The inflammatory consequences of psychologic stress: Relationship to insulin resistance, obesity, atherosclerosis and diabetes mellitus, type II

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Summary Inflammation is frequently present in the visceral fat and vasculature in certain patients with cardiovascular disease (CVD) and/or adult onset Diabetes Mellitus Type II (NIDDM). An hypothesis is presented which argues that repeated acute or chronic psychologically stressful states may cause this inflammatory process. The mediators are the major stress hormones norepinephrine (NE) and epinephrine (E) and cortisol together with components of the renin–angiotensin system (RAS), the proinflammatory cytokines (PIC), as well as free fatty acids (ffa), the latter as a result of lipolysis of neutral fat. NE/E commence this process by activation of NF$_\kappa$B in macrophages, visceral fat, and endothelial cells which induces the production of toll-like receptors which, when engaged, produce a cascade of inflammatory reactions comprising the acute phase response (APR) of the innate immune system (IIS). The inflammatory process is most marked in the visceral fat depot as well as the vasculature, and is involved in the metabolic events which culminate in the insulin resistance/metabolic syndromes (IRS/MS), the components of which precede and comprise the major risk factors for CVD and NIDDM.

The visceral fat has both the proclivity and capacity to undergo inflammation. It contains a rich blood and nerve supply as well as proinflammatory molecules such as interleukin 6 (IL-6), tumor necrosis factor $\alpha$ (TNF$\alpha$), leptin, and resistin, the adipocytokines, and acute phase proteins (APP) which are activated from adipocytes and/or macrophages by sympathetic signaling. The inflammation is linked to fat accumulation. Cortisol, IL-6, angiotensin II (angio II), the enzyme 11$_b$-hydroxysteroid dehydrogenase-1 and positive energy balance, the latter due to increased appetite induced by the major stress hormones, are factors which promote fat accumulation and are linked to obesity. There is also the

Abbreviations: ACE, angiotensin converting enzyme; ADN, adiponectin; Angio II, angiotensin II; APP, acute phase proteins; APR, acute phase response; 11$_b$HSD-1, 11 beta hydroxysteroid dehydrogenase type I; BP, blood pressure; CRF, corticotrophin releasing factor; CRP, C reactive protein; CVD, cardiovascular disease; DHEA, dihydroepiandrosterone; E, epinephrine; ffa, free fatty acids; HDL-C, high density lipoprotein cholesterol; HPA, hypothalamic pituitary axis; HSL, hormone sensitive lipase; IFN$\gamma$, interferon gamma; IIR, innate immune response; IIS, innate immune system; IKK$\beta$, I-kappa B-kinase beta; IL, interleukin; IRS, insulin resistance syndrome; LPL, lipoprotein lipase; LPS, lipopolysaccharide; MS, metabolic syndrome; NE, norepinephrine; NF$\kappa$B, nuclear factor kappa B; NIDDM, non-insulin dependent diabetes, type II; NO, nitrous oxide; PAI-1, plasminogen activator inhibitor-1; PIC, proinflammatory cytokines; RAS, renin–angiotensin system; SAA, serum amyloid A; SNS, sympathetic nervous system; TLR, toll-like receptor; TNF$\alpha$, tumor necrosis factor alpha; TZD, thiazolidinedion; VLDL, very low density lipoprotein.

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capacity of the host to limit fat expansion. Sympathetic signaling induces TNF which stimulates the production of IL-6 and leptin from adipocytes; these molecules promote lipolysis and ffa fluxes from adipocytes. Moreover, catecholamines and certain PIC inhibit lipoprotein lipase, a fat synthesizing enzyme.

The brain also participates in the regulation of fat cell mass; it is informed of fat depot mass by molecules such as leptin and ffa. Leptin stimulates corticotrophin releasing hormone in the brain which stimulates the SNS and HPA axes, i.e. the stress response. Also, ffa through portal signaling from the liver evoke a similar stress response which, like the response to psychologic stress, evokes an innate immune response (IIR), tending to limit fat expansion, which culminates in inflammatory cascades, the IRS–MS, obesity and disease if prolonged. Thus, the brain also has the capacity to limit fat expansion. A competition apparently exists between fat expansion and fat loss. In “western” cultures, with excessive food ingestion, obesity frequently results.

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In recent years, much evidence indicates that a low grade inflammatory process is present in the large arteries which is involved in the pathogenesis of cardiovascular disease (CVD); such a process is also associated with certain metabolic disorders such as the insulin resistance (IRS) and metabolic syndromes (MS), and adult onset diabetes, type II (NIDDM), all of which share many common risk factors with CVD. It is the author’s view that these inflammatory processes are all related, that the IRS and/or the MS precede and are causally related to the development of both atherosclerosis and NIDDM, and that the inflammation is secondary to activation of the acute phase response (APR) of the innate immune system (IIS). Furthermore, it is hypothesized that such activation may be induced by repeated acute or chronic psychologic stressful states which elicit the elaboration of stress hormones such as norepinephrine (NE), epinephrine (E), cortisol, and glucagon, together with activation of the renin–angiotensin system (RAS).

