsible for protein synthesis. As a result, intracellular ROS increase due to heightened mitochondrial activities, leading to prolonged intracellular oxidative stress (Cai and Liu 2012). All these events can determine intracellular accumulation of dysfunctional mitochondria and other cytosolic proteins, leading to increased cellular stress and autophagic defects. In parallel, high levels of cellular metabolic activities demand increased protein synthesis and folding by heat shock proteins (HSPs) in ER, leading to ER stress. HSPs are

a class of functionally related proteins involved in the folding and unfolding of other proteins. Their expression is increased when cells are exposed to elevated temperatures or other stress (De Maio 1999).

Another molecule that adipocytes release and that triggers TLR-4 is HSP60, a protein that in turn can stimulate adipocytes to secrete TNF-α, IL-6, and IL-8. Plasma HSP60 levels were higher in obese than in lean males and correlate positively with BMI, blood pressure, leptin, and insulin resistance (Märker et al. 2012). HSPs might therefore be another factor underlying adipose tissue inflammation and obesity-associated metabolic disorders.

When we sought to confirm the pathogenetic role of HSPs in atherosclerosis, we detected strong HSP90 immuno-reactivity in the muscle, endothelial cell layer and in the inflammatory infiltrate from the carotid plaques. These findings implicate HSP90 as a possible target autoantigen in the pathogenesis of carotid atherosclerosis (Businaro et al. 2009, 2012b) .

Inflammasome, ECM and adipogenesis

Inflammasomes recognize microbial products or endogenous molecules released from damaged or dying cells both through direct binding of ligands and indirect mechanisms. The potential of the IL-1 family of cytokines to cause tissue damage and chronic inflammation emphasizes the importance of regulating inflammasomes (Tracey 2010).

Disrupted cells and ECM degradation products detected in inflammatory tissue after psychological stress may be a danger signal because they activate TLRs, and may thus contribute to immune activation (inflammasome). To all these sequelae, macrophage-activated collagenase and metalloproteinase induces adipose fragments and ECM protein breakdown (Straub et al. 2010). A study conducted by Mauney and Volloch (2010) that especially helps to advance current knowledge on adipogenesis, describes the critical role of native or denatured ECM. Collagen IV is the major matrix component associated with differentiating adipocytes in adipose tissues. Native collagen IV provides little support for adipogenic differentiation and very little, if any for adipogenesis in response to adipogenic stimuli. In contrast to native collagen IV, the same matrix in the denatured structural state drives highly efficient adipogenic differentiation suggesting that it might be the major adipogenesis driver in adipose tissues and that the ratio of native to denatured matrix might regulate the intensity of adipogenesis and possibly underlie obesity (Mauney and Volloch 2010).

Committed preadipocytes are localized in adipose endothelial and perivascular cells (Gupta et al. 2012a, b). Gain and loss of function studies in vitro and in vivo clearly indicate that adipocyte differentiation is driven by the nuclear hormone receptor PPARγ (Tang et al. 2008). This master regulatory gene is expressed in mural cell subsets in white adipose tissue blood vessels and studies in recent years have clearly shown that perivascular cells isolated from adipose tissue can differentiate into adipocytes. In both white and brown fat deposits, adipocytes originate from cells that display morphological and genetic evidence of endothelial characteristics (Gupta et al. 2012b; Tran et al. 2012). Similar plasticity can be seen in the murine 3 T3-L1 fibroblastic cell line which can be induced to differentiate into mature adipocytes in cells cultured with dexamethasone and insulin (Frost and Lane 1985) and this experimental procedure has been used as a model system to study the mechanisms involved in adipogenesis (Calzadilla et al. 2011). In primary cultures, others have studied differences between various adipose depots either as a condition per se or in the cellular context of the stromal-vascular fraction (Skurk and Hauner 2012).

Strategies and perspectives

Stress is a major concern in our modern world because it can facilitate illness and is responsible for a surge in medical spending especially for CVD, as well as for reduced worktime and higher absenteeism rates in the business world (Esch 2002; Esch and Stefano 2010b).

Interventions should focus on top-down strategies intended to alter brain function in ways that will improve allostasis and minimize allostatic load (McEwen and Wingfield 2003). Lack of physical activity, especially among children, is a major cause for obesity and the early onset of many cardiovascular and metabolic diseases and consecutive aggravation in adult life (Hillman et al. 2008). Physical activity may in part, help to reduce chronic stress and thus neurobiologically involve the limbic brain system as well as the underlying metabolic pathways (Ben-Sefer et al. 2009; Esch and Stefano 2010a, b; Businaro et al. 2012a; Ricci et al. 2012).

Epidemiological studies have specifically linked measures designed for social integration with increased lifespan, better cognitive aging, reduced risk for stroke and longer survival times in patients with CVD (McEwen and Wingfield 2003).

Many obese individuals identify specific foods that promote continued consumption despite the known consequences of obesity. This concept is important to understand how the disease arises and to prevent and minimize the deleterious effects induced by psychological or psychosocial stress or an inadequate lifestyle in youth (Heber 2010).

Conclusion

Our review confirms the close relationships linking chronic (psychological) stress, obesity, and progressive CVD. It also

strongly suggests that NIM by regulating body energy activates immune and metabolic pathways. NIM elicits specific individual epigenetic responses to chronic stress. These responses generate low-grade neurogenic inflammation thus driving plasticity in adipose tissue and generating visceral obesity secondary to altered eating behaviors. Environmental stressors, eating disorders and inadequate lifestyle, seem to play a central role, enhancing the production of the proinflammatory cytokines and stress hormones that increase risk for obesity-related diseases. Although we could in theory prevent "globesity" simply by restricting calorie intake and improving physical exercise, the NIM responses to chronic stress we describe here render this strategy quite difficult and favor obesity.

The up-to-date information on NIM we now provide helps to explain the relationship among chronic (psychological) stress, obesity, low-grade inflammation, energy dysregulation (leptin-insulin resistance) and multifactorial diseases including the metabolic syndrome and CVD. Finally, our review may help others to develop strategies to combat the obesity epidemic.

Conflict of interest The authors declare that they have no conflict of interest.

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