**Neurobiology of stress**

Stress is a state of threatened homeostasis provoked by a psychological, environmental, or physiologic stressor [1]. One can also define stress as a stimulus, either internal or external, that activates the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (SNS), resulting in a physiological change or adaptation so that the organism can deal with the threat [2]. In addition to these aspects, stress is now construed more broadly to include personality and socioenvironmental factors that are pertinent to individual adaptation.

Our focus will be on psychologic (i.e. emotional) stress. Experimentally, such stress can be induced in humans by mental tasks such as complex mental arithmetic, color-word conflict tests or public speaking, for example [3]. Such stressors have been shown to induce release of hypothalamic and/or amygdala corticotrophin releasing factor (CRF) which activates the HPA to produce cortisol and the sympathetic nervous system (SNS) to produce NE and E. The RAS also participates in the stress response. SNS innervation of the kidney may result in the production of renin, which initiates a series of reactions whereby renin and angiotensin converting enzyme (ACE) convert angiotensinogen to angiotensin II (angio II), a powerful vasoconstrictor that elevates, among other effects, both the blood pressure (BP) and the heart rate.

Of necessity, the details of each stress mentioned cannot be given in detail and may be referred to simply as psychologic or mental stress without necessarily mentioning the particular stress/stressors. These stressors have been shown to activate the SNS and/or the HPA axis. In most instances, both axes are activated because of the release of CRF.

**Induction of the acute phase response (APR)**

The APR is the body’s response to tissue damage and infection. It is a major component of the IIS. It consists of production of acute phase proteins (APP) which are induced in the liver and/or fat by cytokines, particularly interleukin 6 (IL-6), the major inducer of the APP. Catecholamines and/or corticosteroids, the major stress mediators, may each induce an APR as may glucagon; each of the major
stress hormones may also participate in the coinduction of the APR with IL-6.

IL-6 administered to humans induces an APR [4]. Two important APP, C-reactive protein (CRP) and fibrinogen, have IL-6 response elements in the promotor regions of their genes; the presence of IL-6, therefore, may facilitate the production of CRP and fibrinogen. A very tight correlation of the presence of IL-6 and CRP exists; such a correlation does not exist for other cytokines [4]. A number of studies indicate that psychologic stress alone can induce the APR [5].

**NFκB and stress**

One of the earliest events in the stress-inflammatory hypothesis is the activation of nuclear factor kappa B (NFκB), an enzyme which is capable of promoting activation of cells by binding to DNA and promoting transcription of molecules involved in cell regulation, inflammation or apoptosis; it is involved in the control of transcription of greater than 150 target genes and it responds to, or is induced by, approximately 150 stimuli [6]. It resides in the cytoplasm where it is bound to and inhibited by IκBα and/or IκBβ, which, upon phosphorylation by IκB-kinase-beta (IKKβ), is released from NFκB; NFκB then travels to the nucleus.

NFκB is generally activated during the response to psychological or physical stressors and can be considered the central regulator of the stress response since it controls the transcription of many of the APP, stress response and inflammatory genes [6]. Humans and animals responding to many stressors exhibit an increase in NFκB in the nucleus as well as elevations of NE and cortisol [7]. The response may be mediated by NE which causes a time and dose dependent activation of cellular NFκB. It is dependent on the presence of α1 adrenergic receptors. Cortisol potentiates downstream α1-adrenergic signaling [8]. Small doses of E also cause NFκB activation and this may synergize with NE [7]. Such activation in the macrophage leads to cytokine and/or other inflammatory mediator production, as well as the synthesis of toll-like receptors (TLR) which, when engaged, activate the IIR to produce an APR [9]. NFκB appears to be a downstream effector for, and the first response to, the NE induced inflammatory stress response.

There is, therefore, evidence that inflammation accompanies a stress response or, stated differently, that the inflammatory response is an integral part of the stress response [10]. NFκB activation is also involved in the inflammatory and metabolic events which accompany the IRS and/or the MS.

**Insulin and insulin resistance**

During stress, there is an excessive control of metabolism by the stress hormones which is generally opposed by insulin [11]. However, a state of insulin resistance (IR) frequently develops during acute, repeated acute, or prolonged stress or other situations such as obesity or inflammation. IR is a diminution of the ability of insulin to metabolize glucose and is manifested by glucose intolerance with hyperglycemia; the IRS also includes a compensatory increase in plasma concentrations of insulin and dyslipidemia including increased plasma concentrations of triglycerides and diminished concentrations of high density lipoprotein cholesterol (HDL-C) (see below). The IRS may or may not be accompanied by an elevation of BP, abdominal obesity (see below), or an increased tendency for thrombosis [i.e. increased plasminogen activator-1 (PAI-1)]. When ≥ 3 of the following characteristics i.e. abdominal obesity, hypertriglyceridemia, decreased HDL-C, increased BP and hyperglycemia are present the IRS may be referred to as the MS [12]. It is believed to be an adaptive mechanism preventing glucose from being consumed thereby sparing it for brain metabolism which would obviously enhance survival in an acute fight-flight situation. In most instances, the IRS is generally preceded or is accompanied by an inflammatory process.

**Causes of the IRS**

There are several causes of the IRS. In promulgating the hypothesis that psychologic stress induces the IRS, we will consider the pathophysiological events which occur subsequent to exposure to the major stress hormones, the catecholamines and corticosteroids, the proinflammatory cytokines (PIC) and free fatty acids (ffa). These may act alone or, more commonly, in combination with each other to produce the IRS following psychologic stress.

**SNS and the IRS**

Infusion of E can cause acute IR which persists for hours and can be blocked by propranolol [13]. Moreover, chronic β adrenergic stimulation by a β agonist also causes IR. Catecholamines are known to diminish insulin sensitivity since patients with pheochromocytoma, (a disease in which large amounts of catecholamines are produced) have
very low insulin sensitivity [14]. In addition, β adrenergic stimulation diminishes insulin signaling and glucose uptake in brown adipose tissue (BAT). There is a strong positive correlation between blood flow and sensitivity to insulin. Compromise of blood flow to muscle causes IR likely due to α adrenergic-induced vasoconstriction which would shunt nutritional blood flow away from active glucose metabolizing cells in skeletal muscle; this would impede glucose extraction due to a pressure-induced restriction in the microcirculation [15]. There is also a strong correlation of glucose uptake with capillary density upon prolonged adrenergic stimulation. A loss of capillaries occurs due to structural factors such as capillary attrition and/or impaired angiogenesis or, functionally, due to impaired recruitment of non-perfused capillaries during stimulation; such factors lead to capillary rarefaction. These changes develop during human hypertension, are thought to be due to chronic β adrenergic stimulation, and act to aggravate and sustain insulin resistance in muscle [16]. There is also evidence that capillary density, as well as insulin sensitivity, may be regulated by sustained SNS activation [17]. Insulin resistance, with particularly high levels of ffa in patients with NIDDM, is associated with similar changes in skeletal muscle blood flow, capillary recruitment and capillary rarefaction. Such changes may contribute to obesity-associated hypertension [18].

SNS, RAS, cytokines, and IR

Sympathetic stimulation activates the RAS resulting in renin release from the kidney. NE and angio II may act synergistically in promoting inflammation thereby enhancing IR. PIC may also stimulate renin secretion. Angio II, like NE and PIC, activate NFkB in macrophages, adipocytes and endothelium. The RAS plays an important role in the inflammatory processes and IR in visceral fat and in the vasculature, two important loci involved in inflammation and IR (see below). Consistent with this is the finding that ACE inhibition improves the IRS [19].

Proinflammatory cytokines, especially TNFα and IL-6, also may induce the IRS by dysregulating insulin signaling; these cytokines, especially TNFα, serine phosphorylate the insulin receptor and insulin receptor substrate-1-associated proteins which impede insulin binding and signaling. In TNFα or IL-6 knockout mice, there is an attenuated response to psychosocial stress compared to control mice. Both the SNS and RAS induce production of IL-6 from endothelial and smooth muscle cells and it is possible that IL-6 may serve as mediator/modulator of certain SNS–RAS effects including the pressor response. This interaction is of interest in view of the finding that NE enhances both the production and the response to PIC in adipose tissue surrounding lymph nodes [20]. This type of reaction would increase whole body IL-6 and TNFα by β adrenergic stimulation (i.e. stress) and would enhance the sensitivity of adipose tissue to IL-6 and TNFα. Thus, there is an inflammation-producing SNS–RAS–PIC network which is intimately involved in the inflammatory syndrome (see below). The additional finding that sympathetic nerves may release and respond to IL-6 [21] adds further support for the inflammation-inducing potential of the SNS. Stress, therefore, may also induce cytokines indirectly through the SNS–RAS systems, the latter amplifying the effects of PIC. The emphasis here is that the SNS–RAS–PIC network is both proinflammatory and induces IR. A number of reports indicate that psychologic stress, via activation of the SNS, can induce the IRS–MS [22].

Cortisol, visceral fat, ffa and IR

Corticosteroids may also play a large role in the production and maintenance of the IRS. For example, IR can be induced by high fat feeding in humans. Approximately 60–70% of the IR induced can be prevented by treatment with RU486, a compound that inhibits corticosteroid synthesis. Also, adrenalectomy reverses many of the metabolic abnormalities of the genetic and lesion-induced rodent models of obesity and IR [23]. In addition, the IRS accompanies Cushing’s disease, in which excess cortisol is produced, and may be alleviated by treatment of this disease.

There is frequently an interdependence in the functioning of the major stress hormones i.e. cortisol and catecholamines. For example, cortisol receptors are present on sympathetic nerves [24] and cortisol has important enhancing effects on the cardiovasculature due to their augmentation of neuronal excitability to NE [25]. This would enhance pressor responses. Also, polymorphisms in the cortisol receptor and/or cortisol genes have been identified which control NE secretion. This

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1 Cortisol is frequently utilized therapeutically and is known for its strong antiinflammatory (suppressing) effects; however it also has proinflammatory (permissive) effects as well (see reference #25 for review).
interdependence of the major stress hormones is apparent in the adipocyte which differentiates from cells lacking β2 adrenergic receptors to fully differentiated triglyceride containing cells expressing β2 adrenergic receptors [26]. This differentiation is dependent on dexamethasone and NFkB indicating that the differentiated adipocyte is poised to participate in IR and inflammation [26].

Of critical importance in the development of the IRS is visceral (mesenteric/intraabdominal or central) obesity. Visceral obesity (occurring predominately in males) is to be distinguished from glutero-femoral obesity (occurring predominately in women). Women who have visceral fat accumulations, however, develop similar risk factors as men (see below). Visceral fat has unique properties which distinguish it from other fat depots. This fat has a rich blood and nerve supply, an abundance of β adrenergic (especially β2 and β3) receptors and a corresponding decrease in the CAMP lowering effects of β2 adrenergic agonists. It is also less responsive to the antilipolytic effects of insulin. Visceral fat is also unique among other fat depots in that it contains a high concentration of glucocorticoid receptors; when engaged and internalized, the glucocorticoid-receptor complex binds to the lipoprotein lipase (LPL) gene in the adipocyte and activates LPL located at the endothelial cell surface where it hydrolyzes intravascular triglycerides, resulting in fatty acid uptake, reesterification, and storage of triglycerides as fat. Thus, LPL responds to and reflects corticosteroid presence.

Corticosteroid presence is also enhanced by the enzyme IIβ hydroxysteroid dehydrogenase type I (IIβHSD-1) in the stromal cells of visceral fat. This enzyme converts inactive cortisone to active cortisol. IL-6, a PIC, increases the activity of this enzyme, thereby enhancing expansion of visceral fat [27]. Point mutations in this gene give rise to an animal unable to develop visceral obesity [28]. Moreover, inhibition of IIβHSD-1 ameliorates the IRS and prevents progression of atherosclerosis in mice [29].

Adrenalectomy or cessation of corticosteroid therapy promotes disappearance of the visceral fat. It is, therefore, quite likely that excessive corticoid secretion associated with subacute/chronic stress would also promote visceral obesity. Indeed, rats subjected to uncontrollable stress, have redistribution of their fat promoting visceral fat accumulation [30]. Moreover, a large number of studies have indicated that psychological stress is associated with the accumulation of abdominal fat [31]. For example, a recent study revealed that depressed women may have increased visceral fat accumulations, decreased insulin sensitivity and elevations of serum IL-6 and TNFα; the diminished insulin sensitivity correlated with the amount of visceral fat and serum IL-6 concentrations [32]. Major depression is a proposed model for extreme stress [33].

With psychologic stress, and a marked increase of corticosteroid, there is a concomitant decrease in the levels of sex steroids and growth hormone, diminution of these functions, not needed in an acute fight-flight situation, also conserves energy. This would enhance the accumulation of abdominal fat since these hormones promote lipolysis and generally antagonize the effects of glucocorticoid. The elevation of cortisol concentrations with aging is likely due, in part, to diminished levels of these hormones [30]. Visceral obesity is strongly correlated with the IRS as well as with certain APP such as the inflammatory mediators CRP and fibrinogen, as well as IL-6.

**Manifestations of IRS—MS**

Visceral fat characteristically has a high turnover of ffa, consistent with a very high lipolytic rate; it is most sensitive to hydrolysis by catecholamines, mostly via the β2 and β3 adrenergic receptors, whose expression is regulated by cortisol. β3 receptors, whose primary role is to regulate the metabolic rate and lipolysis, are especially sensitive [34]. IL-6, TNFα, leptin, and glucagon, all of which are elevated subsequent to psychologic stress, are also lipolytic. Insulin normally suppresses the activity of hormone sensitive lipase (HSL), an enzyme that hydrolyzes intracellular triglyceride in adipose tissue; during the IRS, enhanced HSL activity would lead to sustained release of ffa into the circulation [35]. Large amounts of ffa and glycerol generated from these lipolytic events enter the portal blood which drains to the liver where they cause a number of metabolic changes such as gluconeogenesis, providing the substrate for and, together with cortisol, enhancing the synthesis and secretion of very low density lipoproteins (VLDL) from the liver. Ffa diminish hepatic insulin binding, thereby diminishing receptor mediated uptake and degradation resulting in a diminished clearance of insulin which contributes to hyperinsulinemia. There is an inverse correlation between insulin concentrations and HDL; the low HDL concentrations are likely to occur because of the inability of HDL to be formed from VLDL. It is of interest that HDL has anti-inflammatory properties, perhaps contributing to the inflammatory state [36].
Ffa accumulate in muscle and tissues (peripheral and hepatic); in muscle, ffa contribute to a loss of insulin stimulated glucose uptake, and diminished glycogen synthesis, indicative of IR. Indeed, ffa cause IR in a dose and time dependent manner. Ffa also exert a lipotoxic effect in the β pancreatic islet cell thereby diminishing insulin secretion and contributing to glucose intolerance and hyperglycemia [37].

LPL activity (see above) normally upregulated by insulin, would be diminished in an IR state. In addition, LPL is inhibited by catecholamines and PIC. Since triglyceride (either circulating or as components of either chylomicrons or lipoproteins i.e. VLDL) would not be hydrolyzed by LPL, it recirculates contributing to the hypertriglyceridemia of stress and the IRS.

The changes described comprise the dyslipidemia of the IRS–MS as well as the major components of both the CVD risk profile, and the risk profile for development of NIDDM. Each component of the IRS (hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and diminished HDL-C), in particular, has been associated with an increased risk of CVD, as have visceral obesity, elevated BP (see below) and elevated PAI-1 [38].

Endothelium, hypertension, and vasculitis

An acute psychologic stress (public speaking) causes an impairment of endothelium dependent vasodilation in healthy young individuals, thought to be due to a decrease in the bioavailability of nitrous oxide (NO) which was mediated by the SNS [39]. Thus, one of the earliest events in the acute response to stress is endothelial dysfunction. Indeed, exposure to ffa or PIC, which are increased with stress, result in the same effect [40]. Moreover, an inverse correlation exists between the IRS and the bioavailability of NO [41]. There is also a strong correlation between a low grade inflammation, endothelial dysfunction and diminished NO function [42]. A number of factors, therefore, affect the endothelium: elevations of BP due to heightened SNS activity; pressure-flow induced changes in gene expression; the IRS; vasculitis; as well as direct effects of PIC and the absence of protective factors. Each of these will be briefly addressed.

Approximately 50% of essential hypertensives are IR or are hyperinsulinemic [43]. Insulin normally modulates endothelial function by controlling lipolysis and ffa levels. Insulin also has vasodilatory actions and stimulates NO production; these functions are likely to be impaired during the IRS. Much evidence suggests that the IRS generally precedes the development of essential hypertension. Many borderline hypertensive patients are already IR in that they have increased weight, increases in total cholesterol, insulin, triglycerides with decreased HDL-C [44]. These individuals are at increased risk of developing CAD [43]; this is consistent with data indicating that each component of the IRS–MS is a cardiovascular risk factor [38] (see above). It is of interest that ”white coat” hypertensives, where a strong emotional component of the hypertension is suspected, may also have some components of the IRS, further suggesting that stress is a factor inducing the IRS [44].

There is a strong correlation between increased activity of the SNS, hyperinsulinemia and elevated BP [16,43]. Cogent arguments have been presented indicating that IR with resulting hyperglycemia and compensatory hyperinsulinemia are caused by increased sympathetic activity [16,43]. Sympathetic activity together with increased BP may be further heightened since insulin stimulates SNS activity centrally, as does leptin. This action of leptin may contribute to the hypertension of obesity since leptin levels are increased in obesity. Both increased SNS activity as well as leptin concentrations are also elevated after eating [45].

SNS activation and increases in BP are associated in a dose dependent way with increased secretion of IL-6 from the endothelium [46] and β adrenergic blockers decrease the expression of both IL-6 and CRP in unstable angina patients [47]. Vascular smooth muscle cells also release IL-6 dose dependently subsequent to exposure to angio II which also promotes the synthesis of adhesion molecules (i.e. intracellular adhesion molecule) and enhances monocyte adhesion to the endothelium [46]. IL-6 may cause endothelial dysfunction by increasing the expression of the angio II receptor [48]. These interactions help explain the association statistically between BP, IL-6 and IR [49]. Additionally, PIC, especially TNFα, cause endothelial injury [42,50].

Compromised endothelium may also arise from increases in the pressure within blood vessels due to pulsatile blood flow and the shear forces imposed by blood flow under pressure; such forces may affect endothelial gene expression and give rise to inflammatory mediators [51]. For example, shear stress-induced changes in the subendothelial matrix, which modulates blood flow, induces NFκB activation at these sites [52]. Flow disturbances due to low shear and disruption of laminar flow may also give rise to TLR; engagement of these
TLRs with certain molecules such as LPS or certain cytokines e.g. IFN\(_\gamma\) can activate the IIS giving rise to a cascade of inflammatory mediators and the APR [53].

One may conclude that a vasculitis is present which is induced by inflammatory mediators of the SNS—RAS—PIC cascade, components of the IRS, and an endothelium, compromised by these factors as well as pressure induced endothelial flow disturbances, in which the early events of atherosclerotic plaque development occur. Of interest is the finding that the endothelial dysfunction i.e. endothelial dependent vasodilation disappears subsequent to treatment with corticosteroids and/or aspirin further indicating an inflammatory process [54,55]. In a previous publication, evidence was presented that these factors, together with a predisposition at certain endothelial loci, provided a nidus for atherosclerotic plaque development [33].

**Portal signaling**

The liver may inform the brain of metabolic events by a number of reflexes. Accumulation of ffa in the liver engage ffa receptors which stimulate afferent vagus nerve fibers which signal the HPA axis in the hypothalamus and sympathetic nerve centers in the medulla via the nucleus tractus solitariou, resulting in the release of NE and corticosteroid [56]. This “portal signaling” can be induced experimentally by inoculation of sodium salts of various long chain fatty acids (oleic acid is the most prevalent ffa) into the portal vein or hepatic artery which results in the production of catecholamines and corticosteroids, the major stress hormones, as well as an increase in BP and heart rate [56,57]. One may conclude that the body is attempting to conserve energy during a period of “perceived caloric restriction” or “perceived starvation” i.e. a decrease in glucose utilization in muscle, with a resulting rapid increase in lipolysis and ffa release [56,57]. Leptin may provide an additional fat sensing reflex; for example, afferent signals from leptin receptors in white adipose tissue (epididymus) signal the brain to activate SNS outflow to the epididymus thereby facilitating lipolysis and increased ffa release [58]. Leptin is known to increase SNS drive to a number of tissues including brown adipose tissue. Therefore, it is likely that CNS stimulation of the SNS, as from stress, utilizes this same efferent pathway and increases lipolysis resulting in large increases of ffa content of the blood. Thus, the brain sensing obesity and/or excess ffa responds as it would to psychologic stress by conserving energy and engendering an inflammatory response via the stress hormones. Is an inflammatory response engendered in the fat?

**Obesity and inflammation**

An inflammatory process is present in obesity, predominantly visceral obesity which is fat specific [59]. Indeed, the largest number of activated genes in obesity (white adipose) are inflammatory genes, most of which are from macrophages but are fat specific [59,60]. APP are also present in visceral fat; these include CRP, serum amyloid A (SAA3), x\(_4\) acid glycoprotein, PAI-1, leptin and lipocalin 24p3 [61]. These APP may be induced by hyperglycemia, PIC, such as TNF and IL-6, or may be expressed constitutively. Moreover, adipose tissue responds to the PIC by TLRs, induced by NF\(_\kappa\)B which is induced by cytokines such as IFN\(_\gamma\) as well as LPS, indicating that an IIR is engendered. Indeed, the appearance of inflammatory markers precedes and predicts the onset of obesity [62], and the extent of weight gain is directly proportional to the number and concentration of these inflammatory markers [62].

A prominent feature of the inflammatory process in visceral fat is the presence of activated macrophages recruited from bone marrow; these appear prior to the onset of IR [59,60,63]. They are attracted to the fat depots by the powerful macrophage chemoattractant protein-1 (MCP-1), derived from adipocytes and they increase in proportion to fat depot expansion [63]. A number of molecules such as cortisol, PIC, angio II, leptin (and diminished adiponectin (ADN)) (see below) are present which promote the synthesis and secretion of adhesion molecules in the endothelial cells in the vascular beds of adipose tissue thereby guiding macrophages to this locus. Leptin stimulates the production of granulocyte macrophage colony stimulating factor (GM-CSF) which stimulates macrophage growth [64] and IL-6 inhibits production of ADN, thereby enhancing macrophage activation [65].

**Coronary artery disease and NIDDM**

Both of these diseases have many similar risk factors which has led to the common soil hypothesis (i.e. they both arise from a similar cause(s) [66].
The data presented herein support the hypothesis that they may both arise from stress-induced inflammatory changes, mainly in the visceral fat and vasculature, which give rise to the IRS and MS [67]. These metabolic syndromes may occur with small accumulations of visceral fat which are clinically inapparent. They may also occur in lean individuals who are "metabolically obese" [68].

IRS–MS may precede atherosclerosis by variable lengths of time while NIDDM may be preceded by the IRS–MS, almost invariably present, by as long as ten years. Supporting this contention is the fact that abnormal changes in mediators/modulators of these diseases may return toward normal values after treatment with ADN which improves insulin sensitivity and reverses diet induced IR. Also, treatment with the insulin-sensitizing agent thiazolidinedion (TZD) or related derivative compounds, improves the degree of the IR and the abnormal levels of the factors comprising the IRS–MS, as well as atherosclerosis and NIDDM.

**Models of stress, insulin resistance, CAD, and NIDDM in primates**

There are several primate models in which various types of psychological stress (e.g. social subordination) leads to the IRS–MS, CVD, and NIDDM ([33] review). Several studies in humans also indicate that stress is operative in the pathogenesis of the syndromes discussed ([69,70] reviews).

**Infectious agents as etiological factor(s) in chronic inflammatory disease**

Many studies have sought infectious agent(s) as the cause(s) of the vascular and adipose inflammation ([33] review). No organism has been consistently and convincingly isolated from patients with the IRS–MS, CVD or NIDDM. Additionally, CRP and IL-6, which are related to all measures of obesity, are not related to antibodies to *H. pylori*, *Chlamydia pneumoniae*, or Cytomegaloviruses, organisms implicated in the causation of the inflammatory process discussed herein [46]. The studies of Wright are revealing in that they indicate that infectious agents are neither necessary nor sufficient for development of murine atherosclerosis. Atherosclerosis occurred in mice prone to get atherosclerosis (apoE-negative) who were pathogen (germ) free, and in animals who do not respond to LPS (i.e. LPS resistant) [71]. Moreover, it is unlikely that activity and diminished activity of a chronic infectious process would correspond so directly with growth of a fat mass (high inflammatory markers) and loss of fat tissue (diminished inflammatory markers) respectively. It is certainly possible that an infectious process, by inducing an APR, may augment stress-induced inflammatory reactions described herein.

**Discussion and hypothesis**

It is the author’s view that psychologic stress via mediators comprised of the major stress hormones NE and cortisol, together with the RAS and PIC, as well as ffa, produce an inflammatory response. The major stress hormones commence this process by activation of NF₅B in macrophages, visceral fat and endothelial cells which induces the production of TLR which, when engaged, produce a cascade of inflammatory reactions comprising the APR of the IIS. The inflammatory process is most marked in the visceral fat depot as well as the vasculature and is involved in the metabolic events which accompany the IRS–MS, the components of which precede and comprise the major risk factors for CVD and NIDDM. The inflammation in visceral fat is likely to be the sentinel event [80] since inflammatory mediators appear in the fat either before or concomitantly with obesity Fig. 1.

Why the inflammation in fat, especially visceral fat? A number of signaling molecules such as IL-6, TNF, leptin and resistin which are proinflammatory and ADN are present in the visceral fat cell depot. Collectively, these mediators, with the exception of TNFα and resistin, are located in adipocytes and are called the adipokines [72]. ADN is anti-atherosclerotic and anti-inflammatory, inhibiting many of the inflammatory events leading to atherosclerosis and NIDDM. Diminished concentrations of ADN are found in the inflammatory state associated with IR and obesity. ADN influences IR by inhibiting the action of TNF on IKKβ; such an action would activate NF₅B [73]. Concentrations of resistin, which activate NF₅B, promote inflammation (vascular and fat), atherosclerosis, and NIDDM, and are increased in obesity [74].

The visceral fat is especially well endowed to mount an inflammatory response [30] and it is postulated that stress-induced inflammatory mediators trigger such a response. Stress induced sympathetic signaling via β₂ and β₃ adrenoreceptors would give rise to increased secretion of the PIC IL-6 and leptin from the adipocyte and activation of the macrophage, through α₁ and β adrenoreceptors, would result in NF₅B activation, TLR production, and PIC and
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resistin secretion \[7,26\]. Catecholamines, as well as corticosteroids, with or without IL-6, would induce the APP in the visceral fat cell depot as well as in the liver but the extent of involvement of the latter in this process is not clear \[61\]. The fact that several APP are constitutively expressed in visceral fat is indicative of the proclivity of this tissue for inflammation \[61\]. The IRS would develop from various combinations of the stress hormones, PIC, resistin, and ffa, the latter generated by the increased lipolysis in fat by the SNS, cortisol, PIC and HSL, and would be promulgated by further inflammation due to these mediators \[35,37,38\]. The enhancement of the inflammation and the IRS–MS by the interaction of the components of this network should be emphasized.

The inflammatory process in visceral fat is linked to fat metabolism. Inflammatory markers and inflammation increase as the accumulation of visceral fat occurs \[62\]; the latter is likely due to stress-induced cortisol \[69\] and the inflammatory mediators (i.e. IL-6 and angio II) which promote fat depot expansion, IIβ HSD-1 activity \[27\], and/or positive energy balance. The latter would occur due to increased food intake in response to the increased appetite likely caused by the major stress hormones (i.e. the catecholamines by release of neuropeptide Y in the brain \[75\], and cortisol which may produce “stress-eating” as well as the ingestion of “comfort foods”) \[76\]. Sympathetic nerve activity is known to be increased by adiposity \[77\]. Leptin and other macrophage growth factors induced by leptin, as well as the SNS, are likely to be responsible for the correlation of macrophage activation and accumulation with fat cell mass \[77,78\]. Macrophages may also contribute to the angiogenesis (“inflammatory neovascularization”) associated with fat expansion \[78\]. It is of interest that a high fat diet can decrease insulin sensitivity \[3\]. Moreover, consumption of four eggs per day for one month leads to increased concentrations of CRP, SAA and non-HDL-C in lean, insulin sensitive subjects \[79\]. Thus, fat cell accumulation triggers production and secretion of inflammatory markers such as TNFα (from macrophages) which induces both leptin and IL-6 from adipocytes; these three molecules act to decrease fat storage by lipolysis and promoting ffa fluxes from adipocytes \[80\]. Thus, the macrophage here stimulates the adipocyte \[9\]. Moreover, catecholamines and PIC decrease LPL activity which would diminish fat synthesis. It is reasonable to conclude that the inflammation in response to fat is likely to be the first or an early event in an attempt to limit its expansion. This is consistent with the fact that the IIS is activated in the organism presumably in response to fat accumulation deemed to be threatening by the organism \[80\]. It is also adaptive and would act to prevent obesity which might make an animal a less formidable prey since it would limit its agility in a fight-flight situation \[4\].

Leptin may be an important link between fat and inflammation since the SNS stimulates leptin production and leptin is proinflammatory \[81\]. Indeed
leptin stimulates dose-dependently the activation of CRF (a satiety factor) in the brain which induces the production of NE and corticosteroid, the major stress hormones [81]. Portal signaling by excess ffa signal the brain which also produces the major stress hormones. In addition to portal signaling by nervous input, the hypothalamus senses elevated ffa in the blood and stimulates hepatic gluconeogenesis [82].

The brain, in receiving these excess fat signals from the periphery, as well as from the blood (i.e. leptin and ffa), "perceives starvation" and responds by conserving energy, increasing gluconeogenesis, and elaboration of the major stress hormones, catecholamines and cortisol, to what might be considered a "metabolic stress". The brain, therefore, is striving to conserve energy, etc., by elaborating the same factors operative in inducing the psychologic stressed state, i.e. the major stress hormones [56]. Thus, the IR state (to protect the brain) is later perceived as starvation during the IRS. It is apparent that the same axis is being utilized; indeed, it is known that the response to stress is similar to the response to caloric restriction. In both, an inflammatory response is engendered, especially in visceral fat, and in both, there is an effort to conserve energy. It is likely that the "metabolic stress" against "perceived starvation", which originates from the periphery [56] or from the blood [82] and reflects fat signals, preceded the capacity to mount a psychologic stress response (fight-flight) which evolved later with development of a nervous system, but which, nevertheless, utilizes the same pathway. It was apparent that an existing mechanism was adapted to a related problem during evolution which would have course be easier than creating a whole new circuit [95]. With persistent psychologic stress, however, and according to the hypothesis contained herein, chronic inflammation and a persistent IR state occur; such a state, by sparing glucose, will continue to produce ffa and fat signals to the brain which will further inflammation and the IRS-MS, obesity, and the likelihood of disease.

If expansion of the fat cell mass is associated with inflammation, could this be reversed by diminution of the fat mass? Weight loss would diminish the number of fat cells, especially visceral fat, and insofar as these produce and secrete adipocytokines which induce the APR and promote lipolysis with increased ffa, the inflammatory effect would be lessened together with a diminution in insulin resistance and increased insulin sensitivity [83]. Thus, exercise increases glucose uptake and diminishes the APR (i.e. hyperglycemia also induces the APR [61]) and lowers ffa concentration with a resultant lowering of triglyceride and VLDL blood concentrations [84]. Weight reduction also improves endothelial dysfunction by increasing NO bioavailability shortly after commencement of exercise, decreasing vasoconstriction by diminution of NE concentrations in the endothelium and by promoting increases in vasodilators such as certain prostaglandins [85]. Blood pressure would be lowered by a diminution of both SNS activity and the IRS [86]. A diminution of ffa would enhance the decrease in BP since ffa cause the release of vasoconstrictive molecules from the endothelium, while they also increase the sensitivity of the vasculature to pressor agents such as NE [85]. MCP levels are also diminished with exercise and weight loss and the anti inflammatory molecule ADN is increased in the blood while resistin concentrations are lowered [87]. TLR, induced by factors inducing the APR through NF-B (i.e. interferon γ and/or LPS), are also reduced during weight loss [61,88].

Decreased intake of food would diminish HPA axis and SNS stimulation with diminution of corticosteroids and catecholamines, respectively. Obesity and hyperglycemia, especially, are associated with an increase in reactive oxygen species [88]; these are known to cause inflammation and are lowered with weight reduction [89]. Thus, it is possible that the protective effect of exercise may be due, in part, to its anti-inflammatory effect in fat. Perhaps, the most striking finding pertaining to weight loss reveals that the pattern of gene expression in white subcutaneous adipose tissue of obese subjects, 28 days after commencing a very low caloric diet, was closer to the profile of lean subjects than to the pattern of the obese subjects before the diet; the genes involved were found to be from macrophages which resided in the stromavascular fraction of the adipose tissue [90]. This suggests that the diminution of fat is accompanied by deactivation and/or decrease in the number of macrophages.

Could these restorative effects be achieved by removal of fat? Simply removing fat (up to 20%, or approximately 9 g in women) by liposuction did not change the concentrations of factors affecting insulin sensitivity or lipoproteins [91]. However, after by-pass surgery, with a concomitant reduction in visceral fat, a reduction in inflammatory mediators occurred [92]; this indicates that the improvement in inflammatory mediators is dependent on the loss of adipose tissue accompanying weight reduction. The hormone dihydroepiandrosterone (DHEA), the most abundant human steroid, is known to decrease body fat [93]. It also increases ADN in epidydimal white adipose tissue when
administered to animals. DHEA is atheroprotective and improves insulin sensitivity and glucose tolerance. Thus, fat removal by DHEA is found to be protective and restorative [93]. The therapeutic agent TZD, which lowers fat, can also diminish IR and certain features of the IRS–MS [94] (see above).

In conclusion, psychologic stress-induced inflammatory mediators would commence the inflammatory process in visceral fat and blood vessels, thereby creating the IRS–MS which, if prolonged, would provide the risk factors and enhance the likelihood of developing CVD and NIDDM. This process is enhanced by a similar inflammatory response by the host which "perceives starvation" and attempts to limit an expanding fat mass. All these processes utilize the same stress hormones from the brain, evoked as a similar efferent response, in reaction to different afferent stressors. Since the efferent response to both "metabolic" and "psychologic" stresses are similar, and the former is inflammatory, it is all the more likely that the latter response would also be inflammatory, which is the view presented herein.

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